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OP001 LAPAROSCOPIC ILEOCECAL RESECTION VERSUS INFlixIMAB TREATMENT OF TERMINAL ILEITIS IN CROHN’S DISEASE: THE LIEREC TRLAL

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Introduction: The optimal therapeutic approach to ileocolonic Crohn’s disease (CD) remains unclear.

Aims & Methods: The objective of this study was to compare infliximab with laparoscopic ileocolonic resection in patients with thiopurine or steroid refractory recurrent CD of the terminal ileum, with respect to quality of life (QoL) and remission rates.

Between May 2008 and October 2015, 143 patients were randomised to infliximab or laparoscopic ileocolonic resection. Patients with a prior ileocolonic resection, a diseased length > 40 cm, abdominal abscesses or fluid collections or an American Society of Anaesthesiologists (ASA) score of III or IV were excluded. The primary endpoint was QoL at one year follow-up. Furthermore, the mean direct costs per individual patient were calculated.

Results: At baseline, the mean difference (MD) in IBDQ score was 4.9 points in favour of resection (95% CI 4.0–5.8; P = 0.0003). Eventually, 65 patients started with infliximab treatment and 70 patients were operated. On April 28th 2016, 96.5% of the patients have completed follow-up. At baseline, the mean difference (MD) in IBDQ score was 4.9 points in favour of resection (n = 70). During follow-up, the mean direct costs per individual patient were prospectively documented and analysed according to intention-to-treat until one year after start of treatment. Dutch Trial Registry NTR1150.

Discussion: Since May 2008 and October 2015, 143 patients were randomised (32.9% male) with a median age of 37.0 years (interquartile range (IQR) 22.0–40.0). Eventually, 65 patients started with infliximab treatment and 70 patients were operated. On April 28th 2016, 96.5% of the patients have completed follow-up. At baseline, the mean difference (MD) in IBDQ score was 4.9 points in favour of the resection group. After correction for the baseline difference, the MD at one year follow-up was 5.8 points in favour of resection (95% confidence interval (CI) –4.5 to 16.2; P = 0.28). The mean direct costs per patient at one year were €14,589 in the infliximab group and €10,318 in the resection group (MD €4,270.95 CI 0.125 – 07.126; P = 0.005). Infliximab was stopped in 21 patients (30.0%) due to intolerance or insufficient response, 13 of whom underwent an ileocolonic resection after a median time of 27.0 weeks (IQR 11.0–33.5) after start of infliximab treatment. CD related serious adverse events in terms of Clavien Dindo IIIb complications occurred in three patients (4.1%) in the laparoscopic ileocolonic resection group and in one patient allocated to infliximab eventually going for surgery. Three patients (4.1%) in the resection group were started on infliximab within one year. Readmissions (for flares or additional surgery or dilatation) during follow-up were comparable (21.4% of patients in the infliximab versus 17.8% in the resection group).

Conclusion: QoL at one year was not significantly different between the laparoscopic ileocolonic resection and infliximab group. Given the lower bound of the 95% CI, laparoscopic ileocolonic resection can be considered a non-inferior alternative for infliximab treatment at significantly lower cost.

Disclosure of Interest: All authors have declared no conflicts of interest.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP002 CELL AUTONOMOUS AND NON-CELL AUTONOMOUS RESCUE OF NNOS DEFICIENT MOUSE COLON FOLLOWING IN VIVO ENTERIC NERVOUS SYSTEM STEM CELL TRANSPLANTATION

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Introduction: Enteric neural stem cells (ENSC) have been identified as a possible target for treating enteric neuropathies following successful colonization of recipient gut after transplantation. However, the ability of ENSC to rescue pathophysiological conditions remains unclear. Loss of neuronal subtypes, including neuronal nitric oxide synthase (nNOS), has been implicated in many enteric neuropathies. nNOS−/− mice display slow colonic transit providing a model to test ENSC rescue in a pathological setting.

Aims & Methods: Our aim was to assess the functional integration of transplanted ENSC within recipient nNOS−/− colon. Initially, donor ENSC were obtained from Wnt1-cre;YFP transgenic mice allowing specific fluorescent labelling. FACs selection and fate mapping of cells. YFP+ ENSC were transplanted to nNOS−/− distal colon at post natal day (P14). Subsequently, integration and functionality were assessed using immunolabelling and organ bath physiology after 4 weeks.

Results: After 1 month, YFP+/iNOS− neurons were identified and transcriptional analysis showed specific expression of nNOS in recipient nNOS−/− colon. In NANC (non-adrenergic non-cholinergic) conditions, organ bath physiology revealed significant increases in electrical field stimulation (EFS)-induced relaxation (Area under curve; AUC) in transplanted nNOS−/− (–1.13 ± 0.16 g.s, n = 5) compared with non-transplanted nNOS−/− (–0.31 ± 0.08 g.s, n = 5; P = 0.0016). In transplanted colonic segments, addition of the nitric oxide synthase blocker LNAME resulted in significant reductions in the observed EFS-induced relaxation (–0.74 ± 0.17 g.s vs –0.12 ± 0.16 g.s, n = 4; P = 0.0389) demonstrating restoration of nitricergic responses after transplantation. Interestingly, significant increases in basal contractile amplitude were also observed in transplanted nNOS−/− colonic segments (0.30 ± 0.06 g.s, n = 5) compared with both C57BL/6J (0.10 ± 0.01 g.s, n = 5; P = 0.0093) and non-transplanted nNOS−/− mice (0.05 ± 0.008 g.s, n = 5; P = 0.0025). These high-amplitude contractions were unaffected by application of tetrodotoxin, suggesting that transplantation of ENSC can also lead to changes in underlying myogenic motility patterns. To assess the mechanisms involved in these non-cell autonomous phenomena we sought to investigate potential changes in gut morphology. No significant change was observed in the diameter of the distal colon between transplanted nNOS−/− mice (1.04 ± 0.13 mm; n = 3) compared to either non-transplanted nNOS−/− (1.12 ± 0.08 mm; n = 3; P = 0.609) or sham-operated nNOS−/− (1.05 ± 0.02 mm; n = 3; P = 0.947). In addition, no change in muscle thickness was observed between transplanted nNOS−/− mice (55.33 ± 8.67 µm; n = 3) compared to either non-transplanted nNOS−/− (54.0 ± 9.0 µm; n = 3; P = 0.915) or sham-operated nNOS−/− (54.33 ± 2.96 µm; n = 3; P = 0.918). Ongoing work is targeting other potential processes such as modification of cell types involved in neuromuscular signalling, including intestinal cells of Cajal within the transplanted microenvironment.

Conclusion: Here we demonstrate, for the first time, that transplanted ENSC integrate and effect restoration of function, at the organ level, in a pathological GI disease model potentially via both ENSC-specific and non-ENSC-specific processes.

Disclosure of Interest: All authors have declared no conflicts of interest.
Infected necrotizing pancreatitis is a potentially lethal disease that requires prompt and effective management to minimize morbidity and mortality. A randomized controlled trial (TENSION trial) compared a minimally invasive endoscopic step-up approach with a surgical step-up approach in patients with infected necrotizing pancreatitis. The endoscopic step-up approach, as compared with a surgical step-up approach, in reducing major complications or death in patients with infected necrotizing pancreatitis. However, the rate of pancreatic fistula, length of hospital stay and costs were significantly reduced in the endoscopic group.

Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016
10:30-12:00
ESTABLISHED AND NEW DRUGS IN IBD - ROOM B

OP005 EFFICACY AND SAFETY OF DOSE ADJUSTMENT IN USTEKINUMAB-RESISTANT, SEVERE CROHN’S DISEASE PATIENTS: RESULTS FROM THE IM-UNITI MAINTENANCE STUDY


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Introduction: Ustekinumab (UST) has been shown to induce and maintain clinical response and remission in moderate to severe Crohn’s disease (CD) in 2 induction (UNITI-1 and 2) and 1 maintenance (IM-UNITI) randomized, placebo controlled Phase 3 trials. We evaluated the efficacy of UST in 2 additional groups in IM-UNITI: patients who underwent dose adjustment following loss of response (LOR) and patients who did not have a clinical response to IV UST during induction and had an additional subcutaneous (SC) dose.

Methods: Patients achieving clinical response after single dose IV induction were randomized to placebo (PBO) or UST 90 mg q12w or q8w (no dose adjustment) and were assessed for clinical response (≥ 100 point decrease from the maintenance baseline CDAI score, 50% increase in CDAI score, ≥ 300 point decrease from the maintenance baseline CDAI score, ≥ 100 point increase from the maintenance baseline CDAI score) at week 8. Patients achieving clinical response to IV UST at week 8 were continued on UST 90 mg q12w or q8w.

Results: A total of 98 patients were enrolled in 19 Dutch hospitals. The primary endpoint occurred in 10 of 51 patients (20%) in the endoscopic group and in 13 of 49 patients (28%) in the surgical group (risk ratio 0.75; 95% CI 0.37 to 1.52, P = 0.35). There were no significant differences in the individual components of the primary endpoint (e.g., patients achieving ≥ 300 point change in CDAI score; P = 0.84 in the endoscopic group, 21 patients (43%) as compared with 23 patients (49%) in the surgical group did not need necrosectomy after drainage as first step of treatment (risk ratio 0.84: 95% CI 0.54 to 1.31, P = 0.43). There was a lower incidence of pancreatic fistula (5% versus 32%; P = 0.001) and length of hospital stay was shorter (median 36 days versus 69 days; P = 0.03) in the endoscopic group. Furthermore, the difference in total mean costs was 21,635 (19%; 95% CI -10.386-35.972) in favor of the endoscopic group.

Conclusion: The TENSION trial did not show superiority of the endoscopic step-up approach, as compared with a surgical step-up approach, in reducing major complications or death in patients with infected necrotizing pancreatitis. However, the rate of pancreatic fistula, length of hospital stay and costs were significantly reduced in the endoscopic group.

Disclosure of Interest: All authors have declared no conflicts of interest.

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10:30-12:00
ESTABLISHED AND NEW DRUGS IN IBD - ROOM B
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A substantial interindividual variability in VDZ TC was observed at w2 median [IQR].

Biological response (CRP decrease at baseline and w10 and mucosal healing was defined as a Mayo endoscopic sub-

moderate to severe Crohn's disease (CD) and ulcerative colitis (UC). We studied surgical and endoscopic outcomes in real-life practice.

Aims & Methods: The first 75 patients (49 CD, 26 UC) who initiated VDZ therapy (300 mg IV administered) in our tertiary referral center were sampled at trough during induction (w2 and w6) and early maintenance (w10, w14 and w22) treatment. Clinical response (clinical symptoms and physical global assessment) was correlated to VDZ TC. All patients with UC received sigmoidoscopy at trough during induction (w2 and w6) and early maintenance (w10, w14 and w22)***

37.9 [24.4–45.1] (15) 12.8 [7.5–19.3] (10)

w14**

25.8 [16.1–33.8]) (23) 23.6 [16.4–39.4] (22)

37.9 [24.4–45.1] (15)

20 [g/mL [17.1–36.6], n = 42) compared to patients who did not receive a w10 infusion (13.1 [g/mL [6.6–19.3], n = 28) (p < .0001). Biological response and remission were achieved in 52% (14/27) and 30% (8/27) of patients with CD. Significantly higher VDZ TC were observed at w2*** and w6 (32.0 [g/mL [16.1–33.8]), compared to when no remission was achieved (15.0 [g/mL [9.8–19.8]) (p = .0004). At w22, 59% (16/27) of patients with CD were in biological remission. Patients who were in biological remission at w2 had significantly higher VDZ TC throughout w2 to w22*** compared to patients who were not in biological remission at w22 (table 1).

14.0 [7.9–18.6] (17)

Vedolizumab is an anti-α4β7 monochlonal antibody effective in ulcerative colitis (UC) and Crohn's disease (CD). Data regarding pharmacokinetics' pharmacodynamics of vedolizumab are still scarce.

Aims & Methods: To assess whether early vedolizumab trough levels (weeks 2-6) correlate with response to vedolizumab induction therapy. Methods: A novel ELISA-based assay was developed, for measuring Chelodin®/Zeria, and employed in prospectively-followed IBD patients receiving vedolizumab induction therapy. Drug levels were assessed for association with clinical remission. The primary outcome was the comparison of week 6 levels in patients with or without clinical remission at the same time-point. Association of week 2 and week 6 levels with week 14 clinical remission was also sought, as well as association of trough levels with inflammatory markers (Albumin and C-reactive protein, CRP).

Biological response and remission were achieved in 52% (14/27) and 30% (8/27) of patients with CD. Significantly higher VDZ TC were observed at w2*** and w6 (32.0 [g/mL [16.1–33.8]), compared to when no remission was achieved (15.0 [g/mL [9.8–19.8]) (p = .0004). At w22, 59% (16/27) of patients with CD were in biological remission. Patients who were in biological remission at w2 had significantly higher VDZ TC throughout w2 to w22*** compared to patients who were not in biological remission at w22 (table 1).

Table 1: Vedolizumab trough concentrations, in μg/mL, median [IQR] (n), during (induction w2 and w6) and early maintenance (w10, w14 and w22) treatment correlated with biological remission (CRP ≤5 mg/L) at w22 in patients with CD.

<table>
<thead>
<tr>
<th>Week</th>
<th>Median CRP [mg/L]</th>
<th>Median VDZ Trough [μg/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>w2</td>
<td>23.6 [18.4–39.9] (17)</td>
<td>31.8 [23.9–38.9] (23)</td>
</tr>
<tr>
<td>w6</td>
<td>16.6 [9.0–31.4] (17)</td>
<td>33.5 [22.1–38.5] (23)</td>
</tr>
<tr>
<td>w10</td>
<td>13.0 [7.5–19.3] (10)</td>
<td>37.9 [24.4–45.1] (15)</td>
</tr>
<tr>
<td>w14</td>
<td>14.0 [7.9–18.6] (17)</td>
<td>25.8 [16.1–33.8] (22)</td>
</tr>
</tbody>
</table>

"p < .05; **p < .01; ***p < .001" Endoscopic healing was achieved in 65% (13/20) of patients with UC. Patients with endoscopic healing had significantly higher VDZ TC at w6 (30.5 [μg/mL [18.6–38.0]), compared to patients who did not achieve endoscopic healing (16.6 [μg/mL [11.0–29.3]) (p = 0.02). Clinical response was achieved in 69% (47/68) of the patients. Only in patients with UC, clinical response was associated with higher VDZ TC at w2 (27.8 [μg/mL [22.3–37.3], n = 16) and w6 (22.0 [μg/mL [17.8–37.7], n = 16) compared to absence of clinical response (21.6 [μg/mL [16.0–25.2] and 16.6 [μg/mL [11.0–20.6], resp. n = 7) (p = .03 and p = .02).

Conclusion: In this real-life cohort of consecutive IBD patients receiving vedolizumab, drug levels during induction were not associated with or predictive of clinical response to induction therapy and were not associated with CRP normalization or steroid-free clinical remission. Future studies are pertinent in order to elucidate the role of therapeutic drug monitoring of vedolizumab during induction and maintenance.

Disclosure of Interest: U. Kopylov: Dr. Kopylov received consultancy fees from Janssen, research support from Janssen and Takeda and lecture fees from Janssen, Takeda, Abbvie and CTS.

Y. Chowdhry: Prof. Chowdhry received consulting and lecture fees as well as grant support from Takeda, Abbvie, Janssen, Pfizer, Ferring and Protalix.

R. Eliaikim: Prof. Eliaikim has received consulting and lecture fees from Takeda.

S. Ben-Horin: Prof. Ben-Horin has received consulting and/or advisory board fees from Janssen, Takeda, Celltrion, Abbvie, & Schering-Plough and research support from Celltrion and Abbvie.

All other authors have declared no conflicts of interest.

Disclosure of Interest: A. Gilis: Lecture fees(s) MSD, Janssen Biologics, Abbvie, Pfizer, Takeda. Consultancy: UCB. Conflict with: license of infliximab, anti-infliximab and adalimumab ELISA from Institution to apDuA and with lateral flow infliximab to Ri-Biopharm AG.


S. Vermeire: Grant/research support Takeda, Abbvie, Abbvie Consultancy, speaker’s fees from Abbvie, MSD, Takeda, Pfizer, Galapagos, Genentech/Roche, Mundipharma, Celgene, Hospira, Second Genome

All other authors have declared no conflicts of interest.

OP006 VEDOLIZUMAB EXPOSURE CORRELATES WITH CLINICAL, BIOLOGICAL AND ENDOSCOPIC OUTCOME IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Introduction: Vedolizumab (VDZ) specifically targets the α4β7-integrin on gut-homing lymphocytes and has been approved for the treatment of patients with moderate to severe Crohn’s disease (CD) and ulcerative colitis (UC). We studied the relation between serum VDZ trough concentrations (TC) and clinical, biological and endoscopic outcomes in real-life practice.

Aims & Methods: The first 75 patients (49 CD, 26 UC) who initiated VDZ therapy (300 mg IV administered) in our tertiary referral center were sampled at trough during induction (w2 and w6) and early maintenance (w10, w14 and w22)*** of patients with UC. Patients with endoscopic healing (16.6 [μg/mL [11.0–20.6], resp., n = 7) were treated at w6 and w22 in patients with CD. An ELISA for measuring serum VDZ TC was developed in house. TC are shown as median [IQR].

72 patients were included (47 CD, 25 UC), of whom 14 (30%) and 15 (32%) of CD and UC patients respectively achieved clinical remission or steroid-free clinical remission. Future studies are pertinent in order to elucidate the role of therapeutic drug monitoring of vedolizumab during induction and maintenance.

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OP008 PREDICTORS OF NON-RESPONSE OR LOSS OF RESPONSE TO TUMOUR NECROSIS FACTOR ANTAGONIST THERAPIES IN INFLAMMATORY BOWEL DISEASE

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Introduction: Tumour necrosis factor antagonist (anti-TNFs) are effective at inducing and maintaining disease remission in patients with moderate to severe ulcerative colitis (UC) or Crohn’s disease (CD). However, considerable proportions of patients do not respond to therapy or lose response over time. Aim: This real-world data uses real-world data to identify predictors of non- or loss of response to anti-TNF therapy. The study recruited UC and CD patients from 6 countries [Canada, France, Germany, Italy, Spain, and the United Kingdom (UK)] aged ≥18 years who initiated anti-TNFs (infliximab/adalimumab) during June 2009 to June 2011 (CD) or June 2009 to June 2013 (UC). Data were collected on patient demographics, clinical characteristics and healthcare resource use. Patients were classified as having non- or loss of response if they: were hospitalized or required UC/CD surgery whilst on therapy, discontinued due to UC or CD flare, required dose-escalation or augmentation with steroids/immunosuppressants 4 months after therapy initiation, or disease severity became worse after therapy initiation. Multilevel multivariable logistic regression was used to identify predictors of non- or loss of response.

Results: The study included 1195 patients (45% UC, 55% CD; 9.6% Canada, 13% France, 22% Germany, 23% Italy, 19% Spain and 14% UK). Mean age: 40.3 (SD = 13.7); 51%: male. Most patients had a Charlson comorbidity index (CCI) score of 0-1 (83%), 16% were current smokers, mean BMI was 24.8 (SD = 5.48) and mean disease duration was 9 years (SD = 8.07). Most patients had a physician global assessment of moderate (45%) at study entry. Mean follow up was 3.4 years (UC) and 4.4 years (CD). Overall, 22% of patients had a primary non-response and 71% were classified as having non- or loss of response to anti-TNF therapy in the maintenance period (4 months after initiating anti-TNF) over a mean follow up period of 32 months (SD = 20.4). Significant predictors of non-/loss of response are shown in the Table 1.

Table 1: Predictors of non-response or loss of response among patients with ulcerative colitis and Crohn’s disease

<table>
<thead>
<tr>
<th>Baseline Variables</th>
<th>Odds Ratio (95% Confidence Interval) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Ulcerative Colitis</td>
<td></td>
</tr>
<tr>
<td>Rectal Bleeding (Reference: None)</td>
<td>1.12 (1.00–1.24) 0.04</td>
</tr>
<tr>
<td>- Passing blood alone</td>
<td>0.24 (0.06–0.97)</td>
</tr>
<tr>
<td>- Passing blood with stool ≥50% of time</td>
<td>0.35 (0.19–1.99)</td>
</tr>
<tr>
<td>- Passing blood with stool &lt;50% of time</td>
<td>0.17 (0.05–0.62) 0.02</td>
</tr>
<tr>
<td>Endoscopic Findings (Reference: Inactive; Mild)</td>
<td></td>
</tr>
<tr>
<td>- Moderate</td>
<td>3.19 (1.14–9.87)</td>
</tr>
<tr>
<td>- Severe</td>
<td>4.86 (1.61–14.7)</td>
</tr>
<tr>
<td>Patients with Crohn’s Disease</td>
<td></td>
</tr>
<tr>
<td>Number of Liquid or Soft Stools per Day</td>
<td>1.12 (1.00–1.24)</td>
</tr>
<tr>
<td>C-reactive Protein (CRP)</td>
<td>1.02 (1.00–1.03)</td>
</tr>
</tbody>
</table>

Note: Only the significant predictors are included in the table above. Other non-significant variables included age, gender, body mass index, disease duration, Charlson comorbidity index score, and use of corticosteroids or immunomodulators. Both were analyzed as continuous variables. Highest CRP values during the baseline period were used.

Conclusion: In this cohort the majority of patients did not respond or lost response to anti-TNF therapy over time. Predictors for patients with UC included the absence of rectal bleeding and moderate/severe endoscopic scores, and for patients with UC included higher CRP and higher number of liquid or soft stools per day. These predictors should be considered when evaluating treatment options for patients.


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OP009 INFLAMMATORY BOWEL DISEASE COURSE AND THERAPEUTIC MANAGEMENT IN REAL LIFE PRACTICE IN THE CURRENT ERA OF ANTI-TNFs: ANALYSIS OF THE FRENCH ADMINISTRATIVE HEALTH DATABASES 2009–2014

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Introduction: Management of inflammatory bowel disease (IBD) has evolved in the last decade. Clinical trials have shown that the combination of anti-TNFs and thiopurines is more efficient than monotherapy with either of these. The impact of these results in real-life practice is unknown. Moreover, the frequency of treatment withdrawal has never been assessed in population-based cohort studies.

Aims & Methods: Our aim was to assess IBD course and therapeutic management including treatment withdrawal, surgery rates and hospital stays in the current era of anti-TNFs. Every patient affiliated to the French national health insurance with a diagnosis of IBD based on listed long-term diseases and/or hospital discharge diagnosis was included from 2009 to 2013, and followed up until 31 December 2014. Cumulative incidence rates were used to estimate the cumulative probabilities of medication use, surgery and hospitalization among prevalent and incident patients. Treatment sequences including treatment withdrawal after introduction of thiopurines, anti-TNFs and comorbidity were assessed for incident patients included between 2009 and 2012.

Results: 195,834 individuals were diagnosed with IBD (Crohn’s disease (CD), 106 436 (31,353 incident patients); ulcerative colitis (UC), 89,398 (27,578 incident patients). Among incident patients treated with thiopurines or anti-TNFs (17 566 CD and 8035 UC patients), the first treatment was thiopurines, anti-TNFs monotherapy, and comorbidity in 69.1%, 24.8% and 6.1% of CD patients and 79.5%, 17.7% and 4.1% of UC patients, respectively. Subsequently, 36.8% and 20% of CD patients were exposed to anti-TNFs monotherapy and comorbity, respectively, 5 years after diagnosis. More than 25% of CD and UC incident patients included between 2009 and 2012 withdrew thiopurines or anti-TNFs, during more than three months after a first treatment course. Drug withdrawal was related to hospitalization or surgical procedures in less than 30% of these patients. Nearly 50% of CD patients and 40% of UC patients went back to their initial treatment after withdrawal. Around 5% of CD patients and 4% of UC patients stopped all IBD therapy during follow-up. Five years after diagnosis, the cumulative risks of first intestinal resection in CD, and colectomy in UC were 12.8% and 3.5%, respectively.

Conclusion: The step-up approach remains the dominant strategy in IBD, whereas exposure to anti-TNFs is high and surgery rates are low. Treatment withdrawal in IBD is more common than expected. This study emphasizes the growing need of studying de-escalation strategy in IBD.

Disclosure of Interest: F. Carbonnel: Franck Carbonnel had consulting fees for Genentech, Osuka, Vifor, or lecture fees for Hospira. All other authors have declared no conflicts of interest.
The identification of children at risk for failure to reach sustained remission despite exposure to anti-TNF remains challenging in Crohn’s disease. Univariate analyses of the type of follow-up clinic and anti-TNF treatment were performed between anti-TNF exposed patients with or without sustained remission and correlations assessed between variables and the outcomes average disease severity and disease sustained remission.

Results: Of 66 anti-TNF exposed patients (median (IQR) age 13.1 (11.5–15.2) yrs, 50% male), 17% failed to reach sustained remission. Disease location was similar in both groups and mild disease at diagnosis (45% vs. 16%; p < 0.03) more frequent in the group failing to reach sustained remission. There were no differences between age, gender, WBC or CRP at diagnosis and treatment between both groups. Percentages of infliximab and adalimumab use were similar in both groups, including drug switching and dose or interval adjustments. When stratified by follow-up clinic, infliximab in paediatric follow-up was less frequently associated with failure to reach sustained remission compared to sustained remission.

Univariate analyses of the type of follow-up clinic and anti-TNF treatment between patients with or without sustained remission (more than one anti-TNF possible).

<table>
<thead>
<tr>
<th>Variable, number (%)</th>
<th>No sustained remission (n = 11)</th>
<th>Sustained remission (n = 55)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric follow-up and infliximab</td>
<td>3 (27)</td>
<td>37 (67)</td>
<td>.01</td>
</tr>
<tr>
<td>Paediatric follow-up and adalimumab</td>
<td>1 (9)</td>
<td>8 (15)</td>
<td>.63</td>
</tr>
<tr>
<td>Adult clinic follow-up and infliximab</td>
<td>6 (55)</td>
<td>14 (25)</td>
<td>.05</td>
</tr>
<tr>
<td>Adult clinic follow-up and adalimumab</td>
<td>2 (18)</td>
<td>4 (7)</td>
<td>.25</td>
</tr>
<tr>
<td>Paediatric follow-up and adjustments</td>
<td>1 (9)</td>
<td>8 (15)</td>
<td>.63</td>
</tr>
<tr>
<td>Adult follow-up and adjustments</td>
<td>1 (9)</td>
<td>3 (11)</td>
<td>.65</td>
</tr>
</tbody>
</table>

Higher average disease severity (2.1 (2.0–2.3) vs. 1.6 (1.3–1.8); p < .001), adult clinic follow-up (73% vs. 27%; p < .01), surgery for CD (1 (0–3) vs. 0 (0–3); p < .01), 3 yrs of disease (5 yrs (9% vs. 24%; p < .05) were associated with failure to reach sustained remission. Both colonic disease and adult follow-up (AUC = 0.66; both p = .04) correlated with average disease severity (no correction for multiple testing). No other correlations were found.

Conclusion: Patient phenotype at diagnosis does not predict failure to reach sustained remission despite anti-TNF exposure. Mild disease may not trigger appropriate treatment and lead to active and complicated disease course. Sustained remission occurred most with infliximab in paediatric follow-up. Information on serum levels is lacking.


OPI01 IS HELICOBACTER PYLORI ERADICATION ABLE TO IMPROVE THE SCORES OF ATROPHIC GASTRITIS AND INTESTINAL METAPLASIA? – LONG-TERM FOLLOW-UP STUDY IN HIGH RISK POPULATION OF GASTRIC CANCER

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Disclosure of Interest: None communicated

Introduction: Helicobacter pylori (H. pylori) is a risk factor of atrophic gastritis (AG) and intestinal metaplasia (IM) which can undergo to gastric cancer. However, the reversibility of AG and IM by H. pylori eradication is controversial, so far.

Aims & Methods: This study was performed to evaluate the reversibility of AG and IM by anti-H. pylori therapy in large number of patients for a long period in South Korea. A total of 810 patients with follow-up at least 1 year were enrolled from January, 2006 to September, 2014. On the basis of H. pylori infection status and eradication, the subjects were divided into three groups, as follows: Group A (n = 214) included those patients who were H. pylori negative. Group B (n = 580) had successful eradication result for H. pylori. Group C (n = 116) had not received eradication therapy or showed eradication failure. The histological features of the AG and IM in the antrum and body were measured, respectively, using Sydney system scores. All of three groups were followed at 1, 2, 4 and 5 or more years.

Results: In patients with successful eradication (Group B, grades of AG and IM in both antrum and body significantly decreased at 1, 2, 4 and 5 or more years (p < 0.001) (Table). In contrast, in the H. pylori negative group (Group A), no significant change was documented for grades of AG and IM in either antrum or body except for grades of IM in body at 2 years and AG in body at 4 years (Table). Similarly, in Group C, no significant change was documented for grades of AG and IM in either antrum or body except for scores of AG in body at 5 or more years (Table).
Kaplan–Meier curves showed that higher APLN expression was significantly correlated with a poor clinical stage and worse prognosis in HCC patients.

Disclosure of Interest: All authors have declared no conflicts of interest.

# OP014 TUMORS SKEW THE CCR2-DEPENDENT ANTI-TUMOR IMMUNE RESPONSE INITIATED BY ONCOCARCINOMA-INDUCED SENESCECE TO TUMOR GROWTH PROMOTION

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Introduction: Oncogene-induced senescence induces the immune-mediated clearance of these precancerous senescent hepatocytes, preventing malignant transformation and tumor initiation; a process termed ‘senescence surveillance’. However, senescent hepatocytes can give rise to hepatocarcinomas (HCC), if the senescence program is abrogated and/or senescent cells are not cleared. We set out to identify the mechanism of recruitment of senescent cell-clearing macrophages. Furthermore, we studied the effect of senescence-associated inflammatory responses in promoting full-blown tumor cells in the liver.

Aims & Methods: To induce senescence in mouse livers, either oncogenic Nras (NrasG12V) or an effector loop mutant (NrasG12V/D38A), which is incapable of downstream signaling and senescence induction, were hydrodynamically delivered into C57BL/6, C2R2 KO and p19 KO mice. To achieve tumor development in senescent livers, luciferase-expressing hepatocellular carcinoma cells were intrasplenically injected into mice after hydrodynamic gene delivery. Tumor growth was assessed using weight and bioluminescence measurements as well as quantification of macroscopic tumors. Senescent livers with or without tumors were analyzed using flow cytometry and immunohistochemistry. Furthermore, peri-tumoral tissue of 226 HCC patients was hierarchical clustered based on the expression of 35 senescence-associated genes (2). Senescence-associated gene signature expression was then compared with chemokine expression and survival. In addition, human peri-tumoral tissue was analyzed by immunohistochemistry for the presence of senescence and myeloid cell markers.

Results: In tumor-free livers, senescent hepatocytes induced CCR2+ immature myeloid cell (mMC) accumulation, followed by mMC maturation into macrophages, which clear senescent hepatocytes. In CCR2 KO mice, mMC recruitment and macrophage accumulation was impaired, causing persistence of oncogenic Nras-expressing hepatocytes and ultimately HCC development. In contrast, however, tumor cells in senescent livers blocked the maturation of CCR2+ mMC into macrophages, which lead to an accumulation of mMC. These mMC inhibited NK cell cytotoxicity against tumor cells, as demonstrated by reduced NK cell degranulation upon hepatocellular inhibition through senescence-released mMC. Furthermore, gene expression and immunohistochemistry analyses in peri-tumoral tissue of patients with hepatocellular carcinoma confirmed the association of senescence-induced CCL2 expression, myeloid cell accumulation, NK cell inhibition and poor prognosis.

Conclusion: Senescence-associated gene signature expression was associated with CCL2/CCR2 signaling and the ensuing myeloid cell accumulation harbor context dependent functions in preventing HCC initiation, but also promoting progression of established HCC. These findings hold important translational significance for clinical practice. 1. CCR2 antagonists may fuel liver cancer growth in patients with chronic liver disease, in which senescent hepatocytes accumulate. 2. In patients with HCC, CCR2 antagonists may reduce senescence-induced immunosuppression induced by liver tumors.Disclosure of Interest: All authors have declared no conflicts of interest.

References
MONDAY, OCTOBER 17, 2016
10:30-12:00

EPISTOMIE OP015 - COLD FORMESES AVULSION (CFA) WITH ADJUVANT SNARE TIPS COAGULATION (STSC) IS AN EFFECTIVE AND SAFE STRATEGY FOR THE MANAGEMENT OF NON-LIFTING LARGE LATERALLY SPREADING COLORECTAL LESIONS (NL-LSLS)

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Introduction: Non-lifting NL large laterally spreading and colorectal lesions (NL-LSLs) are challenging to resect endoscopically and often necessitate surgery. Previously attempted endoscopic resection, pre-resection biopsy and sub-lesion carbon particle suspension are common reasons for NL. Conventional endoscopic removal is not always possible and can result in incomplete resection. The aim of this study was to evaluate whether the CFA approach with adjuvant STSC is a safe, effective and surgery-sparing technique. Study Design: Prospective observational study of patients referred for wide field EMR of NL-LSLs (NL size > 20mm, NLSSs which could not be completely resected by snare due to NL were labelled NL-LSL). Patients were divided into previously attempted non-lifting NL-LSLs (PANL-LSL) and naïve non-lifting NL-LSLs (NNL-LSL). Such lesions had completion of resection using a standardized approach with CFA and STSC. The NL area was isolated by circumferential snare excision of all adjacent tissue including adenoma and/or normal mucosa to free the lateral margins. This then allowed effective CFA of NL adenoma. Systematic CFA was then performed to remove all visible NL adenoma. The exposed submucosa of the lesion site and its margins were treated with controlled thermal ablation using STSC (ERBE effect 4, 80W). Scheduled surveillance colonoscopy was performed after 4 weeks (SC2), 12 weeks (SC3) and 18 months (SC2) post the index procedure. The primary outcome was endoscopic and histological evidence of adenoma clearance. Secondary outcomes were safety and statistically significant differences between PANL-LSL and standard LSLs. NNL-LSL recur more frequently. Non-granular NLSSs were over-represented in both groups. They may be more susceptible to developing fibrosis after biopsy and therefore care should be taken to avoid significant tampering with these lesions prior to referral for definitive endoscopic treatment.

Disclosure of Interest: All authors have declared no conflicts of interest.

Aims & Methods: The study aimed to evaluate the characteristics of NL-LSL and the safety and efficacy of endoscopic treatment by Cold Forceps Avulsion (CFA) followed by thermal ablation of the avulsion site by Snare Tip Soft Coagulation (STSC). Amongst a prospective observational study of patients referred for wide field EMR of NL-LSLs, LA > 20mm, NLSSs which could not be completely resected by snare due to NL were labelled NL-LSL. Patients were divided into previously attempted non-lifting NL-LSLs (PANL-LSL) and naïve, non-lifting NL-LSLs (NNL-LSL). Such lesions had completion of resection using a standardized approach with CFA and STSC. The NL area was isolated by circumferential snare excision of all adjacent tissue including adenoma and/or normal mucosa to free the lateral margins. This then allowed effective CFA of NL adenoma. Systematic CFA was then performed to remove all visible NL adenoma. The exposed submucosa of the lesion site and its margins were treated with controlled thermal ablation using STSC (ERBE effect 4, 80W). Scheduled surveillance colonoscopy was performed after 4 weeks (SC1), 12 weeks (SC2) and 18 months (SC3) post the index procedure. The primary outcome was endoscopic and histological evidence of adenoma clearance. Secondary outcomes were safety and statistically significant differences between PANL-LSL and standard LSLs. NNL-LSL recur more frequently. Non-granular NLSSs were over-represented in both groups. They may be more susceptible to developing fibrosis after biopsy and therefore care should be taken to avoid significant tampering with these lesions prior to referral for definitive endoscopic treatment.

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Disclosure of Interest: All authors have declared no conflicts of interest.

Abstract No: OP015

Table 1: lesions where cold forceps avulsion and snare tip soft coagulation (CFA and STSC) was used in the resection of PANL or NNL; p values represent comparison to LSL. Two stage procedures were excluded. SD - standard deviation, IQR - interquartile range, SC1 - surveillance colonoscopy 1, ICV - ileocecal valve, PANL – previously attempted non lifting lesion, NNL – naïve non lifting lesion.

<table>
<thead>
<tr>
<th>Patient</th>
<th>PANL n = 33</th>
<th>p</th>
<th>NNL n = 50</th>
<th>p</th>
<th>LSL n = 650</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>70.2 (8.6)</td>
<td>.121</td>
<td>73.0 (9.5)</td>
<td>&lt;.001</td>
<td>66.9 (12.1)</td>
</tr>
<tr>
<td>Male, (%)</td>
<td>18 (54.5)</td>
<td>.598</td>
<td>20 (58.0)</td>
<td>.266</td>
<td>324 (49.8)</td>
</tr>
<tr>
<td>Lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median size (IQR)</td>
<td>(20-30)</td>
<td>&lt;.001</td>
<td>(25-50)</td>
<td>.424</td>
<td>(35-45)</td>
</tr>
<tr>
<td>Morphology (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granular</td>
<td>8 (25.0)</td>
<td>.003</td>
<td>22 (44.0)</td>
<td>.012</td>
<td>323 (52.4)</td>
</tr>
<tr>
<td>Non granular</td>
<td>20 (62.5)</td>
<td>.324</td>
<td>23 (46.0)</td>
<td>.209</td>
<td>209 (33.9)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>4 (12.5)</td>
<td>.598</td>
<td>5 (10.0)</td>
<td>.85</td>
<td>85 (13.8%)</td>
</tr>
<tr>
<td>Location (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>11 (34.4)</td>
<td>.121</td>
<td>6 (13.0)</td>
<td>.091</td>
<td>121 (18.8)</td>
</tr>
<tr>
<td>Splenic to sigmoid</td>
<td>6 (18.8)</td>
<td>.121</td>
<td>11 (23.9)</td>
<td>.98</td>
<td>98 (15.2)</td>
</tr>
<tr>
<td>Transverse</td>
<td>5 (15.6)</td>
<td>.156</td>
<td>14 (28.0)</td>
<td>.132</td>
<td>132 (20.5)</td>
</tr>
<tr>
<td>Ascending and caecum (+ICV)</td>
<td>10 (31.3)</td>
<td>.156</td>
<td>15 (28.0)</td>
<td>.294</td>
<td>294 (45.6)</td>
</tr>
<tr>
<td>Submucosal fibrosis</td>
<td>33 (100)</td>
<td>&lt;.001</td>
<td>50 (100)</td>
<td>&lt;.001</td>
<td>179 (27.6)</td>
</tr>
<tr>
<td>Previous attempt at resection (%)</td>
<td>33 (100)</td>
<td>&lt;.001</td>
<td>0 (0)</td>
<td>&lt;.030</td>
<td>56 (8.7)</td>
</tr>
<tr>
<td>Previous biopsy (%)</td>
<td>na</td>
<td>16 (32.0)</td>
<td>.001</td>
<td>90 (13.8)</td>
<td></td>
</tr>
<tr>
<td>SPOT mark within 10mm of lesion (%)</td>
<td>na</td>
<td>13 (26)</td>
<td>&lt;.001</td>
<td>25 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Histopathology (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional adenoma</td>
<td>25 (79.2)</td>
<td>.324</td>
<td>44 (90.0)</td>
<td>.147</td>
<td>482 (77.5)</td>
</tr>
<tr>
<td>Serrated adenoma</td>
<td>2 (7.4)</td>
<td>4 (10.0)</td>
<td>135 (21.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, minutes, median (IQR range)</td>
<td>(15-45)</td>
<td>.004</td>
<td>25 (15-40)</td>
<td>.003</td>
<td>20 (10-30)</td>
</tr>
<tr>
<td>Intraprocedural bleeding requiring endoscopic control (%)</td>
<td>2 (7.7)</td>
<td>.078</td>
<td>11 (22.4)</td>
<td>.966</td>
<td>144 (22.2)</td>
</tr>
<tr>
<td>Deep injury</td>
<td>6 (18.2)</td>
<td>.181</td>
<td>1 (2.0)</td>
<td>.049</td>
<td>66 (10.7)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopic Recurrence at SC1 (%)</td>
<td>4 (16.0)</td>
<td>.578</td>
<td>11 (22.8)</td>
<td>.005</td>
<td>59 (12.2)</td>
</tr>
</tbody>
</table>
Rectal polyps extending to the dentate line (RPDL) pose a technical challenge to endoscopic resection due to the narrow lumen, rich venous/haemorrhoidal plexus and proximity to the skin. Conventional snare EMR is challenging given.

The polyp margin on the anal side was injected with lifting solution consisting of four patients in the SB Jr group in whom ESD was completed using the Flushknife alone, with no increase in procedure time or adverse events. (University hospital Medical Information Network Clinical Trials Registry number UMIN000009497).

Disclosure of Interest: All authors have declared no conflicts of interest.

OP008 THERMAL ABLATION OF THE MARGIN OF THE POST ENDOSCOPIC MUCOSAL RESECTION (EMR) MUCOSAL DEFECT TO PREVENT RECURRENCE FOLLOWING EMR. THE "SCAR" STUDY

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Introduction: Endoscopic mucosal resection (EMR) of large sessile and lateral spreading colon lesions ≥20 mm (LSLs) is safe and effective. The main limitation is adenoma recurrence, which occurs in up to 20% at first surveillance colonoscopy (SC1), mandating a structured surveillance program. Surveillance procedures create compliance burdens, additional costs and potential patient morbidity. Endoscopically invisible micro-adenoma present at the margin of the resected LSL may account for adenoma recurrence. Adjuvant thermal ablation of the EMR defect margin may reduce adenoma recurrence rates.

Aims & Methods: A prospective multi-center randomized control study was performed (NCT01789749). The primary end-point was endoscopic and histological recurrence at SC1. Standard inject and resect EMR technique was used for all lesions. Exclusion criteria included previously attempted lesions, incomplete snare excision or involvement of the ileocaecal valve. After successful complete LSL excision by EMR and careful inspection of the defect to ensure no residual adenoma, mucosal defects were randomized 1:1 to either thermal ablation of the defect edges using a STSC (Active arm) or active control arm (Null arm). Endoscopic assessment of the post EMR scar had a sensitivity of 100%, a specificity of 98% and a negative predictive value of 100% for correctly identifying recurrence using EMR scar alone.

Results: Over 32 months to January 2015, 768 lesions ≥20 mm were referred for EMR at 4 centers (407 were enrolled, 48 were later excluded, 359 were randomized). None of the patients experienced perforation, or post-procedural sepsis.

Table 1: Endoscopic and histological recurrence in patients randomised to null versus active arm of the SCAR study. Relative risk (RR); Confidence interval (CI)

<table>
<thead>
<tr>
<th>Null arm (n=359)</th>
<th>Active arm (n=359)</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic recurrence (95% CI)</td>
<td>26/129 (20.2%) (14.1–27.9%)</td>
<td>8/138 (5.8%) (2.9–11.0%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Histological recurrence (95% CI)</td>
<td>20/97 (20.6%) (13.8–29.7%)</td>
<td>6/104 (5.8%) (2.7–12.0%)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Conclusion: Thermal ablation of the margin of the post EMR mucosal defect with STSC, results in significantly lower adenoma recurrence rates at first surveillance colonoscopy. Routine implementation of this simple and safe technique may enhance EMR efficacy and reduce surveillance requirements with fewer procedures and extended intervals.

Disclosure of Interest: All authors have declared no conflicts of interest.

A8

United European Gastroenterology Journal 4(58)

Disclosure of Interest: All authors have declared no conflicts of interest.

Table 1: Lesion characteristics and histology

<table>
<thead>
<tr>
<th>Lesion size, median (range), mm</th>
<th>50 (12–150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology, n (%)</td>
<td>LST – G: 29 (72.5) 2 (5) 5 (17.5) nodular mixed LST – G: 13 (32.5) homogenous LST – NG Is: 30 (75) 6 (15) 3 (7.5) 1 (2.5)</td>
</tr>
<tr>
<td>Scarring, n (%)</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td>30 (75) 6 (15) 3 (7.5) 1 (2.5) Adenoma with LGD Adenoma with HGD Cancer Other – Condyloma acuminatum</td>
</tr>
</tbody>
</table>

Conclusion: This is the largest reported series of KAR for RPDLs. Our data demonstrates that for Western endoscopists, KAR is a very safe and effective technique in the treatment of RPDLs. As KAR is a viable alternative to full ESD, TEMS and TAM, it will play an increasingly significant role in the management of RPDLs.

Disclosure of Interest: All authors have declared no conflicts of interest.

Disclosure of Interest: All authors have declared no conflicts of interest.
Aims & Methods: We aimed to evaluate the feasibility and long-term outcomes of ESD performed with an SB knife Jr for treating early colorectal neoplasms. ESD was performed for 227 lesions in 211 patients (male:female ratio = 116:95; mean age = 69.1±14.0 years) between October 2010 and March 2016. We compared ESD performed with an SB knife Jr for treating early colorectal neoplasms with those performed with a conventional knife, to compare the number of hemoclips used per case and total closure time. The results were as follows: right colon, 94 lesions (41.4%); left colon, 85 (38.3%); and rectum, 55 (24.3%). Regarding the macroscopic type of lesions, there were 95 (41.9%) laterally spreading tumors (LSTs) of the first type (LST1), 79 (36.8%) LSTs of the second type, and 48 (21.1%) polyoid lesions. Histological examination findings showed that 102 lesions were the granular type, 79 (34.8%) LSTs of the nongranular type, and 48 (21.1%) flat lesions. The incidence of perforation was as follows: right colon, 227 lesions (9.2%); left colon, 227 lesions (9.2%); and rectum, 227 lesions (9.2%). All lesions were treated easily and safely without an unexpected incision, and no perforations occurred during the procedure. Postoperative observation and data collection continued for 30 days, with the median observation time being 3.8% (6.2/7), 0.4% (1/277), and 0.4% (1/227) of the lesions, respectively, and all of these complications were cured conservatively. The median follow-up time was 18.1±9.76 years. Local recurrence was observed in only 0.8% of the lesions (2/227). One patient (0.5%) died of colorectal cancer, and 5 patients (2.2%) died of other diseases. The 5-year overall survival rate and disease-specific survival rate were 94.8% and 98.7%, respectively.

Conclusion: ESD performed with an SB knife Jr is a technically efficient and safe method that is associated with favorable long-term outcomes in cases of early colorectal neoplasms. Disclosure of Interest: All authors have declared no conflicts of interest.

References
It is important highlight that only one session of Spyglass + EHL was performed in each patient of our protocol. Better success rates can be achieved with two or more sessions and increase up to 90%. Cross-over of the failure cases in both groups is bringing us a very interesting result and suggests that in some cases the methods can be complementary. There was no statistical difference between the groups, although spyglass group had numerically a higher success rate. The study provides us an evidence-based algorithm of difficult stones endoscopic treatments. In addition, we observed potential advantages when we associate the methods, providing one step more before declaring endoscopic failure in treating a difficult biliary stone.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

Disclosure of Interest: All authors have declared no conflicts of interest.

**Aims & Methods:** We aimed to evaluate the safety and efficacy of hybrid-APC in naïve or refractory GAVE patients. Methods: This is a prospective, longitudinal study. Results: Between July 2015 and March 2016 9 patients were included, 8 women (defined as more than 5 previous APC or 3 BL without endoscopic, clinical and laboratory response) between 18 and 90 years old were included. We excluded patients with GAVE without clinical manifestations or anemia of other GI source. After a creation of a "safety cushion" with the APC catheter in the GAVE zone, all received APC with forced coagulation at 80W effect 2 in a single session and then were followed at 1,3 and 6 months. New session was applied if anemia and endoscopic picture of GAVE were documented. Characteristics of the patients were described and expressed in means and SD or median and IQR and percentages as appropriate. Comparisons between quantitative variables was done using paired t-test and considering p < 0.05 as statistically significant.

**Results:** Between July 2015 and March 2016 9 patients were included, 8 women and 1 man. Mean age was 64.7±12.5y. 44% presented anemia and 55.6% melena. Median number of transfusions was 9 (2-15). 3 had liver cirrhosis, 2 chronic renal failure, 1 cardiac disease and 3 without any association. GAVE type was "watermelon" in 6 and "punctate" in 3. 44.4% were naïve and 55.6% chronic renal failure, 1 cardiac disease and 3 without any association. GAVE melena. Median number of transfusions was 9 (2–15). 3 had liver cirrhosis, 2 with chronic renal disease are usually concomitant. Patients often require high doses of iron and often have low normal Hb levels after 6 months. The mean difference between prehybrid-APC (5.98 ±1.49 gr/dl) and 6 months after hybrid-APC (13.7 ±0.76 gr/dl) was +7.74 gr/dl (p < 0.0000 CI 95% 6.84-8.64) student T-test. 8 patients received 1 session and 1 required 2. No major complications were observed (Table 1).

**Conclusion:** Based on these preliminary results, Hybrid-APC is safe and effective for the treatment of GAVE (naïve or refractory) with the advantage of needing only 1 or maximum 2 applications and with excellent results at medium term.

**Disclosure of Interest:** All authors have declared no conflicts of interest.
Aims & Methods:

In this study, we aimed to address whether loss of PTPN2 in macrophages, mice with a floxed PTPN2 gene were crossed with mice expressing Cre under LysM promoter, showed enhanced inflammasome activation in the intestine, and further developed chronic colitis.

Results:

Acute colitis was induced in 10–12 week old female mice by administration of 2% DSS for 7 days, chronic colitis by administration of four cycles of 1.5% DSS for 7 days. In vivo, PTPN2-LysMCre mice suffered from pronounced acute colitis, accompanied with enhanced secretion of mature IL-1β and IL-18, confirming the role of macrophage PTPN2 in the regulation of inflammasome activation. Secretion of mature IL-1β was inhibited, while down-regulation of IL-1β restored susceptibility to AOM-DSS treatment because of the stiffness induced by the needle assembly on the echoendoscope shaft, the authors recommended the use of a 19-gauge needle made of nitinol with increased flexibility (1).

Aims & Methods: To test the validity of this recommendation, we performed a prospective multicenter study aimed at evaluating the technical feasibility, procurement yield, and diagnostic accuracy of the newly developed 19-gauge nitinol flexible needle in patients with solid lesions or enlarged lymph nodes that could be punctured only from the duodenum. Consecutive patients with solid lesions who needed to undergo EUS sampling from the duodenum were prospectively enrolled in 6 tertiary care referral centers. Puncture of the lesion was performed after the 19-gauge flexible needle (EUS-FNB) can result in a greater chance to reach a diagnosis than a typical EUS-FNA sample. Based on a previous study (2), which reported a 19-gauge flexible needle to be able to sample transduodenal lesions and be diagnostic in all 32 included patients, an algorithm for EUS-tissue acquisition (EUS-ROSE) has been proposed. In institutions with no availability of ROSE, for lesions accessed from the duodenum, which represent the most difficult sampling position because of the stiffness induced by the needle assembly on the echoendoscope shaft, the authors recommended the use of a 19-gauge needle made of nitinol with increased flexibility (1).

Introduction: Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is the procedure of choice to obtain samples for reaching the definitive diagnosis of lesions of the gastrointestinal (GI) tract (1). The performance of the 19-gauge flexible needle has a wide intercenter variability, not in our population was 86%, this finding cannot be considered negligible. The performance of the 19-gauge flexible needle for transduodenal EUS-FNB. Thus, the correct diagnosis was missed in about 1 in 4 patients. Since the prevalence of malignant disease in our population was 86%, this finding cannot be considered negligible. The results of our study are of particular interest since we showed that the diagnostic performance of the 19-gauge flexible needle has a wide intercenter variability, not

Disclosure of Interest:

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Introduction: Variants in the gene locus encoding protein tyrosine phosphatase non-receptor type 2 (PTPN2) are associated with Crohn's disease (CD) and non-receptor type 2 (PTPN2) are associated with Crohn's disease (CD) and ulcerative colitis (UC). We have previously shown that loss of PTPN2 in T cells results in enhanced colitis and signs of autoimmunity. Inflammasomes form upon cytosolic presence of danger molecules and induce the cleavage of pro-IL-1β and pro-IL-18 into their active forms. Secretion of IL-1β is an important activator of stromal and adaptive immune functions, while IL-18 is involved in epithelial cell protection.

Aims & Methods: In this study, we aimed to address whether loss of PTPN2 in macrophages, mice with a floxed PTPN2 gene were crossed with mice expressing Cre recombinase under the Lysozyme promoter (PTPN2-LysMCre mice). Acute colitis was induced in 10–12 week old female mice by administration of 2% DSS for 7 days, chronic colitis by administration of four cycles of 1.5% DSS for 7 days, followed by 10 days normal drinking water each. For tumour induction, mice were injected with AOM at day 1 and day 10 of each DSS cycle during chronic colitis induction.

Results: PTPN2-deficient macrophages show enhanced levels of cleaved caspase-1 and IL-1β upon in vitro activation of the NOD-like receptor protein 3 (Nlrp3) and absent in melanoma 2 (A2M) inflammasomes, finally resulting in enhanced secretion of active IL-1β and IL-18. This effect was mediated by increased phosphorylation of the inflammasome adaptor apoptosis associated speck-like protein containing CARD (ASC), a mechanism shown to promote inflammasome activation. In vivo, PTPN2-LysMCre mice, with a floxed PTPN2 gene were crossed with mice expressing Cre recombinase under the Lysozyme promoter (PTPN2-LysMCre mice). Acute colitis was induced in 10–12 week old female mice by administration of 2% DSS for 7 days, chronic colitis by administration of four cycles of 1.5% DSS for 7 days, followed by 10 days normal drinking water each. For tumour induction, mice were injected with AOM at day 1 and day 10 of each DSS cycle during chronic colitis induction.

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that the use of the 19-gauge flexible needle for transduodenal FNB cannot be
warranted since its withdrawal should receive a local validation, with
careful evaluation of both the local technical success rates and diagnostic yields.

Disclosure of Interest: L. Palazzo: Laurent Palazzo has received educational funds
from Boston Scientific Corp.
A. Larghi: Alberto Larghi is a consultant for Boston Scientific Corp.
All other authors have declared no conflicts of interest.

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1. Panic N and Larghi A. Techniques for endoscopic ultrasound-guided fine-

Abstract No: OP026
Comparison of procedure outcomes according to needle size and use of suction

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OP027 EUS-GUIDED BILIARY DRAINAGE VERSUS PERCUTANEOUS BILIARY DRAINAGE: RESULTS OF A MULTICENTER RANDOMIZED PHASE II STUDY

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Introduction: For 10 years, EUS-guided biliary drainage has been an option as EUS guided choledochoduodenostomy or hepato-gastrostomy. Two small randomized studies showed no difference between EUS guided drainage vs Percutaneous drainage. The aim of this work was to evaluate in a multicenter randomized study the percutaneous biliary drainage (PBD) vs EUS-guided biliary drainage (EBD) in patients with an obstructive jaundice when ERCP failed or impossible due to duodenal involvement or previous Surgery as gastroscopy or Whipple resection.
Aims & Methods: Inclusion criteria were: benign or malignant obstructive jaundice with failure of ERCP. Exclusion criteria were: ascites, blood coagulation disorder, patient deemed unsuitable for EUS guidance, pregnancy. The median age of 352 patients was 69 years, 54.3% male, median size of the sex ratio (Female: Arm A, n 22G Suction 25G Suction
|                  | 88 (100) | 86 (97.7) | 85 (100) | 91 (100) | 0.182 |
|                  | 1.8 (1.9) | 2.8 (2.7) | 1.7 (1.5) | 2.0 (2.2) | 0.0276 |
|                  | 52 (59.1) | 34 (38.6) | 20 (22.7) | 1 (1) | 1 (1) | 1 (1) | 52 (59.1) | 34 (38.6) | 20 (22.7) | 1 (1) | 1 (1) | 1 (1) | 52 (59.1) | 34 (38.6) | 20 (22.7) | 1 (1) | 1 (1) | 1 (1) | 52 (59.1) | 34 (38.6) | 20 (22.7) | 1 (1) | 1 (1) | 1 (1) |
|                  | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) |

Final results: Sixty-five patients from 4 centres were screened between 2011 to 2015. Eight patients were excluded (ascites, ERCP finally feasible). Fifty-six patients were randomized (Arm A = 21/ Arm B = 35). The 2 groups were similar except the sex ratio (Female: Arm A, n = 11; Arm B, n = 7; p = 0.012). The biliary drainage was malignant in 52 cases (Arm A = 19; Arm B = 33). Biliary access was successful in 100% in the Arm A and in 94% in the Arm B. However, technical success was respectively 17/21 (85%) in the Arm A and 33/36 (94%) in the Arm B. No difference was showed regarding the decrease of the bilirubin level after the drainage in the two arms. Median hospitalization duration was shorter in the Arm B (6 days range 3-30 days) than the Arm A (12 days range 2-32 days). Ten patients died 30 days following the biliary drainage, 7 deaths were reliable to biliary drainage procedure (Arm A = 3, Arm B = 4) p = 1. Specific complication occurred in twelve patients (62%) in the Arm A versus 7 (31%) in the Arm B p = 0.0276. Bleeding (A = 5/24%, B = 30%), Sepsis not related to cholangitis (A = 7 [35%], B = 5 [25%]) Peritonitis (A = 1 [5%], B = 1[5%]), external biliary fistula (A = 1 [5%]).
Conclusion: This randomized prospective study showed similar high technical and clinical success rates in PTB and EUS-guided biliary approach. Specific complication rate was higher in the PTB arm than in the EUS-guided biliary drainage. EUS guided biliary drainage should be the first therapeutic approach after failure of ERCP, in selected patients.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP028 EUS-GUIDED GASTROENTEROSTOMY IS COMPARABLE TO ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY: A COMPARATIVE STUDY

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Introduction: Endoscopic retrograde enteral stenting (ES) in malignant gastric outlet obstruction (GOO) is limited by high rates of stent obstruction. EUS-guided gastroenterostomy (EUS-GE) is a novel procedure that potentially offers sustained gastric emptying, tumor ingrowth/overgrowth.

Aims & Methods: The aim of this study is to compare EUS-GE with ES in terms of 1) need for re-intervention, 2) technical success (proper stent positioning as defined by endoscopy, absence of necrosectomy, clinical need to tolerate oral intake without vomiting), and 4) procedure-related adverse events (AEs).

This is a multicenter retrospective study of all consecutive patients who underwent either EUS-GE at 4 centers between 2013 and 2015 or ES at one center between 2008 and 2012.

Results: A total of 82 patients (mean age 66.5 years ± 13.5 and 40.2% female) were identified: 30 in EUS-GE and 52 in ES. Technical and clinical success were not significantly different: EUS-GE success rate was 86.7% EUS-GE vs. 94.2% ES (p = 0.2) respectively. Need for re-intervention, however, was significantly lower in EUS-GE 3.3% vs. 46.2% ES (p < 0.001). Post-procedure median hospital stay in EUS-GE was 11.3 days ± 6.6 for EUS-GE vs. 9.5 days ± 8.3 for ES (p = 0.3). Rates and severity of AEs (as per the ASGE lexicon) were also similar occurring in 16.7% EUS-GE vs. 11.5% ES (p = 0.5). On multivariable analysis, EUS-GE was independently associated with fewer needs for re-intervention (OR 0.03, p < 0.002).

Conclusion: EUS-GE may be ideal for malignant GOO with comparable effectiveness and safety to ES while being associated with fewer requirements for re-intervention.

Disclosure of Interest: M. Khashab: Consultant for Boston Scientific
All other authors have declared no conflicts of interest.

OP029 DEDICATED BI-FLANGED METAL STENT WITH ENDOSCOPIC “STEP-UP APPROACH” REDUCES THE NEED FOR DIRECT NECROSECTOMY IN WON - LARGE EXPERIENCE FROM A SINGLE TERTIARY CARE CENTRE


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Introduction: EUS-guided trans-mural drainage using plastic stents may be inadequate for pancreatic fluid collections (PFC) having solid debris, i.e. Walled Off Necrosis (WON). Recent publications have reported variable outcome using covered metal stents for PFC drainage, using either conventional or dedicated metal stents. There are few reports on dedicated metal stent for EUS guided drainage of only WON. Treatment strategy using a “step-up approach” by endoscopic methods has not been systematically addressed.

Aims & Methods: To evaluate the efficacy of a dedicated covered bi-flanged metal stent (BFMS) using a “step-up approach” in drainage of symptomatic WON. Consecutive patients with symptomatic WON undergoing EUS-guided drainage using BFMS were included from January 2013 to December 2015. Patients were reassessed at 24 hours for symptoms improvement and reduction in size of collection. The endoscopic interventions were approached in a step-up manner to manage patients who did not have expected clinical improvement after index drainage of WON with BFMS. Defocleg of blocked lumen of BFMS was the first step. Second step involved a naso-cystic catheter (NCT) placement through BFMS followed by intermittent irrigation with saline and hydrogen peroxide. Third step involved direct endoscopic necrosectomy (DEN), which was performed through BFMS in patients with persisting symptoms. Patients were reassessed between 4 to 8 weeks and BFMS were removed after documenting radiological resolution of collection. The main outcome measures studied were technical success, clinical success, adverse events and the need for various endoscopic reinterventions, using step-up approach.

Results: A total of 205 patients (mean age 34.8 ± 12.5 years, 181 males) underwent EUS-guided drainage with BFMS. Technical success was achieved in 203 patients (99%). Per-procedure adverse events occurred in 8 (3.9%) patients (bleeding in 6 and perforation in 2). WON resolved with BFMS in 158 patients (77.3%). Endoscopic re-interventions were required in 49 (23.9%) patients, for persistent or new onset symptoms, was approached in step-up manner. At first, defocleg of BFMS alone succeeded in 10 out of 21. Second step of nasa-cystic placement through BFMS followed by irrigation with saline and hydrogen peroxide improved 16 out of 21. At final step, DEN improved outcome in 19 out of 23. BFMS migrated in 5 (2.9%) patients (2 internal, 3 external). Four patients failed to achieve clinical success, requiring surgery (n = 2) or additional percuta-

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OP030 CLINICAL OUTCOME AFTER BILIARY DRAINAGE FOR METASTATIC COLORECTAL CANCER: SURVIVAL ANALYSIS

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Introduction: Biliary obstruction secondary to colorectal cancer liver metastases is associated with a poor prognosis with a 5-year survival rate of 20% to 30%. In this study, we report the survival of patients referred to our centre for biliary drainage after failure of initial ERCP. However, little information is known about the benefits of such endoscopic and radiological interventions, as well as the impact of chemotherapy achievement.

Aims & Methods: This retrospective study analyzed patients from two expert French centers between 2005 and 2014. Patients were included after failure of biliary drainage after interventions. Overall median survival was 115 days (5–1876). In univariate analysis, a previous liver surgery, a technical and a functional success of drainage and restarted chemotherapy were significantly associated with an improved survival. Chemotherapy was restarted after a median of 27 days. When drainage was efficient survival improved from 33 days to 262 days (p = 0.001). In multivariate analysis, predictive factors for survival included a previous hepatectomy (hazard ratio (HR) 0.41, 95% CI [0.22–0.73], p = 0.004), functional success drainage (HR 0.29, 95% CI [0.15–0.56], p = 0.0002). Predictive factors for death included increased lines of chemotherapy (HR 1.68, 95% CI [1.36–2.06], p < 0.001), and fever before drainage (HR 2.97, 95% CI [1.39–6.36], p = 0.005).

Conclusion: This is the first study concerning benefits of biliary drainage during the course of chemotherapy of colorectal cancer with malignant biliary obstruction. A successful biliary drainage leads to improved survival and allows achievement of chemotherapy for 50% of patients.

Disclosure of Interest: All authors have declared no conflicts of interest.

References
Disclosure of Interest: All authors have declared no conflicts of interest.

References

OP031 BILE DUCT INFLAMMATION ASSESSED BY BILARY CALPROTECTIN AND NEUTROPHILS CORRELATES WITH RISK OF BILIARY DYSPLASIA AND CHOLANGIOCARCINOMA
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Introduction: Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of biliary epithelium leading to strictures intra- and extrahepatic bile ducts and finally to cholestasis and secondary biliary cirrhosis (1). The chronic inflammation is associated with increased proliferation of biliary epithelial cells and a markedly increased risk of biliary dysplasia and cholangiocarcinoma (2). SIR ranging from 55 to 973 (3–4). The lifetime risk of CCA is around 10% (5).

Aims & Methods: We aimed to evaluate the grade of bile duct inflammation as a risk factor for dysplasia and cholangiocarcinoma in PSC patients. In total, 210 patients with confirmed PSC referred for ERC for ERC for disease surveillance were included (121 females, 59 males). Bile samples were aspirated using balloon catheter and immersed immediately in liquid nitrogen (−196°C) and then stored in −20°C. Brush cytology (BC) was collected from both from extra- and intrahepatic bile ducts for Papanicolau staining included (121 females, 179 males). After cannulation of the common bile duct, a total of 43.5% of PSC patients were positive for either of the two anti-target-specific PAbs according to the baseline disease characteristics. Positivity for the IgA subtype of anti-GP2, but not for the classical serologic markers, predicted a faster progression of the disease. In Kaplan-Meier analysis, anti-GP2 antibody positivity was associated with shorter time to OLTx and/or liver-related death during the follow-up (median: 94 months]. Anti-GP2 antibody positivity was exclusively IgA type, while anti-CUZD1 antibodies were of both IgA and IgG isoatypes. No difference was found in the frequency of PAbs according to the baseline disease characteristics. Positivity for the IgA subtype of anti-GP2, but not for the classical serologic markers, predicted a faster progression of the disease. In Kaplan-Meier analysis, anti-GP2 IgA positivity was associated with shorter time to OLTx and/or liver-related death [pLog-Rank<0.01], and remained an independent predictor after adjusting for the presence of cirrhosis in Cox-regression analysis (HR: 4.31 [1.05–17.61]). Conclusion: Our small-scale study has shown that occurrence of target-specific PAbs is common in PSC. Association of IgA type anti-GP2 antibody with faster disease progression serves as an additional hint towards the significance of gut-liver interaction in the disease course of PSC.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OP032 TARGET-SPECIFIC ANTI-PANCREATIC ANTIBODIES ARE FREQUENT IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS AND ASSOCIATED WITH POOR DISEASE OUTCOME
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Introduction: Glycoprotein 2 [GP2] and CUB zona pellucida-like domain 1 [CUZD1] belong to protein families involved in gut innate immunity processes and have recently been identified as specific targets of anti-pancreatic autoantibodies [PAbs] in Crohn’s disease [CD]. We aimed to determine the prevalence and prognostic potential of novel target-specific PAbs regarding long-term disease course in a cohort of a primary sclerosing cholangitis [PSC] patients.

Aims & Methods: Sera of 69 PSC patients (median age[range]: 32.5[79] years, cumulative patient BMI[and] [cirrhosis]) were tested by indirect immunofluorescence test [IFPT] system with GP2 and CUZD1 expressing transfected HEK 293 cells [anti-GP2 and [anti-CUZD1]. Classical serologic markers of IBD were also assessed (pANCA and pALF/Id1) by IFT, while ASCA IgA/IgG and anti-OMP Plus™ IgA by ELISA). A previously reported inflammatory bowel disease [IBD] patient cohort (CD:264 and UC:179) were the controls. Poor disease outcome was defined as orthotopic liver transplantation [OLTx] and/or liver-related death during the follow-up [median: 94 months].

Results: A total of 43.5% of PSC patients were positive for either of the two target-specific anti-PAbs, with a significant difference compared to patients with CD [26.8%, p < 0.01] or UC [7.6%, p < 0.001]. Distribution of the two types of PAbs was equal and one-third of the positive cases showed double positivity. Anti-GP2 antibody positivity was exclusively IgA type, while anti-CUZD1 antibodies were of both IgA and IgG isoatypes. No difference was found in the frequency of PAbs according to the baseline disease characteristics. Positivity for the IgA subtype of anti-GP2, but not for the classical serologic markers, predicted a faster progression of the disease. In Kaplan-Meier analysis, anti-GP2 IgA positivity was associated with shorter time to OLTx and/or liver-related death [pLog-Rank<0.01], and remained an independent predictor after adjusting for the presence of cirrhosis in Cox-regression analysis (HR: 4.31 [1.05–17.61]).

Conclusion: S-A LP, AST and IgG seem to be good surrogate markers for bile duct inflammation compared to biliary calprotectin levels. Risk of dysplasia is associated with bile duct inflammation assessed by brush cytology neutrophils. B-calprotectin and S-Ca19–9 levels ≥ 26 kU/l. These variables seem be useful for individual risk stratification for PSC patients for disease progression and dysplasia.
OP035 GALL BLADDER FAILURE BIOMARKERS ARE ASSOCIATED WITHagic post-Outcome in Patients with Primary Sclerosing Cholangitis


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Introduction: Gut-liver interaction is a prominent feature of primary sclerosing cholangitis (PSC), however the effect of this cross-talk on the disease course has not been fully elucidated. A panel of serological markers that reflect either microbial or gut barrier dysfunction were assessor a cohort of 361 patients with PSC. Association of these markers with disease specific characteristics and the long-term disease course was evaluated.

Aims & Methods: In PSC patients (median age[IQR]:32.5–79 years), concomitant IBD: 67% and cirrhosis: 20% were assessed for intestinal fatty acid-binding protein(1-FABP) and various immunoglobulin A (IgA) molecules (IgA1, IgA2 and secretory[IgA], anti-F-actin[AAA IgA] and anti-gliadin[AGA IgG]) by ELISA. Poor disease outcome was defined as orthotopic liver transplantation[OLTx] and/or liver-related death during the follow-up (median: 94 months). 155 healthy subjects (HCONT) and 179 ulcerative colitis (UC) patients were the controls.

Results: In PSC, median I-FABP level was similar to that in HCONT (216 vs. 244 µg/ml) but higher than in UC (176 µg/ml; p < 0.05). SLA level (95.7 µg/ml) was twofold higher compared to either the HCONT or the UC (p < 0.001, for both). 28.4%, 9% and 20% of PSC patients were positive for AAA IgA, AGA IgA and AGA IgG, respectively. Frequencies of AAA IgA (p < 0.01, for both) and AGA IgG (p = 0.01, for both) were not AGA IgA were significantly higher to compared to HCONT and UC. Regarding disease-specific characteristics, SLA was significantly lower in PSC patients with concomitant IBD (80.7 vs. 160.4 µg/ml). In Kaplan-Meier analysis only target-specific IgAs and AGA (>175 µg/ml) were associated with a shorter time to OLTx and/or liver-related death, whereas total IgA or IgA2/IgA1 ratio and I-FABP were not. All markers remained significantly different after adjusting for the presence of cirrhosis in Cox-regression analysis (HR[95%CI]: 3.67[1.05–12.82] for SLA, 5.15[2.7–20.86] for AAA IgA and 5.07[2.05–12.82] for AGA IgA). Combining these markers further enhanced their predicative potential (HR[95%CI]: 11.3[0.8—44.93] for ≤2 marker positivity).

Conclusion: This study, gut liver interaction in PSC patients with progressive disease, further highlighting the importance of the gut-liver interaction in PSC.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:

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Introduction: Farnesoid X receptor (FXR), a bile acid (BA)-activated nuclear receptor, plays a critical role in maintaining lipid, glucose and BA homeostasis. FXR expression is significantly decreased in livers of non-alcoholic fatty liver disease (NAFLD) patients and genetic ablation leads to hepatic steatosis and hyperlipidaemia. The FXR gene expression is found in both the liver and other tissues. Herein, we aimed to: 1) screen for potential FXR agonists for their ability to selectively activate different FXR isoforms and protect liver cells against free fatty acid (FFA)-induced steatosis and cytotoxicity.

Aims & Methods: 12 novel BA derivatives, synthesized based on the cholic (CA), deoxycholic (DCA), chenodeoxycholic (CDCA) and ursodeoxycholic (UDCA) acid scaffolds were incubated in HepG2 cells treated with 200 and 500 µM oleic and palmitic acid (1:1 ratio), for assessment of cellular cytotoxicity using the MTS, Live/Dead and TUNEL assays, as well as intracellular lipid accumulation, by Oil Red O (ORO) staining. Additionally, mRNA levels of both direct and indirect key FXR-targets, namely SHP, SREBP1-c, PPAR-α, CYP7a1 and VLDLR, were assessed after incubation of primary mouse hepatocytes with the select BA derivatives.

Results: As a result of the diverse structural modifications, BA derivatives showed differential activation of the FXRα-4 isoforms, when compared to their precursor BAs. From the precursor BAs, only CA, a natural FXR ligand, significantly activated FXRα and u2 isoforms, with CA and UDCA displaying a modest activation of FXRα isoform only. Interestingly, 2 novel CA-, 1 DCA- and 4 UDCA-derivatives were stronger activators of both FXRα and u2, comparing with their corresponding precursors. Further, 3 novel CA-, 2 DCA-, 3 CDCA- and 4 UDCA-derivatives specifically and significantly activated FXRα and u4. Incubation of HepG2 cells with the FAs mixture led to a 25% reduction in cell viability and a ~10–15% increase in cell death, concomitantly with a dose-dependent accumulation of lipid droplets. Pre-incubation of cells with CA-derivatives preferentially activating FXRα and u4 significantly reduced the intracellular lipid accumulation, by Oil Red O (ORO) staining. Additionally, mRNA levels of both direct and indirect key FXR-targets, namely SHP, SREBP1-c, PPAR-α, CYP7a1 and VLDLR, were assessed after incubation of primary mouse hepatocytes with the select BA derivatives.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:

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Introduction: Farnesoid X receptor (FXR), a bile acid (BA)-activated nuclear receptor, plays a critical role in maintaining lipid, glucose and BA homeostasis. FXR expression is significantly decreased in livers of non-alcoholic fatty liver disease (NAFLD) patients and genetic ablation leads to hepatic steatosis and hyperlipidaemia. The FXR gene expression is found in both the liver and other tissues. Herein, we aimed to: 1) screen for potential FXR agonists for their ability to selectively activate different FXR isoforms and protect liver cells against free fatty acid (FFA)-induced steatosis and cytotoxicity.

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Disclosure of Interest: All authors have declared no conflicts of interest.

References:
The PNPLA3 rs738409 C
effect leading to increased triglyceride synthesis and accumulation in liver (1).

Introduction:
PNPLA3 (patatin-like phospholipase domain containing 3) encodes
corneal phospholipase and/or lipolytic enzymes in liver. The mutation of
insulose to methionine at position 148 (I148M) causes a loss of function
fect leading to increased triglyceride synthesis and accumulation in liver (1).
The PNPLA3 rs738409 C
has been associated with steatosis and
fibrosis in various liver disease and increased risk for development of liver cir-
rhosis and hepatocellular cancer (2). The impact of PNPLA3 rs738409 [G] on
liver damage has a strong environmental interaction and is usually associated
concomitant liver insult. PSC is a chronic inflammatory disease of bile duct
leading to strictures and may secondarily cause liver cirrhosis. PSC is
also associated with inflammatory bowel disease and markedly increased risk
of cholangiocarcinoma (3,4). PLPN3 variant has been associated with elevations
of liver enzymes in IBD (5) and in increased risk of bile duct stenosis in male PSC
patients (6). Survival free of liver transplantation is reduced in male PSC patients
with development of dominant strictures in carriers of PNPLA3 I148M variant
(5).

Aims & Methods:
To evaluate the allele dose effect of PNPLA3 variant on the
clinical manifestations, disease severity, progression and prognosis of PSC in
a large patient population from single center.

Results:
The 563 patients (93.9%) had the wild type (CC), 197 (35.7%) were heterozygous (CG) and 32 (5.7%) were homozygous for the mutation (GG). A
concomitant IBD was diagnosed in 80% of the males and 60% the females.
Summary of the results are presented in the table.

PNPLA3 rs738409 in PSC

<table>
<thead>
<tr>
<th>Variable, mean(SD)</th>
<th>CC, n = 334</th>
<th>CG, n = 197</th>
<th>GG, n = 32</th>
<th>p for linearity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%)</td>
<td>193(38)</td>
<td>124(63)</td>
<td>17(53)</td>
<td>0.75</td>
</tr>
<tr>
<td>Age at diagnosis of PSC, y</td>
<td>38(14)</td>
<td>36(13)</td>
<td>35(13)</td>
<td>0.10</td>
</tr>
<tr>
<td>Weight, kg, males</td>
<td>82(14)</td>
<td>80(15)</td>
<td>81(14)</td>
<td>0.37</td>
</tr>
<tr>
<td>Weight, kg, females</td>
<td>69(7)</td>
<td>70(17)</td>
<td>71(13)</td>
<td>0.62</td>
</tr>
<tr>
<td>IBID, n (%)</td>
<td>26(11)</td>
<td>25(17)</td>
<td>26(11)</td>
<td>0.74</td>
</tr>
<tr>
<td>Age at diagnosis of IBID</td>
<td>26(11)</td>
<td>25(17)</td>
<td>26(11)</td>
<td>0.49</td>
</tr>
<tr>
<td>ERC-score (0–16)</td>
<td>5.8(3.5)</td>
<td>5.4(3.3)</td>
<td>5.7(3.7)</td>
<td>0.88</td>
</tr>
<tr>
<td>Dominant strictures, n (%)</td>
<td>128(31)</td>
<td>61(31)</td>
<td>92(31)</td>
<td>0.061</td>
</tr>
<tr>
<td>Progression of ERC score/month*</td>
<td>0.014</td>
<td>0.002</td>
<td>0.004</td>
<td>0.44</td>
</tr>
<tr>
<td>Advanced fibrosis F3/4, %(*</td>
<td>8.1</td>
<td>12.5</td>
<td>15.2</td>
<td>0.25</td>
</tr>
<tr>
<td>S-ALP, U/l&lt;105</td>
<td>183(148)</td>
<td>194(170)</td>
<td>182(135)</td>
<td>0.60</td>
</tr>
<tr>
<td>S-GT, U/l&lt;60</td>
<td>191(249)</td>
<td>236(269)</td>
<td>182(154)</td>
<td>0.94</td>
</tr>
<tr>
<td>S-ALT, U/l&lt;50</td>
<td>74(125)</td>
<td>78(96)</td>
<td>61(50)</td>
<td>0.35</td>
</tr>
<tr>
<td>S-AST, U/l&lt;45</td>
<td>55(73)</td>
<td>54(63)</td>
<td>59(41)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*Adjusted for sex, age and IBID Cholangiocarcinoma was diagnosed in 12 (3.6%) patients with CC, in 6 (3.1%) of CG an in none of GG, (p for linearity=0.42; adjusted for sex, age and IBID). 49 patients underwent liver transplantation during 5 years mean follow up: 2.5% (95% CI: 1.2 to 5.1) in CC, 3.1% (95% CI: 1.3 to 7.3) in CG and 7.1% (95% CI: 1.8 to 24.4) in GG, (p for linearity = 0.12; adjusted for sex, age and IBID).

Conclusion: The PNPLA3 I148M variant did not have any significant impact on clinical manifestation, disease progression, development of dominant strictures, on risk of cholangiocarcinoma or liver transplantation in PSC.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:

Disclosure of Interest: All authors have declared no conflicts of interest.

References:
TUMOR DEVELOPMENT

OP038 CELL-SPECIFIC ROLES OF CALCINEURIN IN INTESTINAL TUMOR DEVELOPMENT


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Introduction: Colorectal cancer (CRC) development is characterized by the sequential accumulation of somatic mutations, which promotes epithelial proliferation and subsequently tumor invasion. Calcineurin is a phosphatase, which contributes to innate and adaptive immunity through the activation of transcription factors of the family of nuclear factor of activated T cells (NFAT). Systemic inhibition of calcineurin as applied in human immunosuppression is associated with an increased incidence of CRC. However, calcineurin and NFAT are also expressed in CRC cell lines and rather promote than inhibit epithelial proliferation in vitro. These findings raise the question of whether calcineurin plays cell-specific roles in CRC and, in particular, whether intestinal epithelial calcineurin promotes tumor development in a cell-intrinsic manner.

Aims & Methods: To investigate the role of calcineurin and NFAT in intestinal tumor development, we generated mice with intestinal epithelial cell (IEC)-specific deletion of the regulatory B1 subunit of calcineurin and analyzed these mice in the Apc<del/+> and Apc<del/+> animals of genetically induced intestinal tumor development as well as in the AOM/DSS model of colitis-associated cancer. For mechanistic studies, organoid cultures, immortalized IECs and CRC cell lines as well as samples of more than 700 CRC patients were studied.

Results: We demonstrate that systemic inhibition of calcineurin with cyclosporine leads to increased intestinal tumor growth in Apc<del/+> mice, which is consistent with an increased CRC incidence observed in patients receiving calcineurin inhibitors. In contrast, intestinal epithelial cell-specific deletion of calcineurin is associated with reduced intestinal tumor formation and growth in the Apc<del/+> and Apc<del/+> model. Antibiotic treatment of mice as well as backcrossing to a Myd88-deficient background revealed that the activation of oncogenic epithelial calcineurin is dependent on the intestinal microbiota and results from tumor-associated alterations in microbial composition and stratification as well as from increased tumor-associated toll-like receptor expression. Tumor-promoting effects of epithelial calcineurin are elicited through NFAT-dependent transcriptional regulation of Lgr5-positive tumor stem cells as shown by chromatin immunoprecipitation (ChIP), gene expression analysis and functional studies together leading to control of tumor stem cell apoptosis and proliferation as shown by FACS and immunofluorescence staining. Moreover, somatic mutations identified in human CRC are associated with constitutive activation of calcineurin, while nuclear translocation of NFAT correlates with reduced survival in a large cohort of CRC patients.

Conclusion: These results support the concept of cell-specific roles of calcineurin in the regulation of colorectal carcinogenesis and reveal novel potential targets for the prevention and treatment of CRC.

Disclosure of Interest: All authors have declared no conflicts of interest.

Disclosure of Interest:

All authors have declared no conflicts of interest.
Introduction: Clinical evidence has shown that extracellular matrix (ECM) proteins mediate pro-tumoral functions in cancer, interacting to bring together key members of signaling pathways that drive cell division and growth. The Na+/H+ exchanger regulatory factor (NHERF) family of proteins is involved in the orchestration of receptors and cellular proteins. Among the NHERF proteins, NHERF1 and NHERF2 share most similarities with tandem PDZ domains and an ERM interacting motif in the carboxyl domain that enables anchoring to the actin cytoskeleton. One major function of NHERF1/2 is to recruit and spatially organize signaling proteins that either alters protein functions or downstream signaling pathways originating from receptor. NHERF1 is reported to be a tumor suppressor. However, the role of NHERF2 in cancer progression has not been reported.

Aims & Methods: We investigated the role of NHERF2 in colon tumor progression. We first determined NHERF2 expression in human colorectal cancer (CRC) using a tissue microarray. Next, the role of NHERF2 on colon cancer growth and invasion was assessed by a loss-of-function approach (shRNA) and a knockdown approach in CRC using a tissue microarray. Next, the role of NHERF2 on colon cancer growth in vivo, and tumor growth in a mouse xenograft tumor model. Histologic analysis confirmed the reduction of cell proliferation by Ki67 immunostaining. In vitro, and tumor growth in a mouse xenograft tumor model. Histologic analysis confirmed the reduction of cell proliferation by Ki67 immunostaining. In addition, deletion of NHERF2 in ApCMin/+ (ApCMin+/-Nherf2-/-) mice resulted in decreased tumor growth compared to the controls. Knockdown of NHERF2 attenuated colon cancer cell proliferation and invasion in vitro, and tumor growth in a xenograft tumor model. Histologic analysis confirmed the reduction of cell proliferation by Ki67 immunostaining. In addition, deletion of NHERF2 in ApCMin/+ (ApCMin+/-Nherf2-/-) mice resulted in decreased tumor growth compared to the controls. Knockdown of NHERF2 attenuated colon cancer cell proliferation. Although NHERF2 is known to facilitate the effects of lysophosphatidic acid receptor 2 (LPA2), transcriptome analysis of xenograft tumors revealed that NHERF2 regulates the expression of Stat3 and CD24. This study provides NHERF2 as a potential new target for cancer treatment.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:
OP046 THE ROLE OF MI-RNA-145 IN COLON CANCER STEM CELLS - CSCs
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Introduction: Cancer stem cells (CSCs) are thought to be responsible for tumour initiation, metastasis and relapse through their unlimited self-renewal and differentiative capacity. CSCs (CCSCs) to self-renew and differentiate. Our results showed that forced miR-145 expression reduced colon sphere formation overexpressing miR-145 (p < 0.01). In addition, HT29 and SW480 cell line-derived colon spheres overexpressing miR-145 displayed reduced OCT4 mRNA levels. Furthermore, miR-145 overexpression significantly increased the proportion of CD44/CD133 cells and ALDH1 activity (p < 0.05). The mature colorectal cancer marker, CK20, was increased in HCT116 spheres over-expressing miR-145 (p < 0.01).

Conclusion: miR-145 appears to be involved in colon sphere formation, self-renewal of colon sphere and differentiation ability of HCT116 colon spheres. miR-145 may contribute to the induction of CSCs differentiation to cells that are sensitive to chemotherapy and targeted agents.

Disclosure of Interest: All authors have declared no conflicts of interest.

Monday, October 17, 2016 10:30-12:00
GASTRODUODENAL DAMAGE: H. PYLORI, ACID AND BILE - ROOM 1.86

OP034 PAN-EUROPEAN REGISTRY ON H. PYLORI MANAGEMENT (HP-EUREG): INTERIM ANALYSIS OF THE TREATMENT WITH BISMUTH, LEVOFLOXACIN AND AMoxicillin
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Introduction: A proton pump inhibitor (PPI)-based triple regimen containing two antibiotics (amoxicillin, PPI, and clarithromycin, CAM) was considered the gold standard for the eradication of Helicobacter pylori for more than a decade. However, low eradication rates have been reported due to the increased prevalence of clarithromycin-resistant H. pylori. Insufficient acid inhibition during treatment also causes eradication failure. This is because the anti-microbial agents are unstable and degraded in the stomach; Esomeprazole (EPZ) is a potassium-competitive acid blocker (P-CAB). P-CABs are a new class of gastric acid suppressants available since February 2015 in Japan. VPZ has a potent and long-lasting anti-secretory effect on H+ + K+/ATPase due to its high accumulation in, and slow clearance from, the parietal vesicles. Therefore, VPZ-based triple therapies were compared with conventional PPIs. The aim of this study was to compare H. pylori eradication rates with EPZ-based and VPZ-based triple therapies with CAM and AMPC.

Aims & Methods: A total of 807 patients who had undergone upper gastrointestinal endoscopy and diagnosis with H. pylori infection from November 2013 to March 2016 were enrolled. From December 2013 to September 2014, 431 patients were treated with VPZ-based triple therapy, while 376 patients were treated with PPI-based triple therapy from April 2015 to March 2016. At baseline, demographic and clinical characteristics including gender, age, body mass index (BMI), smoking status, and consumption of alcohol were the same. The first-line eradication regimen was CAM 200 mg, AMPC 750 mg, and either EPZ 20 mg or VPZ 20 mg, each twice daily for 7 days. The second-line eradication regimen was metronidazole 250 mg, AMPC 750 mg, and either EPZ 20 mg or VPZ 20 mg, each twice daily for 7 days. The eradication of H. pylori infection was diagnosed using13C-urea breath tests at 4-8 weeks after each of therapy.

The overall first-line eradication rate was 79.1% (341/431) for the EPZ regimen and 84.6% (318/373) for the VPZ regimen based on Intention to treat (ITT) analysis. The eradication rates calculated by Per protocol (PP) data for EPZ and VPZ regimens were 79.9% (341/427) and 85.3% (318/373) respectively. Significant differences were found both in ITT analysis (p = 0.045) and in PP analysis (p = 0.046). The overall second-line eradication rate was 72.6% (45/62) for the EPZ regimen and 85.3% (29/34) for the VPZ regimen based on ITT analysis. Using PP analysis, the eradication rate was 88.2% (45/51) for the EPZ regimen and 87.9% (29/33) for the VPZ regimen. There were no statistically significant differences found between the two regimens in any of the ITT and PP analyses.

Conclusion: In conclusion, VPZ has a rapid, sustained, and possibly more potent acid-inhibitory effect than EPZ, irrespective of a CYP2C19 genotype. The rate of H. pylori eradication obtained using the first-line VPZ regimen was significantly higher compared with that of the first-line EPZ regimen. However, for the second-line...
treatment, there were no significant differences between the eradication rates from EPZ and VPZ regimen.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OP045 STROMAL MYOFIBROBLASTS ORCHESTRATE GASTRIC EPITHELIAL WNT-SIGNALING AND STEM CELL KINETICS IN GASTROESOPHAGEAL REFLUX DISEASE
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Introduction: The gastric epithelium is characterised by constant, rapid self-renewal, which in the antrum is driven by long-lived stem cells situated at the base of the glands. Infection with the gastric pathogen Helicobacter pylori is the main risk factor for gastric cancer and increases stem cell and in the turnover kinetics of the glands. Wnt signaling is known to be crucial for stem cell home- ostasis in several tissues and for long-term organoid culture of stomach epithelium, but it is not clear how Wnt signaling is spatially organized in the stomach in vivo and whether it modulates stem cell kinetics and glandular turnover.

Aims & Methods: The aim of the present study was to characterize the cellular and molecular Wnt-network in the stomach and to explore its function in physiological epithelial turnover, as well as upon infection with H. pylori. Using in single molecule situ hybridization, different stem cell- and WNT-signaling reporter mice and the murine and as well as human 3D-organoid system we addressed these questions.

Results: We found that Wnt-responsive cells are limited to the base of the antral glands where stem cells reside. However, in addition to previously described Lgr5-positive cells, we found another Wnt-dependent population of highly proliferative Lgr5-negative stem cells in the gland base. We show that the positional identity of stem cells in the gland base is determined by stem cell Lgr5-positive cells that depend on R-spondin 3, which is pro- duced by stromal myofibroblasts. Wnt signaling stimulated by exogenous R- spondin induces an expansion and increased proliferation of Axin2-positive stem cells in the antral stomach while the Lgr5-positive cells remain silenced. Infection of mice with H. pylori increased expression of R-spondin 3, which also increases the expansion of Axin2-positive cells and results in gland hyperplasia. By increasing gland turnover following infection, R-spondin counterbalances bact- erial glandular colonization through increased shedding of cell-attached bacteria.

Conclusion: Thus, stromal R-spondin hierarchically organizes the stem cell comp- artment producing two Wnt-responsive populations that differ in position within the gland, proliferation kinetics, and sensitivity to R-spondin. In addition, a parallel reaction monitoring mass spectrometry, in situ hybridization and immu- nohistochemistry. Human gastric cancer cell lines were used to study the gastrin- mediated regulation and biological function of secretory CLU in vitro.

Result: CLU was highly expressed in neuroendocrine cells in normal oxyntic mucosa of humans, rats and mice. In response to hypergastrinemia, expression of CLU was significantly increased and localization shifted from neuroendocrine cells to basal groups of proliferating intragastric acidity. To exert such a protective effect the reduced acidity would need to be evident in the majority of H. pylori- infected subjects. To investigate this we have examined the acid secretory capa- city and acid pH in patients infected with H. pylori

Aims & Methods: We studied 31 H. pylori-positive and 28 H. pylori-negative volun- teers, matched for age, gender and BMI. Jumbo biopsies were taken at eleven pre-determined locations from the gastroesophageal junction and stomach. High- resolution pHmetry (12 sensors at 11 mm intervals) and manometry (36 sensors at 7.5 mm intervals) was performed for 20 minutes fasted and then for 90 minutes following a standardised meal. The position of the squamoocellular junction (SCJ), marked with two endoscopically placed radio-opaque clips, was visualised radiologically relative to the probes. The biopsy specimens were scored quantitatively for inflammation and stained with monoclonal antibody to H/K-ATPase and sucrase I for calculating parietal cell and chief cell densities respectively.

Results: The mean age of the H. pylori-positive group was 55 years (38–78) compared to 56 years (24–74) for the H. pylori-negative group.

Under fasting conditions, the H. pylori-positive subjects had less intragastric acidity compared to the H. pylori-negative at all sensors more than 1.1cm distal to the peak lower esophageal sphincter (LOS) pressure (p < 0.01). Throughout the three 30-minute postprandial periods, intragastric acidity was significantly less in H. pylori-positive compared to both LOS pressure (all p < 0.05), but there was no significant difference in the sensors 5.5 and 6.0cm distal to peak LOS pressure (Table 1). The postprandial acid pocket was thus attenuated in H. pylori positives compared to negatives.

The H. pylori positives had a significant reduction in density of both parietal and chief cells compared to H. pylori negatives, and this was seen in 10 of the 11 gastric locations (p < 0.01 for 9 locations). The degree of reduction was similar for the two cell types. The cardiac mucosal length was longer in H. pylori positives (1.5mm vs 0.7mm; p = 0.013).

17/31 (54.8%) of the H. pylori positives were also CagA seropositive and they showed more a more marked reduction in intragastric acidity and increased mucosal inflammation compared to the CagA negative subjects.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

OP046 THE ANTI-APOPTOTIC FACTOR CLUSTERIN IS INVOLVED IN GASSIERNENIEMA-INDUCED REMODELING OF THE GASTRIC OXYNTIC MUCOSA
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Aims & Methods: Using gastric tissue from humans, rats treated with proton pump inhibitors and/or a cholera toxin type B receptor (CtB) gene knockdown (H+/K-ATPase β-subunit knockout (H/K-β KO) mice and Mongolian gerbils infected with Helicobacter pylori and treated with a CCKBR antagonist, we examined the expression pattern and gastrin-mediated regulation of CLU in vitro.

Conclusion: CLU was highly expressed in neuroendocrine cells in normal oxyntic mucosa of humans, rats and mice. In response to hypergastrinemia, expression of CLU was significantly increased and localization shifted from neuroendocrine cells to basal groups of proliferating intragastric acidity. To exert such a protective effect the reduced acidity would need to be evident in the majority of H. pylori-infected subjects. To investigate this we have examined the acid secretory capacity and acid pH in patients infected with H. pylori.

Disclosure of Interest: All authors have declared no conflicts of interest.

Table 1: Median pH (IQR) detected by sensors relative to the peak LOS pressure during the 30-60 minute postprandial period. **p < 0.05, ***p < 0.01

<table>
<thead>
<tr>
<th>Sensor location</th>
<th>H. pylori negative Median pH (IQR)</th>
<th>H. pylori positive Median pH (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1cm proximal</td>
<td>7.06 (1.42)</td>
<td>7.00 (0.75)</td>
</tr>
<tr>
<td>Peak LOS pressure</td>
<td>6.76 (1.02)</td>
<td>6.88 (0.48)</td>
</tr>
<tr>
<td>1.1cm distal</td>
<td>5.25 (4.19)</td>
<td>6.40 (5.00)</td>
</tr>
<tr>
<td>2.2cm distal</td>
<td>1.09 (2.20)</td>
<td>3.21 (1.46)**</td>
</tr>
<tr>
<td>3.3cm distal</td>
<td>5.90 (2.28)</td>
<td>2.07 (2.29)**</td>
</tr>
<tr>
<td>4.4cm distal</td>
<td>1.81 (2.09)</td>
<td>2.93 (3.25)*</td>
</tr>
<tr>
<td>5.5 cm distal</td>
<td>2.13 (2.02)</td>
<td>3.48 (2.89)</td>
</tr>
<tr>
<td>6.6cm distal</td>
<td>3.39 (2.19)</td>
<td>4.10 (2.23)</td>
</tr>
</tbody>
</table>
Conclusion: The majority of H. pylori-infected subjects have reduced intragastric acidity compared to the uninfected population and this is most marked close to the gastrooesophageal junction. The density of parietal cells and chief cells is reduced in H. pylori infected subjects throughout the gastric mucosa. These findings may be negatively associated with H. pylori infection and both gastroesophageal reflux disease and oesophageal adenocarcinoma.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

Monday, October 17, 2016
10:30:12:00

ABSTRACTS ON FIRE: GORD ON FIRE – HOTSPOT

OP048 ASSOCIATION BETWEEN LUMINAL BILE SALT CONTENT AND DUODENAL MUCOSAL INTEGRITY IN HEALTHY VOLUNTEERS

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Introduction: Functional dysphagia (FD) is a functional gastrointestinal disorder with an unknown aetiology. FD is characterized by a 20% in the gastrointestinal symptoms. Recently, impaired duodenal mucosal integrity was reported as a potential pathophysiological mechanism in FD (Vanhee H, Gut 2014). However, the factors controlling duodenal mucosal integrity remain unknown. In this pilot study, we evaluated whether luminal bile salt content is associated with duodenal permeability in healthy volunteers.

Aims & Methods: This study was carried out in 21 healthy volunteers (11 men, 25 ± 10 years). Duodenal biopsies were obtained by gastroduodenoscopy and used to measure the in vitro transepithelial resistance (TEER) using Ussing chambers. Meanwhile, fluorescein isothiocyanate dextran (FITC-dx4, MW 4kDa) was applied to assess paracellular permeability. After the gastroduodenoscopy, an aspiration catheter was placed in the second part of the duodenum under fluoroscopic control. Duodenal fluid aspirates were collected at fixed time points during a 3 h period: at the fed state and 1.5 hour after a liquid meal (200 ml). Concentration and composition of the bile salt pool (including glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid, glycodeoxycholic acid, taurodeoxycholic acid, glycocholate, taurocholate, glycochenodeoxycholic acid and taurochenodeoxycholic acid in these aspirates was evaluated. Correlation analysis was used to look for an association between luminal bile salt content and duodenal mucosal integrity.

Results: Duodenal biopsies of healthy volunteers displayed a paracellular passage of 27.23 ± 7.93 pmol and a TEER of 19.85 ± 2.46 kΩ.cm². A negative correlation was found between the concentration of taurochenodeoxycholic acid and the duodenal mucosal integrity (r = -0.6268, p = 0.0292; r = -0.5154, p = 0.0286; r = -0.4957, p = 0.0364 respectively). The concentration of glycodeoxycholic acid showed a positive correlation with TEER in fed state (r = 0.5747, p = 0.0126). The total BA pool showed no correlation with paracellular permeability and TEER in healthy volunteers.

Conclusion: These results imply that the composition of the duodenal bile salt pool may be impacted in this sensitivity, playing the presence of healthy volunteers. Whether the bile salt concentrations explored in the present study are related to the lumen in patients with NERD, different was found a mean of 7.7 ± 1.3 cell layers from the surface. In the duodenal oesophagus were found a mean of 8.9 ± 2 cell layers from the surface. In contrast, healthy volunteers proximal oesophagus were found 12.3 ± 0.9 cell layers from the lumen in the proximal oesophagus, and 22.2 ± 2.7 cell layers from the lumen in the distal oesophagus. On ANOVA, the most superficial location of distal oesophageal mucosa in patients versus healthy controls was statistically significant (p < 0.001). There was a non-significant trend to more superficial proximal mucosa (p = 0.25) in patients versus healthy volunteers.

Conclusion: Distal oesophageal afferent mucosal nerves are significantly closer to the lumen in patients versus healthy control and the usual differential location between proximal and distal fibre location is lost. This may be relevant for symptomatic acid perception in patients with reflux disease, and may serve as a target for topical treatment of these patients.

Disclosure of Interest: P. Woodland: Research grant from Reckitt Benkiser UK D. Sifrim: Receives a research grant from Reckitt Benkiser

All other authors have declared no conflicts of interest.

Reference

OP050 MUCOSAL INTEGRITY AND SENSITIVITY TO ACID OF THE PROXIMAL ESOPHAGUS IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE

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Introduction: Reflux episodes that extend to the proximal esophagus are more likely to be perceived. Our hypothesis is that the enhanced sensitivity of the proximal esophagus is related to more pronounced impairment of mucosal integrity in this part of the esophagus.

Aims & Methods: We aimed to assess acid sensitivity and mucosal integrity of the proximal and distal esophageal segments separately in patients with gastroesophageal reflux disease (GERD) and to investigate the relationship between these parameters. We included patients with heartburn and evidence of GERD on ambulatory pH-impedance measurement. After PPI washout, an esophageal hydrochloric acid perfusion test measuring segmental acid sensitivity proximally and distally in the esophagus (3 and 18 cm above the Z-line)and an upper endoscopy with biopsies at both levels were performed. During endoscopy, electrical tissue impedance spectroscopy was performed at the two levels and biopsies were taken from macroscopically unaffected mucosa. Biopsies were used to measure quantification of interleukin expression with transmission electron microscopy as a morphological measure of impaired integrity and to investigate transepithelial electrical resistance and transepithelial fluorescein permeability in Ussing Chambers as a functional measure of mucosal integrity.

Results: We included 12 GERD patients (mean age 48 years, range 28–65, M:F 4:8). Lag time to heartburn perception was shorter after proximal acid perfusion (mean (95% CI) 0.8 minutes (0.1–1.5)) than after distal acid perfusion (3.9 minutes (2.4–5.4)); log rank p = 0.002. At both levels, the lag time to heartburn perception was significantly lower in the distal esophagus (median (95% CI) 45.36 ± 30.84 minutes) compared to the proximal esophagus (8.17 ± 10.11)); p = 0.02. Transepithelial fluorescein permeability was higher in the distal than the proximal segment (median 2051 nmol·h⁻¹·m⁻² (IQR 1201–3708) and 364 nmol·h⁻¹·m⁻² (IQR 103–1114)), with a lower transepithelial electrical resistance.
Introduction: Incidence of chronic laryngeal symptoms in primary care is about 2% year and gastroesophageal reflux disease (GERD) is considered by far the main disorder associated to them, leading to a specific syndrome called Laryngopharyngeal Reflux (LPR). Several studies demonstrated that pepsin is a main disorder associated to them, leading to a specific syndrome called Laryngopharyngeal Reflux (LPR). Several studies demonstrated that pepsin measurement in saliva can be adopted as a surrogate marker of GERD in LPR patients. Most of the patients (32%) showed that gastric dysmotility such as delayed gastric emptying or impaired esophageal peristalsis. These findings show enhanced sensitivity to acid in the proximal esophagus is not explained by increased mucosal permeability.

Disclosure of Interest: A.J. Breeden: Received research funding from Endosight. Medical Measurement Systems, Danone and Given and received speaker and/or consulting fees from MMS, Astellas, AstraZeneca and Almirall. All other authors have declared no conflicts of interest.

Conclusion: The LOPA II study is a prospective, multicenter, observational study conducted in 7 general practice clinics. Patients with chronic GERD, taking PPI therapy for at least 1 year, and not satisfied with their treatment were asked to complete a questionnaire. Patients were asked the duration of their PPI therapy, satisfaction with their current condition, frequency of symptoms in the last week, whether they had previously received diagnostic evaluation or surgical consultation related to GERD, whether they plan to consult a reflux specialist for further diagnostics, and reasons for dissatisfaction with their cure-reflux medication treatment. “Lost Patients” were defined as those with a satisfaction score of 1 or 2 on a 5-point Likert scale: (1) very satisfied; (2) satisfied; (3) neither satisfied nor dissatisfied; (4) dissatisfied; (5) very dissatisfied. Half of the patients took medication in addition to PPI to control their reflux. In addition to persistent symptoms, concerns of long-term PPI use and burden of daily medication play a role in patient dissatisfaction with PPI therapy.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP052 INADEQUATE SYMPTOM CONTROL ON LONG-TERM PPI THERAPY IN GERD – FACT OR FICTITIOUS? (LOPA II STUDY)

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Disclosure of Interest: Randomized controlled trials report about 30% of GERD patients complain of bothersome remaining symptoms (heartburn, regurgitation) despite PPI therapy. The LOPA II (Lost Patients) Study of 333 GERD patients showed that current clinical practice revealed 46% of patients experienced heartburn or regurgitation symptoms at least twice per week despite PPI. A total of 20% were dissatisfied with their treatment. Few patients had received specific GERD diagnostics or recommended other options (<10%).

Aims & Methods: The LOPA II study is a prospective, multicenter, observational study conducted in 7 general practice clinics. Patients with chronic GERD, taking PPI therapy for at least 1 year, and not satisfied with their treatment were asked to complete a questionnaire. Patients were asked the duration of their PPI therapy, satisfaction with their current condition, frequency of symptoms in the last week, whether they had previously received diagnostic evaluation or surgical consultation related to GERD, whether they plan to consult a reflux specialist for further diagnostics, and reasons for dissatisfaction with their current reflux medication treatment. “Lost Patients” were defined as those with a satisfaction score of 1 or 2 on a 5-point Likert scale (1: very satisfied; 2: satisfied; 3: neither satisfied nor dissatisfied; 4: dissatisfied; 5: very dissatisfied). GERDQ score at least 8, and have not previously received specialized GERD diagnostics.

Results: 343 consecutive patient responses were collected within one year. Patients suffered from GERD an average of 9.7 years and prescribed PPI therapy for an average duration of 8.2 years. 74% were dissatisfied or very dissatisfied on their current PPI therapy (score of 1 or 2). 89% reported heartburn or regurgitation at least 2 days in the week prior (57% 4-7 days). 53% reported using additional medication other than their prescribed PPI at least 2 days per week (57% 4-7 days). In patients dissatisfied on PPI, most cited insufficient symptom control (91%) as a reason for dissatisfaction. In addition, 26% cited concern long-term use of drugs and 23% reported concern with daily medication. 92% of patients had received an upper endoscopy, 8% had a pH-metry, 5% manometry, and 7% received prior surgical consult for GERD. The rate of “Lost Patients” in this study was 63%.

Conclusion: Chronic GERD patients who are dissatisfied with their PPI therapy are rarely offered specialized GERD diagnostic procedures or treatment alternatives. Half of the patients took medication in addition to PPI to control their reflux. In addition to persistent symptoms, concerns of long-term PPI use and burden of daily medication play a role in patient dissatisfaction with PPI therapy.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP053 EFFICACY OF ACOTIAMIDE IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE UNRESPONSIVE TO PROTON PUMP INHIBITOR THERAPY

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Introduction: Acid suppression is the mainstay of gastroesophageal reflux disease (GERD) therapy, and proton pump inhibitors (PPIs) are the first choice of drug therapy. Patients with GERD often offer specialized GERD diagnostic procedures or treatment alternatives. Inadequate symptom control sometimes leads to patient dissatisfaction. Many patients are dissatisfied with their PPI therapy and the rate of “Lost Patients” in this study was 63%.

Disclosure of Interest: All authors have no conflicts of interest.
showed no significant change. In patients with a symptoms index > 30% or total reflux events > 40, the effective rate was significantly different (p < 0.038) at 60 and 33% for the acottamide and placebo groups, respectively. These results suggest that acottamide may be effective in patients with associated reflux events.

Co-administration of acottamide and PPIs may be a new strategy for PPI-refractory GERD patients.

Disclosure of Interest: All authors have declared no conflicts of interest.

References
1. Pauwels A, et al. The gastric accommodation response to meal intake deter-

References

OP054 A RANDOMIZED CONTROLLED TRIAL TO ASSESS THE CLINICAL EFFICACY AND SAFETY OF EPZ 20 mg ONCE DAILY FOR RESOLUTION OF GASTRO-ESOPHAGEAL REFLUX DISEASE SYMPTOMS IN NEWLY DIAGNOSED PATIENTS
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Introduction: Esomeprazole (EPZ) 20 mg once daily was more effective than VPZ 20 mg once daily for resolution of GORD symptoms in newly diagnosed patients. These findings can suggest that acottamide may be effective in patients with gastric achlorhydria or hypergastrinemia showed impaired gastric motility may be supportive of this point (2).

These findings can suggest that increasing the degree of acid inhibition beyond that afforded by treatment with VPZ 20 mg once daily. In addition, the probability of worsen FD symptoms were significantly lower in the EPZ group, compared to 58.1% in the VPZ group (p < 0.01).

The worsened provability in FSSG Functional Dyspepsia (FD) score were significantly lower in the EPZ group (6.8% / 4.5%) than in the VPZ group (27.9% / 28.6%).

After 4 weeks, proportion of patients with sufficient relief was achieved by 88.6% in the EPZ group, compared to 75.5% in the VPZ group (p < 0.01).

After 4 weeks, proportion of patients with sufficient relief was achieved by 88.6% in the EPZ group, compared to 58.1% in the VPZ group (p < 0.01).

The primary endpoint was the proportion of patients with sufficient relief of upper gastrointestinal symptoms (GOS ≤ 2) after 4 weeks of treatment.

Secondary endpoints were the proportion of patients with complete overall symptom resolution (GOS = 0). Scale for the Symptoms of Gastrooesophageal Reflux Disease (FSSG) score, and tolerance for both treatment. All patients provided informed consent before enrolment in the trial.

Results: 88 patients were entered and randomly assigned to the EPZ group and the VPZ group.

After 4 weeks, proportion of patients with sufficient relief was achieved by 88.6% in the EPZ group, compared to 58.1% in the VPZ group (p < 0.01).

The worsened provability in FSSG Functional Dyspepsia (FD) score were significantly lower in the EPZ group, compared to 58.1% in the VPZ group (p < 0.01).

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The worsened provability in FSSG Functional Dyspepsia (FD) score were significantly lower in the EPZ group, compared to 58.1% in the VPZ group (p < 0.01).
Patient Data and Outcomes

Endoscopy-assisted colonoscopy was performed successfully in all cases. The colonoscopic data were extracted from endoscopy reports, which were evaluated by the first author (M.R.). The adenoma detection rate (ADR) was calculated as the number of adenomas detected divided by the total number of colonoscopies performed. The missed-advanced adenoma rate (MAAR) was calculated as the number of missed-advanced adenomas divided by the number of all adenomas detected. The index colonoscopy was defined as the colonoscopy performed as the first examination on the day of the RC-CT. The RC-CT was defined as the colonoscopy performed after the RC or CT, whichever was performed first. The second colonoscopy was defined as the colonoscopy performed after the RC-CT. The index exam was defined as the first examination in the sequence of RC-CT followed by a second exam, and the second exam was defined as the second examination in the sequence of RC-CT followed by a first exam. The primary end-point of the study was the ADR and MAAR for missed-advanced adenoma.

Results

A total of 200 patients aged 61±10 years were randomized into the study (100 patients per group). The study population is shown in Table 1. The demographic characteristics of the patients were similar between the two groups. The ADR in the RC-CT group was 47.3% (95% CI: 42.7–52.1) and in the RC followed by CT group was 47.3% (95% CI: 42.7–52.1). There was no significant difference between the two groups in terms of ADR (p=0.99). Similarly, the MAAR in the RC-CT group was 31.8% (95% CI: 26.7–37.3) and in the RC followed by CT group was 31.8% (95% CI: 26.7–37.3). There was no significant difference between the two groups in terms of MAAR (p=0.99).

Conclusion

Our study population underwent same-day, back-to-back, (EC as index procedure followed by CC or vice versa, randomly assigned 1:1) colonoscopies by high-volume endoscopists. Our study showed no significant difference in terms of ADR and MAAR between EC-CT and CC-EC. This study provides further evidence that RC-CT followed by a second exam is as effective as RC-CT followed by a second exam in terms of ADR and MAAR. Further studies are needed to determine the optimal sequence of RC-CT followed by a second exam for reducing missed-advanced adenomas.
The overall accuracy of ECV-CAD was comparable to that of experts and significantly better than that of novices. Thus, ECV-CAD could be a powerful decision-making tool for less experienced endoscopists.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

Monday, October 17, 2016
14:00-15:30

LONG-TERM MANAGEMENT OF IBD – ROOM G

OP060 LYMPHOMA IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A FRENCH NATIONWIDE OBSERVATIONAL COHORT STUDY

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Disclosure of Interest: All authors have declared no conflicts of interest.

Aims & Methods: The aim of this study was to assess the risk of lymphoma in patients with inflammatory bowel disease (IBD) treated with thiopurines, anti-TNFs or combotherapy at baseline. This risk should be taken into consideration and weighed against potential benefits of combotherapy.

Disclosure of Interest: F. Carbonnel: Franck Carbonnel had consulting fees from Genentech, Otsuka,Vifor, and lecture fees from Hospira.

All other authors have declared no conflicts of interest.
OP061 INCIDENT CANCER IN INFLAMMATORY BOWEL DISEASE: RISK FACTORS IN A LONG TERM MULTICENTER NESTED CASE-CONTROL IG-IBD STUDY AT 4 YEARS

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Introduction: The objective of this study was to assess the relative risk of cancer in IBD patients in a multicenter case-control study at 4 years. In a prospective, multicenter, nested case-control study, we assessed the incidence of cancer in IBD patients at 4 years; 51 months. The study population also included all the additional IBD patients referring to the same 16 units involved in the study at 3 years (Jan 2012-Dec 2014) were followed for a maximum of 15 months (Jan 2015-Mar 2016: follow up > 4 years; 51 months). The study population also included all the additional IBD patients referring to the same units, with incident cancer from Jan 2015 to Mar 2016. Each IBD patient with cancer (IBD-C) was matched 2:1 with IBD patients without cancer (IBD-C) for: IBD type, gender, age. Risk factors considered: age (at last visit, at diagnosis of IBD, of cancer), IBD extent, CD phenotype [B1-B3], perianal CD, smoking, family history of IBD, IBD-related surgery, current/past use of thiopurines [IS], TNFα antagonists (≥2.6 months), extracolonic diseases, extra-appendiceal diseases, perianal CD, smoking, family history of IBD, IBD-related surgery, current/past use of thiopurines, TNFα antagonists. The study was not sponsored. The authors declare no conflicts of interest specifically related to the study. The author declares no conflicts of interest specifically related to the study. The authors declare no conflicts of interest specifically related to the study. Lecture fees from Abbvie, AstraZeneca, Chiesi, Ferring, MSD, Otsuka, Takeda, Zambon, and served as consultant for Abbvie, Hospira, Lilly, MSD, Sofar; A. Armuzzi: The author declares no conflicts of interest specifically related to the study. Financial support for research not related to the present study from Abbvie, ADVANCE: Lecture fees from Abbvie, MSD, Zambon, Hospira, D’Inca: No conflicts of interest specifically related to the study. The study was not sponsored by any pharmaceutical company. C. Papi: The study was not sponsored by any pharmaceutical company. F. Castiglione: The study was not sponsored by any pharmaceutical company. The author declares no conflicts of interest specifically related to the study. Lecture fees from Abbvie, Hospira, Lilly, MSD, Sofar; M. Daperno: No conflicts of interest specifically related to the study. Financial support for research not related to the present study from Abbvie, MSD, Hospira, Mundipharma, Zambon, Chiesi, Ferring; A. Orlando: The study was not sponsored by any pharmaceutical company. The author declares no conflicts of interest specifically related to the study. Lecture fees from Abbvie, Hospira, Lilly, MSD; M. Vecchi: No conflicts of interest specifically related to the study. Advisory Board from MSD, financial support for research not related to the study: Abbvie, Hospira. W. Fries: The study was not sponsored. The author declares no conflicts of interest specifically related to the study. Lecture fees from Abbvie, MSD, Hospira, Ferrigno. A. Kohn: Financial support for research related to the study studied at Kings College London - ISS on November 25, 2016 ueg.sagepub.com

References

INFLAMMATORY BOWEL DISEASE FIVE, TEN AND 20 YEARS AFTER DIAGNOSIS - DATA FROM THE IBSEN STUDY

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Introduction: Previous population-based cross-sectional studies have shown that health-related quality of life (HRQoL) in patients with the inflammatory bowel disease (IBD) is reduced, especially in association with disease activity. Data describing the course of HRQoL in IBD are scarce.

Aims & Methods: The aim of the present study was to assess the course of HRQoL at three prescheduled time-points during 20 years of follow-up in an inception cohort with IBD patients. IBD patients included in a population-based inception cohort from 1990-93 (Inflammatory Bowel Disease in South-East Norway (IBSEN)) were invited to follow-up visits five, ten and 20 years after diagnosis. In addition to structured interviews and clinical examinations at inclusion and follow-up visits, the Short Form 36 (SF-36) and the Norwegian version of the Inflammatory Bowel Disease Questionnaire (N-IBDQ) were completed by the patients at all follow-up visits. The mean N-IBDQ total scores and the mean SF-36 dimensional scores were calculated. In this abstract, we present the total N-IBDQ scores and the dimensional SF-36 scores for general health (GH), physical functioning (PF), role functioning (RF), and mental health (MH) at each follow-up visit.

Results: Of the initially 756 included patients with confirmed IBD, 599 (79%) were still alive after 20 years. HRQoL questionnaires were answered by 522, 327 and 256 of the initially included patients at five, ten and 20 years, respectively. The mean age of the patients at diagnosis was 34 years, and the mean disease duration was 9 years at the 20-year follow-up.

Conclusion: A longitudinal cohort study with conventional immunosuppressants or anti-TNF agents in patients with IBD and a past history of cancer was associated with an increased risk of serious and opportunistic infections compared to unexposed patients. However, the risk of serious infections is higher with anti-TNFs than with thiopurines and the risk of serious and opportunistic infections should be taken into consideration and weighed against potential benefits of anti-TNFs.

Disclosure of Interest: F. Carbonnel: Franck Carbonnel had consulting fees from Tenebex, Osuka, Vifor, and lecture fees from Hospira. All other authors have declared no conflicts of interest.

OP064 THE COURSE OF HEALTH-RELATED QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE FIVE, TEN AND 20 YEARS AFTER DIAGNOSIS - DATA FROM THE IBSEN STUDY

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Introduction: Previous population-based cross-sectional studies have shown that health-related quality of life (HRQoL) in patients with the inflammatory bowel disease (IBD) is reduced, especially in association with disease activity. Data describing the course of HRQoL in IBD are scarce.

Aims & Methods: The aim of the present study was to assess the course of HRQoL at three prescheduled time-points during 20 years of follow-up in an inception cohort with IBD patients. IBD patients included in a population-based inception cohort from 1990-93 (Inflammatory Bowel Disease in South-East Norway (IBSEN)) were invited to follow-up visits five, ten and 20 years after diagnosis. In addition to structured interviews and clinical examinations at inclusion and follow-up visits, the Short Form 36 (SF-36) and the Norwegian version of the Inflammatory Bowel Disease Questionnaire (N-IBDQ) were completed by the patients at all follow-up visits. The mean N-IBDQ total scores and the mean SF-36 dimensional scores were calculated. In this abstract, we present the total N-IBDQ scores and the dimensional SF-36 scores for general health (GH), physical functioning (PF), role functioning (RF), and mental health (MH) at each follow-up visit.

Results: Of the initially 756 included patients with confirmed IBD, 599 (79%) were still alive after 20 years. HRQoL questionnaires were answered by 522, 327
and 438 patients at the five, ten and 20 years follow-up, respectively. Of these patients, 199 (139 UC, 60 CD) and 191 (133 UC, 58 CD) answered the N-IBDQ at all follow-up visits, and 438 patients at the five, ten and 20 years follow-up, respectively. When combining all available IFX measurements during the follow-up of the study, median IFX concentrations were lower in patients who experienced IFX failure (3.1 [0.3–7.5] mg/mL) compared to patients who did not fail IFX [4.0 (1.4–8.3) mg/mL].

The long-term efficacy of infliximab (IFX) in Crohn’s disease (CD) patients is suboptimal and prognostic factors for real-life long-term efficacy are insufficiently studied.

Aims & Methods: The aim of this study was to identify patient- and disease-related factors influencing the real-life long-term response of infliximab in CD patients treated with IFX between January 1994 and January 2016 at a tertiary centre, were retrospectively analysed. Only patients who responded to an induction dose (5 mg/kg on week 0, 2 and 6), followed by scheduled IFX maintenance treatment were included. Exclusion criteria were: prior infliximab use, ever episodic treatment, drug interval (>14 weeks), CD-related surgery during induction therapy and extra-intestinal manifestations as main indication. IFX failure was the primary endpoint, defined as stopping IFX due to one of the following reasons: 1) loss of response (LOR) despite treatment optimization, 2) presence of persistent antibodies towards infliximab (ATI), and 3) need for IBD related surgery. Since 2010–2011, IFX and ATI serum concentrations at trough were measured in the majority of patients in an in-house-developed and clinically validated drug sensitive bridging enzyme-linked immunosorbent assay (ELISA). Therapeutic drug monitoring (TDM) was used in 202 (77.4%) patients. Estimated 1, 5, and 10 year IFX failure-free survival rates were 93.7% (95% CI 92.7–94.7), 65.9% (59.3%–73.5%) and 58.2% (45.6–70.9%), respectively. When combining all available IFX measurements during the follow-up of the study, median IFX concentrations were lower in patients who experienced IFX failure (3.1 [0.3–7.5] mg/mL) compared to patients who did not fail IFX [4.0 (1.4–8.3) mg/mL].

Disclosure of Interest: All authors have declared no conflicts of interest.

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week 14 were available in 199 (76.2%) patients, and in this subgroup of patients, IFX concentration was also a significant predictor of IFX failure-free survival (HR 0.87 (0.80-0.94), p = 0.001).

Conclusion: This study identified several predictors of clinically relevant IFX failure. Stratifying patients according to the amount of risk factors can identify patients at high risk for IFX failure. Initiating IFX sooner rather than later and using TDM in this group to proactively strive for adequate drug concentrations may ensure optimal disease outcome.

Disclosure of Interest: T. Billiet: Lecture Fee: Ferring

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All other authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 14:00-15:30

OP066 CYCLIC ENTERAL NUTRITION FOR THE MAINTENANCE OF REMISSION IN PEDIATRIC CROHN'S DISEASE PATIENTS

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Introduction: Enteral nutrition (EN) is a well-established treatment in pediatric Crohn's disease (CD) for inducing and maintaining remission. Stratifing patients according to the amount of risk factors can identifying patients at high risk for IFX failure. Initiating IFX sooner rather than later and using TDM in this group to proactively strive for adequate drug concentrations may ensure optimal disease outcome.

Aims & Methods: Nine patients with active luminal paediatric Crohn's disease, L1 (n = 2) or L3 (n = 7), followed at Necker Hospital between 2012 and 2014 were included in this prospective pilot study. After 8 weeks of exclusive enteral nutrition with Modulen IBD, patients who came into complete CRP-negative remission were proposed to continue on cyclic EEN therapy as sole treatment in nutrition with Modulen IBD. CRP-negative thereafter (Table 1).

Results: Patients were followed on a fixed scheme (3 months visits) with collection of anthropometric, clinical and biological data. At inclusion, all patients were in deep remission (CRP-negative). At month 6 and 12 follow-up visit, 8 of the 9 patients (89%) (wPCDAI 8.4±9.2) and 5 of 6 patients at PCDAI 5.7±3.2, respectively were in clinical remission. Concomitant to the clinical response, biological scores markedly improved with mean CRP 21.8±14.2 mg/L at M0, 9.8±11.7 mg/L at M6 (p < 0.05) and 5.4±2.7 at M12 (n = 6) (p < 0.05) and albumin normalisation with 33.8±0.8 mg/L at M0, 36.2±1.5 mg/L at M6 (p = 0.04) and 36.8±1.3 mg/L at M12 (n = 6) (p < 0.05). 3 patients relapsed before M12. Patients presented catch up growth at the analysis revealed that only Ruminococcaceae resulted statistically increased in the colon. Tackling in account only colon biopsy samples, a significant reduction of Paraprevotella and an increase of Bacteroides were observed in patients and an increase of Enterobacteriaceae was observed in controls. Finally, stratifying patients on the bases of disease activity a decrease of Ruminococcaceae, Peptostreptococcaceae and Paraprevotella and an increase in Enterococaceae was associated to active disease status (P < 0.05).

Conclusion: The present study shows that in the mucosal microbiota of IBD patients, irrespective of disease localization and activity, phylum Proteobacteria was significantly more represented, while phylum Firmicutes and Bacteroidetes were reduced. The profiles of fecal microbiota partially replicate those of the mucosal microbiota being more difficult to differentiate from controls. It appears that microbiota adhering to the gut mucosa better discriminates patients from controls especially when considering family species. Our data suggest the high diagnostic potential of microbiota profiling with special reference to mucosal biosystem.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP068 BACTERIOPHAGE THERAPY: A NEW STRATEGY TO TARGET ADHERENT-INVASIVE ESCHERICHIA COLI BACTERIA IN THE GI TRACT OF CROHN'S DISEASE PATIENTS

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Introduction: Adherent-invasive Escherichia coli (AIEC) are abnormally predominant on Crohn's disease (CD) ileal mucosa. AIEC are pathobiont bacteria able to trigger inflammatory responses that could initiate or perpetuate the chronic gut inflammation. Anti-bacterial treatments, such as bacteriophages (viruses infecting bacteria) represent an alternative to eradicate these bacteria from the GI tract without disturbing the microbiota homeostasis. Here, we investigated the therapeutic potential of bacteriophages to reduce AIEC colonization associated to intestinal mucosa.

Aims & Methods: Three bacteriophages were selected to efficiently target AIEC isolated from CD patient. Efficacy of this bacteriophage cocktail was investigated using two in vivo experimental models: transgenic mice expressing CEACAM6 colonized by AIEC strain LF82 and the DSS chemically-induced colitis model infected with AIEC strain LFB2.

Results: In LF82-colonized CEACAM6-expressing mice, 24 h after the oral administration of the three bacteriophages cocktail of three bacteriophages, the fecal

Disclosure of Interest: All authors have declared no conflicts of interest.

A29
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Conclusion:

A total of 86 patients with confirmed IBD diagnosis were included in the Clinical University Hospital 2012–2015 were collected, ulcerative colitis (UC) and Crohn’s disease (CD) hospitalized in Riga East Clinical University Hospital, Riga/Latvia.

Disclosure of Interest: All authors have declared no conflicts of interest.

References


OP070 CARD9 IMPACTS COLITIS BY ALTERING GUT MICROBIOTA METABOLISM OF TRYPTOPHAN INTO ARYL HYDROCARBON RECEPTOR LIGANDS

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Aims & Methods: Germ-free (GF) C57BL/6 wild-type (WT) mice were inoculated by oral gavage with fresh stools from conventional WT (WT → GF) or CARD9−/− (Card9−/−) mice. Colitis was induced by DSS. AHR activity in intestinal immune response was determined using a reporter cell line. Immune response was assessed at transcripts level, at the protein level and at the cellular level using flow cytometry. Patients with IBD were genotyped for the major IBD-associated SNPs including CARD9. Statistical analysis was performed using parametric or non-parametric tests as appropriate.

Results: Bacterial and fungal gut microbiota of CARD9−/− mice (assessed by 16s and ITS sequencing) were altered compared to WT mice. Card9−/− → GF mice were more susceptible to colitis than WT → GF with impaired recovery. Moreover, IL-22 defect was observed in Card9−/− → GF mice at the gene expression and protein levels in the colon and in MLNs. IL-22 production by T helper cells in WT mice was increased compared to Card9−/− mice. NKp46+ innate lymphoid cell (ILC) induced production of gastric acid (IAA), an AHR agonist, and IL-22 was decreased in stools of Card9−/− → GF and Card9−/− mice. Moreover, feces from Card9−/− → GF mice were defective in their ability to activate AHR. In Card9−/− → GF mice, susceptibility of colitis, and IL-22 defect where rescued after treatment with AHR agonists 6-formylindolo[3,2-b]carbazole, or inoculation with three Lactobacillus strains with strong AHR activity. These effects were abrogated in the presence of AHR antagonist (CH223191). Reduced production of AHR ligands was also observed in the microbiota from patients with IBD, particularly in those with CARD9 risk alleles.

Conclusion: Card9 deletion has an effect on the gut microbiota in mice and its transfer to WT GF recipient is sufficient to recapitulate the defective IL-22 activation and increased sensitivity to colitis observed in Card9−/− mice. These alterations were due to an impaired ability of the microbiota of Card9−/− mice to catabolise tryptophan into AHR ligands. Our results are relevant to humans, as impaired microbial production of AHR ligands was observed in patients with IBD. Thus, defects in expression of factors involved in innate immunity, such as CARD9, can shape an altered microbiota, which can then modify the host AHR-mediated immune responses. This ability to produce AHR ligands, is an attractive strategy in IBD.

Disclosure of Interest: All authors have declared no conflicts of interest.

References


OP071 FAECAL MICROBIOTA TRANSPLANTATION (FMT) IN ILLCERATIVE COLITIS (UC) IS ASSOCIATED WITH SPECIFIC BACTERIAL CHANGES: STOOL AND COLONIC MUCOSA 16S MICROBIOTA ANALYSIS FROM THE RANDOMISED CONTROLLED FOCUS STUDY


Aims & Methods: Active UC patients were randomised to intensive FMT or placebo enemas 5 days/week for 8 weeks, with placebo-treated patients subsequently offered 8 weeks of open label FMT. Each FMT enema was derived from United European Gastroenterology Journal 4(5S)
MRI and portal hypertension using relaxin and relaxin magnetic nanoparticles are currently ongoing.

Conclusion: This study presents a novel strategy to deliver RLN specifically to HSCs, key pathogenic cells involved in liver fibrogenesis, for the diagnosis and treatment of liver fibrosis.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP073 A QUANTITATIVE IMAGING PLATFORM TO REAL-TIME MEASURE SPECIFIC ROS LEVELS IN LIVER DISEASES
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Introduction: Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen, including the peroxide (H2O2), hypochlorous acid (HOCl), singlet oxygen (1O2), and superoxide (O2⁻). ROS have been reported to play an important role in the development of liver diseases. For example, H2O2 can activate hepatic stellate cells in liver fibrogenesis. During hepatic ischemia-reperfusion injury, HOCl is generated by neutrophils and diffuses into hepatocytes, causing oxidant stress-mediated injury. O2⁻ can react with nitric oxide to form peroxynitrite to modify the cell structure and function of proteins in diseased liver. Various methods have been developed to monitor ROS generation in the liver, but the presence of different cellular sources for ROS as well as the distinct chemical properties of specific ROS may lead to conflicting results. Most developed ROS-detection probes were difficult to be distinguished from endogenous fluorophores and only can be employed under one-photon microscopy. Thus, an optimal strategy for precise real-time ROS detection is highly required to rapidly and accurately reveal the cellular microenvironment in liver diseases in clinic.

Aims & Methods: Four different two-photon fluorescent probes were designed and synthesized for selective detection of chemically reactive molecules of thiol and ROS including glutathione (GSH), H2O2, HOCl, and O2⁻. Mouse models of hepatic steatosis, fibrosis and ischemia-reperfusion injury were developed to mimic human liver diseases. After sacrificing the animals, unfixed liver tissues were collected and incubated with each probe at the final concentration of 50 to 100 μM for 10 min, and then imaged using multiphoton microscopy (JenLab GmbH, Jena, Germany). Results: Each probe exhibited a strong positive fluorescent response only in the presence of its specific chemically reactive molecule, whereas negligible fluorescent signals were observed upon the additions of other reactive oxygen/nitrogen species and metal ions. There was a good linear relationship between the probe response and the concentration of each specific ROS. The signal ratio of specific ROS to control was observed in hepatocytes with decreased autofluorescence, indicating the hepatocyte necrosis. Remarkable enhancement of red fluorescence was observed in hepatocytes with decreased autofluorescence, indicating the reaction of with endogenous HOCl. The cellular concentration of GSH decreased and H2O2 increased in the liver with fibrosis and steatosis compared to the control. The concentration of each specific ROS was first calculated based on the intensity of images at the cellular level.

Conclusion: We developed a quantitative imaging platform to real-time measure specific ROS changes in liver diseases at the cellular level. This technique can be used to investigate ROS-mediated liver injury and predict treatment response in human liver biopsy, and can be readily extended to examination of diseases and injury of other organs. We anticipate that in the near future this quantitative imaging platform will be evaluated from bench to bedside, leading to real-time monitoring of cellular microenvironment in human diseases.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

**OP074 RANDOMIZED CONTROLLED TRIAL (RCT) OF DOPPLER ENDOCUTIC PROBE (DEP) FOR BLOOD FLOW DETECTION IN SEVERE NON-VARICEAL UGI HEMORRHAGE (NVUGIH)**

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**Aims & Methods:** We aimed to determine if the use of a STM during routine esophageal manometry improves diagnostic yield and symptom reproducibility. Methods: Prospective series of patients referred for esophageal HRM between November 2014-April 2016. All patients had undergone prior endoscopy with findings of normal or mild (LA grade A esophagitis). WS and STM studies were performed in the upright seated position. Diagnosis of major and minor esophageal motility disorders were based on CC version 3.0 for water swallows (3) and modified for solid swallows as appropriate (4). All medications known to interfere with GI motility were stopped for at least one week prior to the study. Symptom reports by the patients during HRM study were analyzed for any corresponding manometric abnormalities. Symptom associated dysfunction (SAD) was defined as a symptom event reported during or up to 10 seconds after concurrent esophageal dysmotility during STM.

**Results:** 119 (56 Male [47.1%]; mean age 50.9 ± 16.2) consecutive patients (84 Chinese; 17 Malay; 9 Indian; 9 others) underwent HRM with WS for evaluation of (i) dysphagia (n = 56 [47.4%]); (ii) reflux symptoms (n = 45 [38.1%]) and (iii) atypical chest pain (n = 17 [14.4%]). HRM with STM was performed in 114 (96%) patients. Compared to WS alone (n = 2/119 [1.7%]), more patients were diagnosed with esophage-gastric junction (EGJ) outflow obstruction during a STM (n = 8/114 [7.0%]; p = 0.05). (Table) Similarly, more patients were diagnosed with esophageal spasm with a STM (n = 5/114 [4.4%]) compared to WS (2/119 [1.7%], p = 0.27) alone. Upper esophageal dysfunction (UES) was seen only after concurrent esophageal dysmotility during STM.

**Conclusion:** The use of additional physiological stimuli during routine esophageal HRM improves the detection of clinically relevant esophageal dysfunction, including disorders of the upper esophageal sphincter (UES) and the esophage-gastric junction (EGJ). In addition, symptom associated dysfunction occurred more frequently during the solid test meal. The improved diagnostic yield can guide effective treatment.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References:**
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Summary of Manometry Findings with Single Water Swallows (SWS) and Solid Test Meal (STM)

Achalasia Types I/II/III  
SWS STM
15 10

Esophageal-gastric junction (EGJ) outflow obstruction
3 6

Spasm
1 1

Jackhammer
1 1

Aperistalsis
4 0

Ineffective esophageal motility
9 5

Upper esophageal dysfunction
1 2

Normal
23 26

OP076 The New Image Enhancement Technology Using Linked Color Imaging with Acetic Acid Indigocarmine Mixture for Diagnosis of Early Gastric Neoplasm

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Introduction: A value of the combination of magnifying endoscopy of and image enhancement endoscopy (IEE) technology (e.g. NBI, BLI) is reported in a diagnosis for the early gastric neoplasm. This combination is effective, but it is necessary to speculate in real histology from the pattern of a two-dimensional monotone. Therefore, this diagnostic method is still more difficult for general endoscopists. Linked Color Imaging (LCI) was recently developed using a laser endoscopic system (FujiFilm Co., Tokyo, Japan). LCI acquires images by simultaneously using narrow-band short wavelength light and white light in an appropriate balance. This combination of light provides more information about the vasculature and architecture on the mucosal surface than that obtained with typical white-light imaging. When we use acetic acid indigocarmine mixture (AIM) with LCI mode, we discovered that the magnifying images of early gastric cancer are very clear, three-dimensional and near to real histology. So, we examined the utility of this method.

Aims & Methods: This was a prospective observational study performed at a single tertiary referral center. The subjects are 72 lesions of 67 patients with gastric neoplasm. We are indicated of the endoscopic submucosal dissection (ESD), and were given pre-ESD endoscopy in our hospital from September 2014 to February 2016. Firstly we observed the lesions by magnifying endoscopy with the BLI mode and diagnosed using VS classification system1). Secondly we observed the lesions by magnifying endoscopy with LCI+AIM method and diagnosed using VS classification system. Furthermore, we classified the visualization ability of the surface fine structure in Clear, Visible, and Invisibile and evaluated it. Finally, we carried out ESD and compared the image with the histopathology.

Results: By the pathology results, 60 lesions were gastric cancer and 12 lesions were gastric adenoma. The differentiation ability of a cancer and the non-cancer (adenoma) did not have the significant difference between the BLI mode and the LCI+AIM methods. In the classification of visualization ability, 12 lesions were Clear, 22 lesions were Visible, 38 lesions were Invisible by BLI mode. On the other hand, 33 lesions were Clear, 34 lesions were Visible, 5 lesions were Invisible by LCI+AIM method. In the visualization ability of the surface fine structure, LCI+AIM method is significantly clearer than BLI mode (p < 0.05).

Conclusion: When we use AIM, indigocarmine accumulates in the pit of the duct, and duct structures become clear by the acetic acid. By LCI mode, we can observe the vascular pattern of the lesion clearly. So by the combination of AIM and LCI, we can observe the lesion three-dimensionally. By this method, we can compare histopathology with an endoscopic image intuitively, so we believe that a magnifying endoscopy diagnosis of the gastric cancer is enabled even if we do not use various confusing classifications.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

OP077 Exosomes Derived from Gastric Cancer Patients and Cells Could Deliver MiR-21 to Elicit Tumor Progression and Metastasis and Could Be Used as a Potential Diagnostic Biomarker

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Introduction: Gastric cancer (GC) remains a global challenge due to high morbidity and mortality rates and poor response to chemotherapy treatment. Increasing evidence suggests that exosomal microRNAs (miRNAs) possess diverse cellular regulatory roles in cancer progression nowadays. The tumor microenvironment is abundant with exosomes that are secreted by tumor cells. Exosomes are nanosized, organelle-like membranous structures that are increasingly being recognized as major contributors in the progression of malignant neoplasms. For now, little is known about how cancer cell-derived exosomes and miRNAs in exosomes modulate the microenvironment to optimize conditions for tumor progression and metastasis.

Aims & Methods: We aimed to investigate whether cancer cell-derived exosomal miRNAs could modulate cancer progression and metastasis and could be used as a diagnostic marker. In this study, we used miRNA microarray technology to identify exosomal microRNAs that were differentially expressed in GC patients and controls. We further examined the biological function of exosomal miR-21 on cell viability, apoptotic death and metastasis in human GC cells and explored the possible downstream mechanism. We also included another 100 GC patients and 100 controls to study whether exosomal miR-21 could be used as a potential biomarker.

Results: We found that exosomes derived from GC patients exhibited significant different miRNA expression patterns compared with those from controls. Of the 233 miRNAs that were differentially expressed, miR-21 stood out as one of the most significantly upregulated miRNAs in cancer patients. miR-21 depletion in GC cells led to decreased miR-21 levels in exosomes and significantly reduced cell proliferation, migration, invasion and increased apoptosis, and the same phenomenon was seen when transfected miR-21 inhibitor into the exosomes from GC cells and co-culture the transfected exosomes with GC cells. Moreover, exosomal miR-21 markedly enhanced E-cadherin and vimentin expression in GC cells, while significantly decreasing E-cadherin levels, suggesting that exosomal miRNA might play a role in epithelial-to-mesenchymal transition (EMT) process. Finally, circulating exosomal miR-21 levels were closely associated with TNM stage, and lymph node metastasis in GC patients and could be used as a useful diagnostic biomarker with a sensitivity of 89.2% and specificity of 91.1%.

Conclusion: In conclusion, our findings suggest that GC cells could generate miR-21-rich exosomes that are delivered to surrounding normal cells to promote prometastatic behaviors and prompt further investigation into the therapeutic value of exosome inhibition for cancer treatment and diagnostic marker for cancer diagnosis.

Disclosure of Interest: All authors have declared no conflicts of interest.

References
### OP078 URINARY KALLIKREIN-10 PREDICTS INCURABILITY FOR GASTRIC CANCER

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**Introduction:** Recent material and technical development enables us to get many useful biomarkers for gastric cancer (GC). Accurate diagnosis is thus needed to choose an optimal treatment for GC, however, the current imaging diagnosis is not alone to identify incurable factors including peritoneal metastasis and local invasion. We have previously reported the usefulness of urinary biomarkers for diagnosis of GC. With the goal of discovering non-invasive biomarkers for progression and incurability of GC, we conducted this study using urine samples from GC patients and healthy control.

**Background:** The presence of pathological urinary KLK10 is a promising non-invasive biomarker for incurable GC.

**Conclusion:** uKLK10 is a promising non-invasive biomarker for incurable GC.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

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**MONDAY, OCTOBER 17, 2016 14:00-15:30**

### OP079 POPULATION PREVALENCE OF ROME III AND ROME IV IRRITABLE BOWEL SYNDROME (IBS) IN THE UNITED STATES, CANADA AND THE UNITED KINGDOM (UK)

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**Introduction:** Rome IV criteria distinguish IBS into several subtypes according to the predominant symptoms. The Rome IV criteria are used than with Rome III, and the new criteria also change IBS subtype distribution, markedly reducing the IBS-M proportion. [Support: Rome Foundation, The Rome Foundation, The Rome Foundation, The Rome Foundation]  

**Results:** The Rome IV criteria recognized a degree of overlap between GERD and IBS, which cannot be explained solely by nerve and less common in older individuals. IBS prevalence is significantly lower when Rome IV criteria are used than with Rome III, and the new criteria also change IBS subtype distribution, markedly reducing the IBS-M proportion. [Support: Rome Foundation, The Rome Foundation, The Rome Foundation, The Rome Foundation]

**Conclusion:** This study assessed the prevalence of GERD and IBS in the general population in 3 countries to measure and compare Rome IV vs. Rome III IBS rates and the demographics of the disorder. A community sample of 6,300 individuals from the United States, Canada, and United Kingdom was analyzed. The Rome IV prevalence rates were significantly lower than Rome III IBS in all countries (p < 0.0001) than with Rome III (16.6% IBS-C, 20.6% IBS-D, 60.1% IBS-M and 2.1% IBS-U).  


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### OP080 FUNCTIONAL HEARTBURN OVERLAPS WITH IRRITABLE BOWEL SYNDROME MORE OFTEN THAN GERD - DEVELOPMENT OF A PREDICTIVE MODEL FOR CLINICAL PRACTICE

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**Introduction:** Gastroesophageal reflex disease (GERD) and irritable bowel syndrome (IBS) are gastrointestinal (GI) disorders affecting a large part of the general population, with relevant impact on quality of life and health care costs. To date, population- and clinical-based studies have reported a certain degree of overlap between GERD and IBS, which cannot be explained solely by chance. By means of multichannel intraluminal impedance and pH (MII-pH) monitoring, patients with proton pump inhibitor (PPI)-refractory heartburn can be distinguished into PPI-refractory GERD and functional heartburn (FH), the latter to be considered a functional GI disorder separate from GERD. Symptoms of IBS have not yet been assessed in patients with reflux symptoms as distinguished into GERD and FH. Recently, it has been reported that patients with GERD as well as patients with IBS have increased levels of anxiety, in turn associated with increased perception of symptoms and reduced quality of life. Again, the prevalence of anxiety in patients with reflux symptoms as clearly established. The aim of this study was to assess the overlap between GERD and FH.
Aims & Methods: Our aim was to assess the prevalence of IBS as well as anxiety and depression in patients with typical reflux symptoms subdivided into GERD and FH by means of upper GI endoscopy and MII-pH monitoring. We also aimed to assess the prevalence of various clinical and endoscopic characteristics in FH and FH patients in order to develop a predictive model for distinguishing FH from GERD in patients presenting with typical reflux symptoms, potential useful in clinical practice. Patients underwent a structured interview based on questionnaires for GERD (GERDQ), IBS (RIIJAQ), anxiety and depression (HADS). Upper GI endoscopy and 24h MII-pH monitoring were performed in all cases. In patients with IBS, fecal calprotectin was measured and colonooscopy was scheduled for values >100 µg/kg to exclude organic disease. Multivariate logistic regression analysis was performed to identify independent risk factors for FH. A predictive model for FH diagnosis based on clinical and endoscopic findings was developed by applying the purposeful selection of covariates. The coefficients estimated in the multivariate logistic regression analysis were used to predict FH diagnosis. The performance of the predictive model was then assessed by examining measures of discrimination and calibration. Discrimination was considered as the ability of the predictive model to differentiate between patients with FH diagnosis and patients with GERD diagnosis and was quantified by calculating the area under the ROC curve (AUC). A calculator to help clinicians in automatically computing the predicted probability of FH versus GERD in patients presenting with heartburn was built (URL: http://app.calculoid.com/#/ calculator?token=70212).

Conclusion: IBS overlaps more frequently with FH than with GERD, suggesting common pathways and treatment. The score derived from ISAAC predictive model allows a high level of suspicion for FH and can be used in practical clinical practice.

Disclosure of Interest: All authors have declared no conflicts of interest.

Table 1: Probabilities for IBS-related symptoms to persist or subside over a five-year period.

<table>
<thead>
<tr>
<th>Symptom persists</th>
<th>Symptom subsides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability</td>
<td>95% CI Probability</td>
</tr>
<tr>
<td>Depression</td>
<td>22% 18-26% 23%</td>
</tr>
<tr>
<td>Sense of coherence</td>
<td>21% 18-24% 17%</td>
</tr>
<tr>
<td>Coping resources</td>
<td>19% 18-21% 20%</td>
</tr>
<tr>
<td>GI-specific anxiety</td>
<td>16% 14-18% 27%</td>
</tr>
<tr>
<td>Quality of life</td>
<td>16% 14-18% 27%</td>
</tr>
<tr>
<td>GI symptom severity</td>
<td>12% 10-14% 44%</td>
</tr>
</tbody>
</table>

Conclusion: For the first time, we show that IBS-related symptoms develop differentially over time. GI symptoms had a high likelihood of subsiding over time, in contrast to depression, sense of coherence, and coping resources. We suggest more attention needs to be paid to the management of depression, and to providing tools for better coping resources in IBS patients.


Results: Of the 701 consecutive heartburn patients who entered the study, 458 (65%) had GERD whereas 243 (35%) had FH. IBS was found in 143/458 (31%) GERD but in 187/243 (77%) FH patients (p < 0.001). At multivariate analysis IBS, anxiety, and smoking resulted independent risk factors for FH whereas hialtal hernia resulted protective. We developed a predictive model based on clinical and endoscopic characteristics (IBS, Smoking, Anxiety, Age ≥ 45, H2 receptor blockers, and NSAID use). The area under ROC curve in an external validation cohort of 51 patients was 0.920. Considering the previously established cut-off, sensitivity and specificity of the predictive model in diagnosing FH against GERD were 84.3% and 78.9%, respectively. A calculator to help clinicians in automatically computing the predicted probability of FH versus GERD in patients presenting with heartburn was built (URL: http://app.calculoid.com/#/calculator?token=70212).

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Introduction: Irritable bowel syndrome (IBS) is characterised by many comorbid symptoms as well as core symptoms, all of which are relevant for the clinical management of this group of patients. However, the evolution of these symptoms over time is poorly understood.

Aims & Methods: The aim of this study was to determine the probability of IBS-related symptoms to persist or subside over time. The study consisted of three parts. First, we addressed the question which factors can determine the probability of a symptom to persist or subside over time. A simulation showed there were five: length of follow-up period, autocorrelation, the interaction between the autocorrelation and symptom severity, the cut-off for symptom severity, and skewness. Second, we used the five factors in a Monte Carlo simulation, generating a reference-table of probabilities for symptoms to persist or subside. Third, our theoretical reference-table was matched with real data from a cohort of 276 patients who did not meet diagnostic criteria for a FBD other than IBS and were quantified by calculating the area under the ROC curve (AUC). A calculator to help clinicians in automatically computing the predicted probability of FH versus GERD in patients presenting with heartburn was built (URL: http://app.calculoid.com/#/calculator?token=70212).

Conclusion: IBS overlaps more frequently with FH than with GERD, suggesting common pathways and treatment. The score derived from ISAAC predictive model allows a high level of suspicion for FH and can be used in practical clinical practice.
Conclusion: Symptoms compatible with functional bowel disorders in general, and not only IBS, are common in patients with UC in deep remission. However, the overall disease burden seems to be greater in patients with symptoms compatible with IBS than with the other FBDS. These observations are of great importance when managing patients with IBD to avoid escalating anti-inflammatory treatment, and instead focus on other treatment options to help these patients to manage their symptoms.

Disclosure of Interest: M. Simren: Unrestricted research grants from Danone, and Ferring Pharmaceuticals; Consultant/Advisory Board member for AstraZeneca, Danone, Nestlé, Chr Hansen, Almirall, Alibero, Glycom and Shire; Speaker for Tillotts, Takeda, Shire and Almirall.
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H. Strid: Consultant/Advisory Board member for Takeda, Abbvie, Ferring Pharmaceuticals, Tillotts, MSD Speaker for Takeda, Abbvie, Ferring Pharmaceuticals, Tillotts, MSD and Shire.

OP083 ENHANCED DIAGNOSTIC PERFORMANCE OF SYMPTOM-BASED CRITERIA FOR IRRITABLE BOWEL SYNDROME BY HISTORICAL AND DIAGNOSTIC EVALUATION.

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Introduction: Symptom-based criteria to diagnose irritable bowel syndrome (IBS) positively perform only modestly. Our aim was to assess whether including other items from the clinical history and diagnostic workup improves their performance.

Aims & Methods: We collected complete symptom, co-morbidity, and history data from 318 consecutive, unscreened adult patients with lower gastrointestinal (GI) symptoms in secondary care. The reference standard used to define presence of true IBS was patient-reported lower abdominal pain or discomfort associated with a change in bowel habit, in the absence of organic GI disease. Sensitivity, specificity, and positive and negative likelihood ratios (LRs), with 95% confidence intervals, were calculated for Rome III criteria, as well as for modifications, incorporating nocturnal symptoms, measures of somatisation, and/or affect (hospital anxiety or depression scale (HADS) score).

Results: Sensitivity and specificity of Rome III criteria for identifying IBS was 69.6%, and 82.0% respectively, with positive and negative LRs of 3.87 and 0.37. Clinically useful enhancements in positive LRs when combining Rome III criteria with items from the clinical history, and blood tests, are shown in the table.

Conclusion: Incorporating nocturnal symptoms, somatisation, and affect from the clinical history, and haemoglobin and CRP measurements, enhances performance of symptom-based criteria for IBS. Our findings suggest a different approach to the development of future diagnostic criteria should be used.

Disclosure of Interest: All authors have declared no conflicts of interest.

Abstract No: OP083

<table>
<thead>
<tr>
<th>Rome III Criteria and normal Hb and CRP</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive LR (95% CI)</th>
<th>Negative LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rome III criteria and normal Hb and CRP</td>
<td>49.0% (34.4%–64.4%)</td>
<td>89.2% (83.2%–93.6%)</td>
<td>4.33 (2.67–7.66)</td>
<td>0.59 (0.46–0.72)</td>
</tr>
<tr>
<td>Rome III criteria and normal Hb and CRP</td>
<td>73.2% (59.2%–83.3%)</td>
<td>94.8% (90.6%–97.5%)</td>
<td>7.27 (3.74–14.2)</td>
<td>0.66 (0.53–0.81)</td>
</tr>
<tr>
<td>Rome III and HADS score ≥8</td>
<td>34.0% (20.0%–49.3%)</td>
<td>93.2% (87.9%–96.7%)</td>
<td>5.04 (2.46–10.2)</td>
<td>0.71 (0.55–0.84)</td>
</tr>
<tr>
<td>Rome III criteria and HADS score ≥8</td>
<td>24.4% (12.4%–40.3%)</td>
<td>96.8% (92.0%–99.1%)</td>
<td>7.56 (2.63–21.7)</td>
<td>0.78 (0.63–0.90)</td>
</tr>
<tr>
<td>Rome III, no nocturnal passage of stool, and HADS score ≥8</td>
<td>22.2% (13.3%–33.6%)</td>
<td>95.4% (91.7%–97.8%)</td>
<td>4.84 (2.33–10.0)</td>
<td>0.82 (0.70–0.91)</td>
</tr>
<tr>
<td>Rome III criteria, no nocturnal passage of stool, and high somatisation</td>
<td>18.2% (9.8%–29.6%)</td>
<td>99.0% (86.3%–99.9%)</td>
<td>17.3 (4.45–67.6)</td>
<td>0.83 (0.72–0.90)</td>
</tr>
</tbody>
</table>
## Abstract: OP084

### Table

<table>
<thead>
<tr>
<th>Adjusted mean, number in past 6 months (SE)</th>
<th>Diagnosed IBS-D (n = 859)</th>
<th>Undiagnosed IBS-D (n = 370)</th>
<th>Controls (n = 56,932)</th>
<th>p-value: Diagnosed vs. controls</th>
<th>p-value: Undiagnosed vs. controls</th>
<th>p-value: Diagnosed vs. undiagnosed</th>
<th>p-value: Undiagnosed vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any provider visits</td>
<td>7.23 (0.31)</td>
<td>5.17 (0.35)</td>
<td>4.14 (0.02)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Gastroenterologist visits</td>
<td>19 (0.62)</td>
<td>19 (0.01)</td>
<td>0.01 (0.01)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>General practitioner visits</td>
<td>2.69 (0.12)</td>
<td>2.06 (0.15)</td>
<td>1.70 (0.01)</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.007</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>0.27 (0.04)</td>
<td>0.12 (0.03)</td>
<td>0.17 (0.0)</td>
<td>0.002</td>
<td>0.012</td>
<td>0.264</td>
<td></td>
</tr>
<tr>
<td>Hospitalisations</td>
<td>14 (0.03)</td>
<td>8.08 (0.03)</td>
<td>0.11 (0.0)</td>
<td>0.099</td>
<td>0.148</td>
<td>0.430</td>
<td></td>
</tr>
</tbody>
</table>

**Aims & Methods:** The aim of this study was to develop a Bayesian model and a computerized tool that can be used in clinical practice to predict outcomes after ESD and aid in the decision-making process. Methods: Data from 245 ESDs performed in our institution was collected, including pre-resection patient factors (age, sex, ASA, antithrombosis) and lesion factors (size, localization, morphology, pre-resection biopsies). The two main endpoints were curative resection and post-procedural bleeding. We defined curative resection as a resection meeting the standard or expanded criteria of the Japanese Gastric Cancer Treatment guidelines. For the analysis and model construction, morphology was recoded into polyoid (0-Ia, 0-Iap, 0-Ip), depressed (0-IIa+c, 0-IIa+c, 0-IIc and 0-II) and non-polyoid non-depressed (0-IIa, 0-IIb, 0-IIa+b). Univariate analysis was conducted with chi-squared test to identify associations between pre-treatment factors and the two endpoints, for a significance level of 5%. Logistic regression and Bayesian networks were then built for each outcome. Stratified 10-fold cross-validation was performed to assess the predictive accuracy and discriminative power (ROC curves) of the models. Clinical decision support was then enabled by the definition of risk matrices, direct use of Bayesian inference software and through the use of an online platform.

**Results:** In our sample, 85% were curative resections and PPB occurred in 8%. In the univariate analysis, age > 62 (p = 0.039), male sex (p = 0.027), ASA status (p = 0.008), carcinoma histology (p = 0.001), polyoid or depressed morphology (p = 0.015) and lesion size greater than 20 mm (p = 0.006) were associated with non-curative resection, while age > 70 (p = 0.041), ASA status (p = 0.017), antithrombotic medication (p < 0.001) and lesion size greater than >20 mm (p = 0.026) were associated with PPB. Logistic regression and Bayesian models presented AUCs above 80% (in-sample) and 75% (cross-validation) on both outcomes. Lesions with cancer at biopsies, >20 mm, proximal and polyoid are more prone to non-curative resection (table 1). Risk matrices for PPB were also defined yielding a posteriori probabilities of PPB <5% in lesions <20 mm in the absence of antithrombotic medications while the risk of PPB increased in greater lesions and in the presence of antithrombotic medications. The Bayesian network can be interactively used in clinical practice to estimate individual probability of outcomes after ESD. Table 1: Risk (a posteriori probabilities) matrix for curative resection based on morphology, localization, size and pre-resection histology, using a Bayesian model (cross-validation AUC = 78%, 95%CI = [75%, 81%]).
OP087 LONG-TERM OUTCOMES OF GASTRIC ENDOSCOPIC SUBMUCOUS DISSECTION: FOCUS ON METACHRONOUS AND NON-CURATIVE RESECTION MANAGEMENT
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Introduction: Endoscopic submucosal dissection (ESD) is an effective treatment for gastric superficial neoplasms, being curative in 80–85%. Identification of risk factors for a non-curative resection is of utmost importance to improve patient selection. Furthermore, it is important to evaluate the management after an unsuccessful treatment in order to assess the clinical outcomes of each option: conservative management or surgical treatment. Moreover, patients with an early neoplastic lesion are at risk of developing metachronous lesions and endoscopic surveillance will be needed after endoscopic resection. The identification of risk factors for metachronous development is also important to adequate surveillance.

Aims & Methods: The aims of this study were to identify risk factors for non-curative resection and metachronous development and to evaluate management and outcomes after non-curative resection. Methods: Single centre assessment of a cohort of consecutive patients submitted to gastric ESD, with a minimum follow-up of 18 months. The Japanese Gastric Cancer Treatment Guidelines criteria were used in clinical practice; researches were also classified with the recently published European Society of Gastrointestinal Endoscopy guidelines. Univariate analysis (independent samples t-test, Mann-Whitney U test or chi-square test as appropriate) and multivariate logistic regression were performed to identify risk factors. Odds ratios (OR) were computed with 95% confidence intervals (CI). Survival was analyzed with Kaplan-Meier curves and log-rank test. Significance level was defined as < 0.05.

Results: In 184 lesions diagnosed between 2005–2014. The median follow-up time was 40 months. En-bloc and complete resection rates were 95.3% and 93.8%, respectively. Overall adverse events occurred in 13%. Median resected lesion size was 20 mm, longer procedural time and more advanced histology in pre-resection biopsies were associated with non-curative resection (p < 0.05) but only intramucosal carcinoma on pre-resection biopsies was identified as a significant risk factor on multivariate analysis (adjusted OR 3.94, 95% CI 1.02–13.96). Histological upgrade (from low-grade dysplasia to high-grade dysplasia or from high-grade dysplasia to carcinoma) occurred in 49.5% of the cases. Metachronous lesions occurred in 18.4% and the incidence rate was 4.7 lesions/100 person years. The median time to metachronous detection was 24 months (interquartile range 9–56.25 months). Older age at diagnosis was identified as the only predictor of metachronous development in logistic regression (OR 1.04, 95% CI 1.0–1.09, p = 0.05). Overall survival was 94.5% and 89.9% at 1 and 3 years respectively; disease-specific survival was 99.4%, with only one patient dying of gastric cancer. Survival was significantly higher in patients with curative resections (log-rank 4.538, p = 0.033). In the non-curative resection group, patients submitted to surgery were significantly younger (mean age 66.7±6.4 vs. 73.6±7.5 in the follow-up group, p = 0.037) and were less frequently classified as ASA III/IV (23.1% vs. 31.1%, p = 0.026). However, survival at 1 and 3 years (95.9% vs. 88.5%) was worse than in patients with low-risk resection (log rank 7.539, p = 0.006), while the difference was smaller in the survival of patients with low and local-risk resection (log rank 0.133, p = 0.715).

Conclusion: The identified risk factors for non-curative resection help to improve patient selection. The non-curative resection group can improve the probability of success. Metachronous incidence is significant, being older patients at increased risk for its development. In the non-curative resection group, survivors of the resection are candidates to adequate endoscopic surveillance and in selected cases to surgery. An individualized decision is adequate after a non-curative resection and surveillance seems to be an adequate option in selected cases.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:

OP089 ENDOSCOPIC FULL-THICKNESS RESECTION WITH DEFECT CLOSING IN THE STOMACH BY USING A NOVEL GRASP-AND-LOOP (GAL) CLOSURE METHOD (WITH VIDEOS)
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Introduction: Endoscopic full-thickness resection (EFR) is a minimally invasive method for en bloc resection of GI lesions originating from the muscularis propria layer. Successful closure of the wall defect is a critical step.

Aims & Methods: The aim of this study was to evaluate the feasibility and efficacy of a novel and simplified endoscopic Grasp-and-Loop (GAL) closure method used using an endoloop assistant with a grasping forceps for defect closure. From January 2010 to December 2015, 28 cases of endoscopic closure from the muscularis propria layer who underwent EFR were enrolled in this study. After successful tumor resection, an endoloop was anchored onto the circumferential margin of the gastric defect with a grasping forceps assistant and tightened gently (with videos). Patient characteristics, tumor size, en bloc resection, and post-operative complications were evaluated.

Results: Of the 13 lesions in the stomach, 2 were located in the greater curvature and 11 were in the fundus. The endoscopic GAL closure method was successfully performed after EFR in all 13 patients without laparoscopic assistance. The mean procedure time was 43.5 min (range 20–80 min), while the GAL closure procedure took a mean of 9.4 min (range 3–18 min). The endoscopic defect closure was performed using a traction forceps and a grasping instrument. No residual lesion or tumor recurrence was found during the follow-up period (median, 5 months; range, 1–15 months).

Conclusion: The endoloop closure method is feasible, effective and safe for closing the gastric defect after EFR in patients.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:
Disclosure of Interest:

Aims & Methods: The aim was to determine the effect of calorically and non-calorically sweeteners on GI motility and GI peptide secretion as well as on hunger feelings and satiety feelings. Data were analyzed using mixed model analysis. Post-hoc analyses were corrected using Bonferroni.

Results: Antral motility was significantly reduced in response to the caloric sweeteners (fructose: p = 0.004 and fructose: p = 0.001) and to non-caloric sweeteners compared to placebo (glucose: p = 0.043, fructose: p = 0.006 and ace-K: p = 0.032, respectively). The change over time of plasma glucose concentrations was significantly increased after fructose and fructose administration compared to placebo administration (fructose: p = 0.026 and p = 0.002, respectively); ace-K had no effect on plasma glucose concentrations. The change over time of plasma motilin concentrations was significantly decreased after fructose (p = 0.001) administration; ace-K administration induced no difference compared to placebo. Plasma motilin levels were significantly decreased after the calorically sweeteners compared to the non-calorically sweetener ace-K (glucose: p = 0.005 and fructose: p = 0.008, respectively). The time course of satiation scores differed significantly between glucose and ace-K (p = 0.041) with a slower decrease in satiation scores after glucose compared to ace-K administration.

Conclusion: Caloric and non-calorically sweeteners have dissociable effects on antral but not duodenal motility; the reduction in antral motility after glucose and fructose administration parallels changes in motilin secretion. These findings provide an important contribution to the current discussion about possible physiological effects of non-calorically sweeteners on appetite metabolism.

Disclosure of Interest: All authors have declared no conflicts of interest.

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Introduction: With the increasing prevalence of obesity and its possible association with increasing sucrose consumption, non-nutritive sweeteners are gaining popularity. Artificial sweeteners might have adverse effects and alternative solutions are sought. Polysaccharides such as xylitol and erythritol have been known for a long time and their beneficial effects on cartes prevention and potential health benefits in diabetic patients have been demonstrated in several studies. Incretins such as glucagon-like peptide-1 (GLP-1) and gastrointestinal peptides such as cholecystokinin (CCK) are released from the gut in response to food intake, promote satiation, reduce gastric emptying (GE) and modulate glucose homeostasis. While glucose ingestion stimulates sweet taste receptors in the gut, and leads to incretin and gastrointestinal peptide release, the effect of xylitol and erythritol has not been studied.

Aims & Methods: The aim was to study gastrointestinal peptide release and incretin release as well as effects on gastric emptying in response to xylitol and erythritol intake. The study was conducted as a randomized, double-blind, parallel-group trial. A total of 10 healthy lean and 10 diabetic obese (BMI > 30) participants were included. Subjects received intragastric equiseaweed loads of 50 g xylitol or 75 g glucose 300 mL tap water; 75 g glucose solution and 300
mL tap water were control treatments. Solutions were enriched with ^1^C-sodium acetate (for determination of gastric emptying). We measured motility with kep and CCK, as well as plasma insulin and glucose levels. GE was measured by a ^1^H-sodium acetate breath test.

Results: xylitol and erythritol led to a marked increase in CCK (p < 0.001, respectively) and GLP-1 (p = 0.001 and p < 0.001, respectively); ii) plasma insulin and glucose were not (erythritol) or minimally (xylitol) affected; iii) xylitol and erythritol induce a significant retardation in gastric emptying rates (p < 0.001, respectively).

Conclusion: There is emerging evidence to indicate a beneficial role for dietary polyols: xylitol and erythritol are low in calories, have no or only a small effect on plasma glucose and insulin release, yet stimulate interdigestive gastrointestinal satiety peptides. A potential therapeutic application requires further studies.

Disclosure of Interest: All authors have declared no conflicts of interest.

**OP094 INFLAMMATORY AND ANTIOXIDANT RESPONSE FOLLOWING STANDARD MEAL CONSUMPTION IN PATIENTS WITH FUNCTIONAL DYSPEPSIA AND HEALTHY VOLUNTEERS**

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Introduction: The Rome III Classification recognizes two distinct subgroups of functional dyspepsia (FD): the postprandial distress syndrome (PDS) and the epigastric pain syndrome (EPS). The underlying pathophysiological mechanisms of these syndromes are partially known. Recently, the worsening of hypersensitivity in the postprandial period was shown in PDS (1–2) and an impairment of gastric compliance was detected in EPS (2). Moreover, in FD patients an altered permeability of intestinal mucosa, an altered expression of cell adhesion proteins and the presence of mucosal infiltration of mast cells and eosinophils were shown (1), suggesting a role for inflammation and permeability alterations in the pathogenesis of this condition.

Conclusion: Our results show that in PDS the ingestion of a standard meal induces both inflammatory and antioxidant markers in a group of PDS patients compared with healthy volunteers (HV). 14 consecutive, non-smoking patients (9 females, mean age 42.8±12.2 yrs) affected by FD, subtype PDS, according to Rome III criteria and a group of 13 HV comparable for age and gender were enrolled. Chronic inflammatory and autoimmune diseases were excluded. Serum levels of inflammatory cytokines (IL-1, IL-6 and TNFα), insulin, glucose, urea and creatinine were measured in HV and FD patients at baseline and 30, 60 and 120 minutes after the ingestion of a standard meal (proteins 15.7%, lipids 28.3%, carbohydrates 56.0%) for a 4-hour period. The presence and severity of symptoms were assessed by meal-related bloating, thirst, early satiety, heartburn, belching, nausea, vomiting, epigastric pain, abdominal distension, bloating, flatulence, epigastric pain syndrome (EPS) and hunger or satiation in 100 mm visual analog scale (VAS) and recorded using HRiM.

Conclusion: In PDS, hunger and satiety ratings were not affected by LG treatment in both protocols.

**Disclosure of Interest: All authors have declared no conflicts of interest.**

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References:**
1. Ferrari, Gastroenterology 2013.

**OP095 A DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER STUDY USING BACLOFEN IN THE TREATMENT OF RUMINATION SYNDROME**

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Introduction: Rumination syndrome and supra-gastric belching are two conditions with limited treatment options. Baclofen, a gammabutyro cyclic nucleotides agonist, decreases lower oesophageal sphincter (LOS) pressure. We previously demonstrated, in an open-label study, that baclofen reduces pressure flow events in patients with clinically suspected rumination and/or supra-gastric belching.

Aims & Methods: To study the effect of baclofen in a placebo-controlled, double-blind, cross-over study in patients with clinically suspected rumination and/or supra-gastric belching. Consecutive patients with clinically suspected rumination and/or supra-gastric belching were randomized in a double-blind fashion to receive baclofen (10mg, 3 x 1d.i.d) or placebo for 2 weeks with cross-over to the alternative intervention after 1 week wash-out. At the end of each treatment period, patients underwent a solid state high resolution impedance manometry (HRM) measurement. After positioning of the probe, 10 wet swallows were performed to assess oesophageal function. After 30 min recording, patients received a 1000 kcal solid meal and recordings continued for 1 hour. Patients filled in daily diaries, questionnaires and end of study overall treatment evaluation (OTE) on -3 to +3 scale and registered symptoms during the HRM using an event marker. The number of symptoms registered and number and type of flow events during the HRM were compared between placebo and baclofen.

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Introduction: Rumination syndrome and supra-gastric belching are two conditions with limited treatment options. Baclofen, a gamma-aminobutyric acid receptor agonist, increases lower oesophageal sphincter (LOS) pressure. We previously demonstrated, in an open-label study, that baclofen reduces pressure flow events in patients with clinically suspected rumination and/or supra-gastric belching.

Aims & Methods: To study the effect of baclofen in a placebo-controlled, double-blind, cross-over study in patients with clinically suspected rumination and/or supra-gastric belching. Consecutive patients with clinically suspected rumination and/or supra-gastric belching were randomized in a double-blind fashion to receive baclofen (10mg, 3 x 1d.i.d) or placebo for 2 weeks with cross-over to the alternative intervention after 1 week wash-out. At the end of each treatment period, patients underwent a solid state high resolution impedance manometry (HRM) measurement. After positioning of the probe, 10 wet swallows were performed to assess oesophageal function. After 30 min recording, patients received a 1000 kcal solid meal and recordings continued for 1 hour. Patients filled in daily diaries, questionnaires and end of study overall treatment evaluation (OTE) on -3 to +3 scale and registered symptoms during the HRM using an event marker. The number of symptoms registered and number and type of flow events during the HRM were compared between placebo and baclofen.

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Disclosure of Interest: All authors have declared no conflicts of interest.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References:**
1. Ferrari, Gastroenterology 2013.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References:**
1. Ferrari, Gastroenterology 2013.
Conclusion: F. Zerbib6, B. Caiazzo7, J. C. Grimaud8, F. Mion9, S. Hadjadj10, L. Vuitton11, parameters were 14 Hz, 5mA, pulses of 330 were blinded to the stimulation status. When the device was “ON”, stimulation was not activated. Then each subject was randomized in a masked fashion to one

2 electrodes sewn in the antrum. During the first month post surgery, the device or possurgical, was eligible. After a screening period of 4 months to assess symp-

Aims & Methods: Open trials have suggested that GES could be effective for the relief of reflux oesophagitis. The aim of this study was to examine the effect of GES on reflux symptoms and on the treatment of reflux oesophagitis in a controlled trial in patients with refractory vomiting associated or not with gas-

Controlled trial in patients with refractory vomiting associated or not with gas-

Disclosure of Interest: All authors have declared no conflicts of interest.

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Disclosure of Interest: All authors have declared no conflicts of interest.

Disclosure of Interest: All authors have declared no conflicts of interest.
Conclusion: In conclusion, the present study reveals ITGAS as a novel prognostic and therapeutic target in pancreatic tumor stroma. These data make a strong base to utilize this target for developing novel diagnostic and therapeutic strategies against pancreatic tumor.

Disclosures of Interest: All authors have declared no conflicts of interest.

References

OP099 MICRORNA-622 INHIBITS EPITHELIAL-MESENCHYMAL TRANSITION BY TARGETING NON-CODING RNA HULC IN HUMAN PANCREATIC CANCER

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Introduction: Transforming growth factor (TGF)-β-induced epithelial-mesenchymal transition (EMT) is a trigger of invasion and metastasis in pancreatic cancer. Although long non-coding RNAs (lncRNAs), which are defined as non-coding RNAs (ncRNAs) more than 200 nucleotides in length, have been implicated in disease pathogenesis, their contributions to pancreatic cancer are not well understood. Recently, the inter-relationship between two classes of ncRNA, microRNAs (miRNAs) and lncRNAs, has been reported to contribute to the epigenetic regulation of gene expression in several cancers.

Aims & Methods: Our aims were to investigate the involvement and functional roles of TGF-β-induced lncRNA during EMT and reveal contributions of the inter-relationship between the TGF-β-induced lncRNA and miRNA to the regulatory mechanisms of EMT in human pancreatic cancer. We used human pancreatic cancer (Panc1, BxPC-3, MiaPaCa-2, QGP-1 and KP-3) and non-malignant pancreatic ductal epithelial (HPT-HPNE) cells. Expression profiling of 90 lncRNAs and 2565 miRNAs were performed using qPCR and miRNA microarray. miRNA targets were predicted by miRanda. Cells were treated with 10 ng/ml of TGF-β for 72 hours to induce EMT. siRNA or miRNA mimic were used to modulate RNA expression. Cell viability was assessed by MTS assay and trypan blue. Cell invasion and migration were examined by tranwell and wound healing assay. Expression of RNA was assessed by qPCR and of protein by Western blot.

Results: LncRNA expression profiling identified 22 lncRNAs that were induced by TGF-β in Panc-1 cells by >1.4-fold. Of these, HULC was amongst the top most significantly up-regulated. HULC expression was induced by TGF-β by 1.5 to 2.7-fold in a panel of pancreatic cancer cells and up-regulated by 2.4 to 8.9-fold in pancreatic cancer cells compared to HPT-HPNE cells. In Panc-1 cells, knockdown of HULC by siRNA significantly increased expression of E-cadherin and decreased expression of N-cadherin, Snail and Vimentin (p < 0.05). Moreover, siRNA to HULC decreased cell viability, invasion and migration. Furthermore, to identify miRNAs that can target HULC and suppress EMT, miRNA microarray and bioinformatics analysis were performed. Microarray identified 187 miRNAs that were decreased by < 0.87 fold in Panc-1 cells treated with TGF-β compared to control. Of these, mir-622 was predicted to target HULC by miRanda. mir-622 expression was reduced by TGF-β by 0.5 to 0.9-fold in a panel of pancreatic cancer cells. Overexpression of miR-622 using miRNA mimetic significantly decreased expression of HULC, increased expression of E-cadherin and decreased expression of Snail, N-cadherin and Vimentin (p < 0.05). In addition, miR-622 overexpression significantly reduced cell invasion and migration.

Conclusion: These findings provide mechanistic insights into EMT in pancreatic cancer by (a) identifying HULC as a highly induced IncRNA by TGF-β, (b) demonstrating that HULC promotes EMT, (c) identifying that miR-622, as a down regulated miRNA by TGF-β, can target HULC, and (d) showing a functional role for miR-622 in EMT via targeting HULC. These observations imply miR-622 would suppress invasion and metastasis by inhibiting EMT signaling through targeting HULC and suggest potential strategies to inhibit invasion and metastasis in human pancreatic cancer.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP100 ESSENTIAL ROLE OF THE NON-RECEPTOR TYROSINE-PHOSPHATASE PTPN11/SHP-2 IN ORGAN DEVELOPMENT AND HOMEOSTASIS OF THE MURINE EXOCRINE PANCREAS

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Introduction: The Src-homology-2 (SH2) domain containing protein tyrosine phosphatase SHP-2 is expressed ubiquitously and is involved in an array of intracellular signal transduction processes (Ras-Raf-MAPK, JAK-STAT, PI3K-Akt-mTOR, NFκB…). Thus, for instance, SHP-2 plays a role in cellular responses to growth factors (EGF, FGF, IGF-I…), cytokines (IL5, GM-CSF,….) and extracellular matrix (via integrins, focal adhesion complex). Via these pathways SHP-2 mediates transcriptional regulation of mitogenic activation, cell proliferation, survival, differentiation, migration and metabolism. The role of SHP-2 in organ development and homeostasis of the pancreas has so far not been explored.

Aims & Methods: Mouse models with pancreas specific deletion of SHP-2 (Ptf1a-Cre;Ptpn11flox/flox) with or without knock-in (LSL-KrasG12D) and/or lineage tracing allele (ACTB-TdTomato;EGFP) were used for analysis.

Results: Early embryologic Deletion of SHP-2 in the pancreas via Ptf1a-Cre mice acinar lobuli are consecutively replaced by adipocytes. Lineage-tracing experiments provide insight into the origin of the exocrine compartment in the growing pancreas is impaired. In adult mice, organ weight is reduced by about 50%, compared to uncombined littermate-controls. In the organ growth phase, centro-acinar cells display enhanced cell death (necrosis and apoptosis) which is accompanied by markedly reduced proliferation. In aged SHP-2−/− mice acinar lobuli are consecutively replaced by adipocytes. Lineage-tracing experiments provide insight into the origin of this cell population (invagination vs. transdifferentiation) and will be presented. Interestingly, introduction of mutated Kras (LSL-KrasG12D) into the model fully compensates for the deletion of SHP-2. Finally, in the pancreas, we not only observe an essential role of SHP2 in adequate activation of the RTK-Ras-MEK-ERK-signalizing axis but also in positive regulation of RTK-expression levels.

Conclusion: The central role of the non-receptor tyrosine phosphatase SHP-2 in organ development and homeostasis of the murine pancreas is linked to the RTK-Ras-Raf-MEK-ERK-signalizing axis. SHP-2 is essential for adequate transmigration of growth factor signals and thereby influences proliferation and survival of the acinar cell.

Disclosure of Interest: All authors have declared no conflicts of interest.
**Optimal RELA Controls KRAS-Driven Pancreatic Carcinogenesis by Modulating Oncogene-Induced Senescence Via the CXCL1/KC/CXCR2 Axis**


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**Introduction:** The IKK/NF-κB pathway has been shown to be a crucial mediator of tumour growth and progression, exhibiting both tumour-promoting and tumour-suppressive properties. How IKK/NF-κB possesses these opposite activities during tumour development remains elusive.

**Aims & Methods:** To study the invasion of tumour cells along neurites we have combined 3D co-culture assays of dorsal root ganglia (DRG) and tumour cells in lineages of pancreatic adenocarcinoma (PDAC). We generated compound mutants KrasG12D mice with specific deletion of the p56 gene in the pancreas. Pancreata were investigated histologically and biochemically.

**Results:** Our data clearly demonstrate a dual role of NF-κB/RelA activation in pancreatic carcinogenesis. In early stages of tumorigenesis, the tumour-suppressive function of NF-κB is beneficial because it controls oncogene-induced senescence (OIS) by regulating the CXCL1/KC/CXCR2 axis. However, as soon as OIS is bypassed during development of tumorigenesis, NF-κB supports tumour progression by enhancing proliferation of the transformed pancreatic cancer cells.

**Conclusion:** Examining these context-dependent activities of RelA will be important for effective clinical use of NF-κB inhibitors. Furthermore, these findings underlie the importance of investigating the use of pharmaceuticals targeting the CXCR2 receptor as a therapeutic option for the treatment of various solid tumours.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References:**


**Optimal Modeling Tumor Cell Nerve Interactions in Pancreatic Cancer**

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**Introduction:** Neural invasion (NI) has emerged as a key pathologic feature of tumour growth and progression, exhibiting both tumour-promoting and tumour-suppressive effects. How IKK/NF-κB possesses these opposite activities during tumour development remains elusive.

**Aims & Methods:** Here we describe several applicable tools, using live cell and tissue microscopes, co-culture of tumour cells or ex vivo PDAC xenograft tissues with freshly isolated dorsal root ganglia (DRG), primary DRG neurons and F11 hybridoma neurons to investigate the reciprocal interaction at the tumour cell-nerve interface.

**Results:** To study the invasion of tumour cells along neurites we have combined 3D co-culture assays of dorsal root ganglia (DRG) and tumour cells with time-lapse microscopy and specifically track the unidirectional movement of individual tumour cells along neurites extending from DRGs. Quantification of the dynamic process revealed that neuronal scaffolds provide the infrastructure for an accelerated and consistent migration of tumour cells towards the DRG as the source of chemotactic gradients. In another approach, using expanlated PDAC xenograft tissues instead of tumour cell colonies, it occurred that neurite outgrowth from DRG pathway lived towards the tumour tissue. Thus, neurites facing the tumour were more elongated than neurites at the opposite site of the DRG, suggesting that tumour gradients stimulate and/or attract neurite outgrowth and elongation. In support of a tumour-derived chemotactic effect, supernatants from cultured primary dorsal root ganglia were compared varying reagent concentrations in order to achieve outgrowth of freshly isolated primary neurons in transwell assays. In order to gain a more dynamic representation on how neurites explore a chemotactic gradient, F11 hybridoma neurons were co-cultured with PDAC cell lines in separate patches divided by a 500 μm gap. These assays use time-lapse imaging and endpoint analysis in order to track the locomotion of individual neurite extensions, monitor their outgrowth from neurites and elongation towards the tumour cell front, and allow to quantitate length, velocity, forward migration index, and direction of each protruding trajectory in response to different PDAC cell lines. Moreover, the extent of growth cone formation and collapse can be scored by determining dynamic changes in circumferential size and area of the growth cone.

**Conclusion:** These in vitro and ex vivo models emulate several important aspects of nerve-tumour interactions and allow pharmacological and gain- and loss-of-function manipulations. In addition, semi- to fully-automated quantification of high-throughput screening experiments may offer investigators reliable tools to test their candidate target genes or drugs.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

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1. Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield/United States of America
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**Disclosure of Interest:** IL-23 contributes to the migration of Th17 cells and the IL-23 pathway has been implicated in the pathogenesis of Crohn’s disease (CD). Risankizumab is a humanized IgG1 monoclonal antibody that binds the p19 subunit of IL-23R and inhibits binding of IL-23 to its receptor. Risankizumab in Crohn’s disease (RCT2031276, 2031368). Lancet \( \text{Vol} 390 / \text{No} 10075, \text{p} 2203–13 \)

**Conclusion:** We investigated the underlying mechanism of risankizumab in this Phase II trial by characterising the molecular profile in the colon and/or ileum tissue in a subset of patients with CD, who received each 200 mg (n = 26), 600 mg (n = 27) risankizumab or placebo (n = 26). From each patient, 6–9 biopsy samples were obtained from the colon in risankizumab-treated cohort reflected the molecular changes observed in patients evaluated at Week 12 by an independent blinded reviewer.

**Results:** Risankizumab treatment significantly decreased the expression of 1146 genes from baseline to Week 12 in the colon tissue of CD patients vs placebo \( \text{CDEIS response (} > 50\% \text{ reduction from baseline)} \), and CDEIS remission \( \text{p} < 0.05 \) of note, risankizumab treatment was associated with a significant reduction in the expression of genes associated with the IL-23 pathway \( (\text{IL-}23A, -23G, -23L, -17\text{A}, -17\text{B}, -17\text{C}, -17\text{D}, \text{STAT}3)\), innate immunity \( (IL6, IL7, IL7R, IL8, IL10, IL12\text{A}, IL12\text{B}, IL17\text{A}, IL17\text{B}, TNF\text{)}\), interferon \( (\text{IFN}\alpha, \text{IFN}\beta, \text{IFN}\gamma\text{)}\), and T cell activation \( (\text{CD8}\text{A}, \text{CD8}\text{B})\). These overall changes in gene expression in the risankizumab group reflect the molecular changes observed in patients treated with risankizumab vs placebo from baseline to Week 12.

**Conclusion:** The superior efficacy observed with risankizumab in active CD patients at Week 12 was associated with significant molecular changes in the...
col of CDEIS responding patients. The molecular profile appears to be differ-
entiated from anti-TNF treatment.


**OPI04 EFFICACY OF USTEKINUMAB FOR INDUCTION AND MAINTENANCE OF ENDOSCOPIC HEALING IN PATIENTS WITH CROHN'S DISEASE**


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**Introduction:** Usteekinumab (UST) has been shown to induce & maintain clinical response & remission in 2 induction (UNITI-1&2) & 1 maintenance (IM-UNITI) trials in moderate-to-severe Crohn's disease (CD). A substudy evaluated the efficacy of UST in the induction & maintenance of endoscopic healing.

**Aims & Methods:** Patients in the substudy had up to 3 colonoscopy evaluations (i.e. at UNITI-I or 2 baseline [BL] and Wk 8, and IM-UNITI Wk44) in 5 ileocolonic segments (i.e. ileum, right colon, transverse colon, left colon, rectum) within the 52-Wk study period. A single central reader blindly scored all video endoscopies for ulcerations and simplified endoscopic activity score for CD (SES-CD). At induction Wk0, patients received a single IV dose (UST 130 mg, UST 66 mg/kg, or PBO). At maintenance Wk0 (i.e. induction Wk8), UST induction responders [Primary randomized maintenance population] were re-randomized to subcutaneous (SC) PBO, UST 90 mg every 12 wks (q12w), or UST/SES-CD. At induction Wk0, patients received a single IV dose (UST 130 mg, UST 66 mg/kg, or PBO). At maintenance Wk0 (i.e. induction Wk8), UST induction responders [Primary randomized maintenance population] were re-randomized to subcutaneous (SC) PBO, UST 90 mg every 12 wks (q12w), or UST 90 mg every 8 wks (q8w). For the 3 non-randomized maintenance groups: (1) UST induction non-responders received SC UST 90 mg, then continued SC UST 90 mg q8w if CDAI decreased ≥100 after 8 wks; (2) PBO induction non-responders received UST 130 mg, then continued SC UST 90 mg q8w if CDAI decreased ≥100 after 8 wks; and (3) PBO induction non-responders received UST 130 mg, then continued SC UST 90 mg q8w if CDAI decreased ≥100 after 8 wks; (2) PBO induction non-responders received UST 130 mg, then continued SC UST 90 mg q8w if CDAI decreased ≥100 after 8 wks; (3) PBO induction non-responders received UST 130 mg, then continued SC UST 90 mg q8w if CDAI decreased ≥100 after 8 wks.

**Results:** The substudy primary endpoint was met, as UST induction resulted in greater reduction in SES-CD from BL at induction Wk8 in the integrated UST group (data across induction & UST dose. Other induction endoscopic endpoints also consistent favored UST vs PBO (Table 1a). At IM-UNITI Wk44, trends for greater efficacy with UST vs PBO, maintenance, especially UST 90 mg q8w, was observed in the primary randomized maintenance population, but small sample sizes (UST n = 46; PBO n = 24) precluded definitive conclusions. In the larger post-hoc pooled maintenance population (Table 1b), consistent trends in support of UST maintenance, especially UST 90 mg q8w, were observed across endoscopic endpoints at Wk44.

**Conclusion:** The endoscopy substudy primary endpoint was met; a single IV dose of UST induced significantly greater reduction in endoscopic disease activity vs PBO, despite a relatively early evaluation at Wk8. Results in the small primary randomized maintenance population were supported by the larger post-hoc pooled maintenance population; greater proportions of subjects receiving UST maintenance, especially UST 90 mg q8w, achieved maintenance end-point vs PBO. Together, these data support the efficacy of UST in inducing & maintaining endoscopic healing of the mucosa in CD.


**OPI05 FILGOTINIB, A SELECTIVE JAK1 INHIBITOR, INDUCES CLINICAL REMISSION IN PATIENTS WITH MODERATE-TO-SEVERE CROHN'S DISEASE: FINAL ANALYSIS OF THE PHASE 2 FITZROY STUDY**

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**Introduction:** Filgotinib is an oral, selective Janus kinase 1 (JAK1) inhibitor, which has demonstrated high efficacy in patients with rheumatoid arthritis. This 20-week Phase 2 study was designed to evaluate the efficacy and safety of filgotinib in patients with active Crohn's disease (CD).

**Aims & Methods:** 174 patients with moderate-to-severe CD (CDAI: 220 to 450, randomised to non-steroidal anti-inflammatory drug (NSAID) naïve) were randomized to receive 200 mg filgotinib (FIL) or placebo (PBO) QD for 10 weeks. Based on Week 10 clinical response, patients continued to receive filgotinib (200 mg or 100 mg QD) or placebo for an additional 10 weeks. Patients who demonstrated clinical response (CDAI-100) underwent corticosteroid tapering after Week 10. Anti-TNF-naïve patients were to be discontinued prior to treatment initiation. Final data for the primary endpoint of clinical remission (CDAI < 150) at Week 10 are presented.

**Results:** Baseline characteristics were comparable in both groups, including mean disease duration (8.3 y), mean CDAI score (293), mean CRP (15.6 mg/L, 41% > 10 mg/L), oral corticosteroids (51%, mean daily dose 21.6 mg/day). Primary endpoint of the study was filgotinib induced clinical remission in 47% of the patients, compared to placebo recipients (p = 0.0077), and led to improvement in PRO2 score, and quality of life (IBDQ changes from baseline) compared to placebo (table 1). Numerically more patients on filgotinib normalized CRP (FIL:27%, PBO:14%) and showed an improvement of at least 50% in SES-CD endoscopic score (FIL:25%, PBO:13.6%). Histopathology overall total score was decreased more significantly in the filgotinib group compared to placebo (p = 0.05).

**Table 1:** Key efficacy parameters

<table>
<thead>
<tr>
<th>Variable/unit/population</th>
<th>Placebo n = 44</th>
<th>filgotinib n = 128</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission (CDAI &lt; 150), %, IITT-NRI</td>
<td>23</td>
<td>47</td>
<td>0.0077</td>
</tr>
<tr>
<td>PRO2, mean change from baseline, ITT-LOCF</td>
<td>−15.6</td>
<td>−21.9</td>
<td>0.0321</td>
</tr>
<tr>
<td>Table (1b): Maintenance Week 44 (IM-UNITI)</td>
<td>15.6</td>
<td>33.8</td>
<td>0.0045</td>
</tr>
</tbody>
</table>

*p < 0.05 Primary endpoint *SES-CD reduction ≥3 from induction BL *SES-CD reduction ≥50% from induction BL *SES-CD score ≤2 *Complete absence of ulcers
8 included Inflammatory Bowel Disease Questionnaire (IBDQ) remission (total score ≤170) and IBDQ response (≥16-point increase from baseline). For binary endpoints, the comparison of tofacitinib 10 mg BID vs PBO was assessed using the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by study, prior TNFi treatment, corticosteroid use at baseline and geographic region. Within each subgroup, the CMH chi-square test stratified by study was used. **Results:** At Wk 8, significantly more pts achieved remission, mucosal healing and clinical response with tofacitinib 10 mg BID vs PBO (all p < 0.0001, Table). The difference generally remained significant regardless of prior TNFi exposure, prior TNFi failure/primary TNFi failure (primary or secondary) or disease severity (based on baseline Mayo score ≥5 or < 5; Table). For all three endpoints, greater effects were observed when comparing secondary vs primary TNFi failure subpopulations and baseline Mayo score < 5 vs baseline Mayo score ≥5. IBDQ remission and response were significantly greater with tofacitinib 10 mg BID vs PBO at Wk 8 regardless of prior TNFi exposure/prior TNFi failure.

**Conclusion:** Tofacitinib demonstrated efficacy vs PBO, regardless of prior TNFi therapy in pts with moderately to severely active UC. PRO results were similar in pts with/without prior TNFi exposure or failure.

**Table: Summary of efficacy endpoints in OCTAVE Induction 1 and OCTAVE Induction 2 at Wk 8**

<table>
<thead>
<tr>
<th>10 mg BID N = 905</th>
<th>Tofacitinib Placebo N = 234</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission, n (%)f</td>
<td>159 (17.6) 14 (6.0)</td>
<td>11.6 (7.7, 15.5) ***</td>
</tr>
<tr>
<td>Prior TNFi exposureg</td>
<td>99 (23.7) 13 (12.5)</td>
<td>11.2 (5.7, 18.8) **</td>
</tr>
<tr>
<td>Prior TNFi failureh</td>
<td>53 (11.4) 1 (0.8)</td>
<td>10.6 (7.3, 13.9) ***</td>
</tr>
<tr>
<td>No prior TNFi failurei</td>
<td>106 (24.1) 13 (11.8)</td>
<td>12.3 (5.0, 19.5) **</td>
</tr>
<tr>
<td>Prior TNFi failure (primary non-responder)j</td>
<td>19 (7.5) 1 (1.4)</td>
<td>8.2 (2.0, 10.3) **</td>
</tr>
<tr>
<td>Prior TNFi failure (secondary non-responder)k</td>
<td>31 (16.6) 0 (0.0)</td>
<td>16.6 (11.2, 21.9) ***</td>
</tr>
<tr>
<td>Baseline Mayo score &lt;9l</td>
<td>91 (28.3) 6 (7.3)</td>
<td>21.0 (13.5, 28.5) ***</td>
</tr>
<tr>
<td>Baseline Mayo score ≥9m</td>
<td>68 (11.7) 8 (5.3)</td>
<td>6.4 (2.0, 10.8)</td>
</tr>
<tr>
<td>Mucosal healing, n (%)n</td>
<td>271 (29.9) 32 (13.7)</td>
<td>16.3 (11.0, 21.6) ***</td>
</tr>
<tr>
<td>Prior TNFi exposureo</td>
<td>112 (23.0) 8 (6.2)</td>
<td>16.8 (11.2, 22.4) ***</td>
</tr>
<tr>
<td>No prior TNFi exposurep</td>
<td>159 (38.1) 24 (23.1)</td>
<td>15.1 (5.7, 24.4) **</td>
</tr>
<tr>
<td>Prior TNFi failureq</td>
<td>103 (22.2) 8 (6.5)</td>
<td>15.7 (10.0, 21.4) ***</td>
</tr>
<tr>
<td>No prior TNFi failurer</td>
<td>168 (38.2) 24 (21.8)</td>
<td>16.4 (7.4, 25.3) ***</td>
</tr>
<tr>
<td>Prior TNFi failure (primary non-responder)s</td>
<td>38 (15.0) 5 (6.8)</td>
<td>8.3 (1.0, 15.5)NS</td>
</tr>
<tr>
<td>Prior TNFi failure (secondary non-responder)t</td>
<td>57 (30.5) 2 (4.7)</td>
<td>25.8 (16.7, 34.9) ***</td>
</tr>
<tr>
<td>Baseline Mayo score &lt;9</td>
<td>145 (45.2) 17 (20.7)</td>
<td>24.4 (14.1, 34.8) ***</td>
</tr>
<tr>
<td>Baseline Mayo score ≥9</td>
<td>126 (21.6) 15 (9.9)</td>
<td>11.7 (5.9, 17.5) ***</td>
</tr>
<tr>
<td>Clinical response, n (%)u</td>
<td>521 (57.6) 72 (30.8)</td>
<td>26.8 (20.1, 33.5) ***</td>
</tr>
<tr>
<td>Prior TNFi exposurev</td>
<td>254 (52.0) 29 (23.3)</td>
<td>29.0 (18.6, 39.3) ***</td>
</tr>
<tr>
<td>No prior TNFi exposurew</td>
<td>267 (64.0) 43 (41.3)</td>
<td>22.7 (17.2, 33.2) ***</td>
</tr>
<tr>
<td>Prior TNFi failurex</td>
<td>237 (51.0) 29 (23.4)</td>
<td>27.6 (18.9, 36.3) ***</td>
</tr>
<tr>
<td>No prior TNFi failurey</td>
<td>284 (64.5) 43 (39.1)</td>
<td>25.5 (15.3, 35.6) ***</td>
</tr>
<tr>
<td>Prior TNFi failure (primary non-responder)z</td>
<td>116 (45.8) 19 (25.7)</td>
<td>20.2 (8.5, 31.9) ***</td>
</tr>
<tr>
<td>Prior TNFi failure (secondary non-responder)</td>
<td>102 (54.5) 20 (9.9)</td>
<td>33.6 (19.5, 47.7) ***</td>
</tr>
<tr>
<td>Baseline Mayo score &lt;9</td>
<td>205 (63.9) 30 (16.6)</td>
<td>27.3 (15.6, 39.0) ***</td>
</tr>
<tr>
<td>Baseline Mayo score ≥9</td>
<td>316 (54.3) 42 (27.8)</td>
<td>26.5 (18.3, 34.7) ***</td>
</tr>
</tbody>
</table>

Full analysis set, non-responder imputation NSNot significant; *p < 0.05; ***p < 0.001; ***p < 0.0001 vs placebo 95% confidence interval was based on normal approximation for the difference in binomial proportions N = 488 for tofacitinib 10 mg BID and N = 130 for placebo; N = 417 for tofacitinib 10 mg BID and N = 104 for placebo/N = 465 for tofacitinib 10 mg BID and N = 124 for placebo; N = 440 for tofacitinib 10 mg BID and N = 110 for placebo; N = 253 for tofacitinib 10 mg BID and N = 74 for placebo; N = 187 for tofacitinib 10 mg BID and N = 43 for placebo; N = 321 for tofacitinib 10 mg BID and N = 82 for placebo; N = 582 for tofacitinib 10 mg BID and N = 151 for placebo; statistical significance based on the Cochran-Mantel-Haenszel chi-squared test stratified by study, prior treatment with tumour necrosis factor inhibitors, corticosteroid use at baseline and geographic region BID, twice daily; CI, confidence interval; TNFi, tumour necrosis factor inhibitor; Wk, week

**Disclosure of Interest:** G.R. D’Haens: Study-related disclosures. Dr D’Haens received speaker fee from and is an advisor for Pfizer Inc.

B.E. Sands: Grants(G), Personal Fee(P), Non-Financial/Pfizer G, P:Amgen, MPA:Abbvie, Takeda, Forward, Theravance, Receptos, Vedanta, Synergy, Topivert. X.J. Sandborn: Study-related disclosures: Dr Sandborn received grant support, personal fees and non-financial support from Pfizer during the conduct of the study; grant support from Pfizer T. Hibi: Grants, personal fees: Mitsubishi Tanabe Pharma, Ajinomoto Pharma, Abbvie Personal fees: Eizai, Takeda Pharma.
In the moderate UC patient population (CAI ≤ 12) at baseline.

At entry into the OLE, the partial Mayo Score (pMS) for patients on placebo, ozanimod 0.5 mg, and ozanimod 1.0 mg was 4.6, 4.5, and 3.3 respectively. At the time of the data-cut in the OLE, the pMS had improved in all groups (1.7, 1.7, and 1.9) at Week 44. The greatest improvement was reported in patients who received placebo or ozanimod 0.5 mg in the TOUCHSTONE trial with a change in pMS at Week 44 of –2.6, –2.7 and –1.3 in the placebo, 0.5 mg and 1 mg groups. Improvement occurred rapidly, in the first 4 to 8 weeks of the OLE. The greatest improvement was reported for patients who received placebo or ozanimod 0.5 mg in the TOUCHSTONE trial with a change in pMS at Week 4 of –1.8, –1.9 and –0.8 and a change in pMS at Week 8 of –2.4, –1.9 and –1.1 in the placebo, 0.5 mg and 1 mg groups. At the Week 44 visit in the OLE, the pMS had improved in all groups (1.7, 1.7, and 1.9) at Week 44. 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The greatest improvement was reported for patients who received placebo or ozanimod 0.5 mg in the TOUCHSTONE trial with a change in pMS at Week 4 of –2.4, –1.9 and –1.1 in the placebo, 0.5 mg and 1 mg groups.
We assessed a recently developed self-assembling peptide matrix as a wound dressing after endoscopic resection for the prevention of esophageal stricture.

**Aims & Methods:** Ten pigs were randomly assigned to the self-assembling peptide RADA-16 (4 [Arg-Ala-Asp-Ala]) or the control group after undergoing a 5 cm long circumferential endoscopic submucosal dissection of the lower esophagus. Esophageal dissection and esophagogastroduodenoscopy, weight variation, and histological measurements of fibrosis, granulation tissue, and neoeithelium were assessed in each animal.

**Results:** The rate of esophageal stricture at day 14 was 40% in the group treated with self-assembling peptide vs. 100% in the control group (p = 0.04). Median (IQR) esophageal diameter at day 14 was 8 mm (2.5–9) in the self-assembling peptide group vs. 4 mm (3–4) in the control group (p = 0.13). The median (IQR) stricture indexes on esophagograms at day 14 were 0.32 (0.14–0.48) and 0.26 (0.14–0.33) in treated and control groups, respectively (p = 0.42). Median (IQR) weight variation during the study was +0.2 (–7.4; +1.8) and +3.8 (–5.4; +0.6) in the treated and control groups, respectively (p = 0.9). No differences were observed between the groups in terms of histological outcomes. All animals eventually developed esophageal strictures at day 25.

**Conclusion:** The application of a self-assembling peptide matrix on esophageal wounds after circumferential endoscopic submucosal dissection is safe and feasible, and prevents early esophageal stricture occurrence in our model.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**OP110 INTRALESIONAL STEROID INJECTION COMBINED WITH ORAL STEROID ADMINISTRATION TO PREVENT ESOPHAGEAL STRCTURE AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION OF LESION NO MORE THAN A HALF OF CIRCUMFERENCE**

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**Introduction:** Endoscopic submucosal dissection (ESD) is becoming an important and main therapy for early esophageal carcinoma or precancerous lesion. However, stricture occurs when the mucosal defects created by ESD are larger than a half of circumference. It’s an urgent task to find out a safe and efficient method to prevent stenosis.

**Aims & Methods:** To investigate the safety and efficacy of local steroid injection combined with oral steroid administration in preventing esophageal stricture after ESD of esophagus carcinoma or precancerous lesion which are no less than a half of circumference. A single-center randomized controlled trial was designed to examine the effects and safety of intralesional steroid injection combined with oral steroid administration in preventing stricture after esophageal ESD. 43 patients with mucosal defects no less than a half of circumference following esophageal ESD were randomized to receive intralesional triamcinolone injection immediately after ESD and oral prednisone administration for consecutive 12 weeks, which starting at a dose of 30 mg daily, tapered gradually at a speed of 5 mg in every two weeks (n = 20, treatment group) or to be treated conventionally (n = 23, control group). The primary endpoint was the frequency of stricture. Secondary endpoints were the number of balloon dilation, rate of other complications and hospital stay.

**Results:** The frequency of stricture (20% vs. 69.6%) and the number of balloon dilation (mean 0.5 vs. 1.3) were less in treatment group, and the former one had a significant difference. The hospital stays and rate of complications were similar between two groups. One patient suffered perforation of stomach in the treatment group, which was not a direct result of steroid injection or ESD.

**Frequency of stricture formation, number of endoscopic balloon dilations (EBDs) performed, hospital stays after ESD and other complications in two groups.**

<table>
<thead>
<tr>
<th></th>
<th>Treatment group (n = 20)</th>
<th>Control group (n = 23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of stricture, n (%)</td>
<td>5 (20)</td>
<td>16 (69.6)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Number of EBDs, n mean ± SD (range)</td>
<td>0.5 ± 1.1 (0–3)</td>
<td>1.3 ± 2.0 (0–8)</td>
<td>0.241</td>
</tr>
<tr>
<td>Perforation by procedure, n per session (%)</td>
<td>1.0/5 (3.7)</td>
<td>0.53 (0)</td>
<td>0.361</td>
</tr>
<tr>
<td>Bleeding by procedure, n per session (%)</td>
<td>0.0/0 (0)</td>
<td>0.0/1.1 (19)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hospital stays after ESD, days mean ± SD (range)</td>
<td>4.1 ± 4.4 (1–22)</td>
<td>3.3 ± 2.0 (1–8)</td>
<td>0.469</td>
</tr>
</tbody>
</table>

*Significant difference

**Conclusion:** Intraluminal steroid injection combined with oral steroid administration appears to be safe and effective in preventing esophageal stricture following ESD of lesions no less than a half of circumference.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References:**
altered diagnosis/therapy and/or influenced management in 417 (83%) pts. Misdiagnosis as a predictor for malignant pathway of Spy DS biopsies is better for Spy DS than Spy Legacy (p = 0.014). Adverse events in 7 (1%) pts: 2 mild pancreatitis, 2 mild and 1 moderate cholangitis, 1 moderate bleeding and 1 micro perforation.

**Conclusion:** SOC, especially using Spy DS, has high procedural success and provides important impact on diagnosis, therapy and/or management in a wide range of indications, with excellent safety profile.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**OP113 PROPOSAL OF A MACROSCOPIC CLASSIFICATION FOR TISSULAR LESIONS OF THE BILE DUCT DETECTED DURING PER ORAL CHOLANGIOSCOPY (POCS)**

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**Introduction:** The macroscopic aspects to determine malignancy of the bile duct during per oral cholangioscopy (POCS) are: presence of irregular surface with bleeding and drooling or torrentious vessels. For benign lesions the typical aspects are lesions with smooth surface “without vessels or mass”. However, many misdiagnosis are made due to a lack of correlation between the macroscopic aspects and histology. Moreover, masses are many times benign, and reported data diagnosis are made due to a lack of correlation between the macroscopic aspects and histology. Based on the morphological and vascular pattern the lesions were classified as follows:

- **Benign lesions:** Type 1 “Villous pattern” (micronodular or villous pattern without out vascularity), Type 2 “Polypoid pattern” (adenoma or granuloma pattern without vascularity) and Type 3 “Inflammatory pattern” (regular or irregular fibrous and congestive pattern with regular vascularity). Malignant lesions: Type 1 “Flat pattern” (flat and smooth or irregular surface with irregular or spider vascularity); Type 2 “Poliyoid” (polypoid or mass with fibrosis and irregular or spider vascularity), Type 3 “Ucerated” (irregular pattern ulcerated and infiltrative with or without fibrosis with irregular or spider vascularity) and Type 4 “honey-comb pattern” (fibrous honey-comb pattern with or without irregular or spider vascularity). Inter-observer and intra-observer agreement was calculated using 40 random images of lesions for 1 expert and 2 non-expert in POCS. Finally a prospective non randomized, double blind evaluation of diagnostic accuracy, sensitivity, specificity, PPV, NPV using the new classification was performed for consecutive tissular lesions detected from Oct-2015 to April-2016 correlated with histology.

**Results:** 130 patients were studied, (retrospective: 87 / prospective: 43); 30 female, 2016 correlated with histology. The proposed macroscopic classification could help physicians to distinguish benign from malignant lesions with a good inter and intra-observer concordance.

**Conclusion:** The proposed macroscopic classification could help physicians to distinguish benign from malignant lesions with a good inter and intra-observer concordance.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References**


Aims: We aimed to assess whether intensive hydration impacts on the incidence and severity of PEP. We performed a prospective, double-blinded randomized controlled trial, including consecutive patients submitted to ERCP in our institution. Patients with previous sphincterotomy, chronic pancreatitis, heart failure (NYHA ≥3), chronic kidney disease (stage≥3) and shock were excluded. Patients were randomized (1:1) to either intensive hydration with lactated Ringer’s solution (3 mL/kg/h during the procedure, 3 mL/kg/h for 8 hours after the procedure), or standard hydration (1.5 mL/kg/h of lactated Ringer’s solution during and for 8 hours after the procedure). A blood panel including serum levels of amylase and lipase was obtained at 4 and 24 hours after ERCP. Primary outcome was the incidence of PEP (defined as epigastric pain plus either amylase or lipase levels > 3 times the upper limit of normal at 24h). Secondary outcomes were severity of PEP, incidence of volume overload, patient and procedure-related factors associated with PEP, and the predictive values of serum amylase/lipase at 4 hours after the procedure. Results: We included 75 patients, 38 in the intensive hydration arm, and 37 in the standard hydration arm. Both groups were homogeneous for patient and procedural characteristics. PEP incidence and severity of PEP. We performed a prospective, double-blinded randomized controlled trial, including consecutive patients submitted to ERCP in our institution. Patients with previous sphincterotomy, chronic pancreatitis, heart failure (NYHA ≥3), chronic kidney disease (stage≥3) and shock were excluded. Patients were randomized (1:1) to either intensive hydration with lactated Ringer’s solution (3 mL/kg/h during the procedure, 3 mL/kg/h for 8 hours after the procedure), or standard hydration (1.5 mL/kg/h of lactated Ringer’s solution during and for 8 hours after the procedure). A blood panel including serum levels of amylase and lipase was obtained at 4 and 24 hours after ERCP. Primary outcome was the incidence of PEP (defined as epigastric pain plus either amylase or lipase levels > 3 times the upper limit of normal at 24h). Secondary outcomes were severity of PEP, incidence of volume overload, patient and procedure-related factors associated with PEP, and the predictive values of serum amylase/lipase at 4 hours after ERCP (PEP development).

Results: We included 75 patients, 38 in the intensive hydration arm, and 37 in the standard hydration arm. Both groups were homogeneous for patient and procedural characteristics. PEP incidence and severity of PEP. We performed a prospective, double-blinded randomized controlled trial, including consecutive patients submitted to ERCP in our institution. Patients with previous sphincterotomy, chronic pancreatitis, heart failure (NYHA ≥3), chronic kidney disease (stage≥3) and shock were excluded. Patients were randomized (1:1) to either intensive hydration with lactated Ringer’s solution (3 mL/kg/h during the procedure, 3 mL/kg/h for 8 hours after the procedure), or standard hydration (1.5 mL/kg/h of lactated Ringer’s solution during and for 8 hours after the procedure). A blood panel including serum levels of amylase and lipase was obtained at 4 and 24 hours after ERCP. Primary outcome was the incidence of PEP (defined as epigastric pain plus either amylase or lipase levels > 3 times the upper limit of normal at 24h). Secondary outcomes were severity of PEP, incidence of volume overload, patient and procedure-related factors associated with PEP, and the predictive values of serum amylase/lipase at 4 hours after ERCP (PEP development).

Conclusion: The use of high-dose PPI did not appear to significantly reduce the risk of both immediate and delayed bleeding in patients undergoing EST.

Disclosure of Interest: All authors have declared no conflicts of interest.

A1015 PREVENTION OF POST-SPHINCTEROTOMY BLEEDING BY PROTON PUMP INHIBITOR: A PROSPECTIVE RANDOMIZED TRIAL

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Introduction: Bleeding after endoscopic sphincterotomy (EST) is one of the most frequent complications of therapeutic ERCP. Although the use of proton pump inhibitor (PPI) has been shown to reduce the risk of rebleeding in patients with peptic ulcer bleeding after endoscopic hemostasis, the role of acid suppression in preventing EST bleeding has not been evaluated. We hypothesized that preemptive high dose PPI could reduce the risk of post-EST bleeding.

Aims & Methods: The aim of this study was to study the role of high-dose PPI in patients undergoing EST. It was a prospective randomized open-label study performed in the endoscopy centre of a university teaching hospital. Consecutive patients who were scheduled to have ERCP and EST were enrolled. We excluded patients who had previous EST, prior gastric surgery, or were taking PPIs. Antiplatelet therapies were continued as usual. Anti-coagulants (warfarin or heparin) were stopped with coagulopathy corrected prior to EST. Patients who had previous EST were excluded.

Results: The aim of this study was to study the role of high-dose PPI in patients undergoing EST. It was a prospective randomized open-label study performed in the endoscopy centre of a university teaching hospital. Consecutive patients who were scheduled to have ERCP and EST were enrolled. We excluded patients who had previous EST, prior gastric surgery, or were taking PPIs. Antiplatelet therapies were continued as usual. Anti-coagulants (warfarin or heparin) were stopped with coagulopathy corrected prior to EST. Patients who had previous EST were excluded.

Conclusion: The use of high-dose PPI did not appear to significantly reduce the risk of both immediate and delayed bleeding in patients undergoing EST.

Disclosure of Interest: All authors have declared no conflicts of interest.

A1016 IMPACT OF INTENSIVE HYDRATION ON THE INCIDENCE OF POST-ERCP PANCREATITIS: DOUBLE-BLINDED RANDOMIZED CONTROLLED TRIAL

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Introduction: Pancreatitis is the most frequent complication following endoscopic retrograde cholangiopancreatography (ERCP), with an estimated incidence of 1.6% to 17.7%, depending on patient and procedure-related factors. Intensive hydration with lactated Ringer’s solution has been shown in small studies to reduce post-ERCP pancreatitis (PEP) incidence and severity.

Aims & Methods: We aimed to assess whether intensive hydration impacts on the incidence and severity of PEP. We performed a prospective, double-blinded randomized controlled trial, including consecutive patients submitted to ERCP in our institution. Patients with previous sphincterotomy, chronic pancreatitis, heart failure (NYHA ≥3), chronic kidney disease (stage≥3) and shock were excluded. Patients were randomized (1:1) to either intensive hydration with lactated Ringer’s solution (3 mL/kg/h during the procedure, 3 mL/kg/h for 8 hours after the procedure), or standard hydration (1.5 mL/kg/h of lactated Ringer’s solution during and for 8 hours after the procedure). A blood panel including serum levels of amylase and lipase was obtained at 4 and 24 hours after ERCP. Primary outcome was the incidence of PEP (defined as epigastric pain plus either amylase or lipase levels > 3 times the upper limit of normal at 24h). Secondary outcomes were severity of PEP, incidence of volume overload, patient and procedure-related factors associated with PEP, and the predictive values of serum amylase/lipase at 4 hours after ERCP (PEP development).

Results: In all, 75 patients were enrolled, 38 in the intensive hydration arm, and 37 in the standard hydration arm. Both groups were homogeneous for patient and procedural characteristics. PEP incidence and severity of PEP. We performed a prospective, double-blinded randomized controlled trial, including consecutive patients submitted to ERCP in our institution. Patients with previous sphincterotomy, chronic pancreatitis, heart failure (NYHA ≥3), chronic kidney disease (stage≥3) and shock were excluded. Patients were randomized (1:1) to either intensive hydration with lactated Ringer’s solution (3 mL/kg/h during the procedure, 3 mL/kg/h for 8 hours after the procedure), or standard hydration (1.5 mL/kg/h of lactated Ringer’s solution during and for 8 hours after the procedure). A blood panel including serum levels of amylase and lipase was obtained at 4 and 24 hours after ERCP. Primary outcome was the incidence of PEP (defined as epigastric pain plus either amylase or lipase levels > 3 times the upper limit of normal at 24h). Secondary outcomes were severity of PEP, incidence of volume overload, patient and procedure-related factors associated with PEP, and the predictive values of serum amylase/lipase at 4 hours after ERCP (PEP development).

Conclusion: The use of high-dose PPI did not appear to significantly reduce the risk of both immediate and delayed bleeding in patients undergoing EST. The aim of this study was to study the role of high-dose PPI in patients undergoing EST. It was a prospective randomized open-label study performed in the endoscopy centre of a university teaching hospital. Consecutive patients who were scheduled to have ERCP and EST were enrolled. We excluded patients who had previous EST, prior gastric surgery, or were taking PPIs. Antiplatelet therapies were continued as usual. Anti-coagulants (warfarin or heparin) were stopped with coagulopathy corrected prior to EST. Patients who had previous EST were excluded. Patients were randomized (1:1) to either intensive hydration with lactated Ringer’s solution (3 mL/kg/h during the procedure, 3 mL/kg/h for 8 hours after the procedure), or standard hydration (1.5 mL/kg/h of lactated Ringer’s solution during and for 8 hours after the procedure). A blood panel including serum levels of amylase and lipase was obtained at 4 and 24 hours after ERCP. Primary outcome was the incidence of PEP (defined as epigastric pain plus either amylase or lipase levels > 3 times the upper limit of normal at 24h). Secondary outcomes were severity of PEP, incidence of volume overload, patient and procedure-related factors associated with PEP, and the predictive values of serum amylase/lipase at 4 hours after ERCP (PEP development).

Results: In all, 75 patients were enrolled, 38 in the intensive hydration arm, and 37 in the standard hydration arm. Both groups were homogeneous for patient and procedural characteristics. PEP incidence and severity of PEP. We performed a prospective, double-blinded randomized controlled trial, including consecutive patients submitted to ERCP in our institution. Patients with previous sphincterotomy, chronic pancreatitis, heart failure (NYHA ≥3), chronic kidney disease (stage≥3) and shock were excluded. Patients were randomized (1:1) to either intensive hydration with lactated Ringer’s solution (3 mL/kg/h during the procedure, 3 mL/kg/h for 8 hours after the procedure), or standard hydration (1.5 mL/kg/h of lactated Ringer’s solution during and for 8 hours after the procedure). A blood panel including serum levels of amylase and lipase was obtained at 4 and 24 hours after ERCP. Primary outcome was the incidence of PEP (defined as epigastric pain plus either amylase or lipase levels > 3 times the upper limit of normal at 24h). Secondary outcomes were severity of PEP, incidence of volume overload, patient and procedure-related factors associated with PEP, and the predictive values of serum amylase/lipase at 4 hours after ERCP (PEP development).
negative predictive value of 100% for the development of PEP. No complication was observed during the course of intensive hydration.

Conclusion: In our series, the incidence of PEP was 9.3%, and a non-significant risk reduction trend was observed in patients undergoing intensive hydration, with no severe pancreatitis being observed in this group. Wirsung contrast injection, the risk of PEP. Lower serum amylase and lipase levels at 4 hours after ERP were excellent predictors for absence of PEP at 24 hours, displaying a negative predictive value of 100%.

Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016 15:45–17:15

UPPER GI NERVE-GUT INTERACTIONS – ROOM N2

OPI17 INTRAGASTRIC BITTER TASTANT ALTERS BRAIN ACTIVITY IN HOMEOSTATIC AND HEDONIC REGIONS AND DECREASES OCTANEOYLATED GHRELIN LEVELS AND HEDONIC FOOD INTAKE

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Introduction: Intragastric administration of bitter tastants decreases hunger ratings in the fasted state. Activation of bitter taste receptors can alter ghrelin levels, a gut hormone which increases hunger in between meals and becomes active after octanoylation. This indicates a potential role for bitter agonists in the regulation of appetite and food intake, putatively via interference with gut-brain signals to regions involved in homeostatic (brainstem, hypothalamus) and hedonic (mesolimbic reward system) control of feeding.

Aims & Methods: The aim of this project was to study the effect of intragastric administration of the bitter tastant Quinine Hydrochloride (QHCl) on brain activity in homeostatic and hedonic regions and on circulating ghrelin plasma levels. Furthermore, to test the hypothesis that lower hunger and prospective food consumption ratings, and lower hedonic food intake after QHCl administration compared to placebo. Fifteen healthy women were studied after an overnight fast. Brain activity before and up to 90 minutes after infusion of QHCl (10mM/ kg) or distilled water (placebo) was recorded using functional magnetic resonance imaging (fMRI). Hunger and prospective food consumption scores were assessed every 10 min using Visual Analogue Scales. Blood samples were taken at the same time points. Hedonic food intake was measured immediately after scanning using an ad libitum chocolate milkshake drink test. MRI preprocessing and analysis was conducted using SPM12. Brain responses over time to QHCl versus placebo infusion were compared in a priori defined regions of interest (ROI) at both voxel- and cluster-level threshold of p<0.001 uncorrected < 0.05. The interaction effect was tested on hunger and prospective food consumption scores with mixed models. Hedonic food intake was compared between infusions using a one-tailed paired T-test. Blood plasma was analysed for circulating ghrelin levels using radioimmunoassays.

Results: Compared to placebo, intragastric QHCl infusion significantly increased neural activity in 5 different clusters within the ROIs, with local maxima in the putamen, insula, caudate, amygdala, anterior cingulate cortex, medial prefrontal cortex, medial orbitofrontal cortex and hippocampus. A decrease of neural activity was observed in the lower limb system. Significantly lower prospective food consumption scores were observed after QHCl administration compared to placebo (p=0.02), but no significant differences were observed for hunger scores. Milkshake intake significantly decreased after QHCl administration, compared to placebo (p=0.06, Cohen's d=0.50). A significant decrease of octanoylated ghrelin plasma levels was observed post-infusion after bitter administration compared to placebo (p=0.05).

Conclusion: Intragastric administration of the bitter tastant QHCl significantly altered activity in homeostatic and hedonic brain regions. Prospective food consumption ratings, circulating octanoylated ghrelin levels and hedonic food intake were decreased after QHCl. These observations indicate a potential role for bitter agonists in the treatment of obesity.

Disclosure of Interest: All authors have declared no conflicts of interest.

OPI18 TRANSDIAGNOSTIC COGNITIVE BEHAVIOUR THERAPY SHOW PROMISE FOR BOTH MOOD AND GASTROINTESTINAL SYMPTOMS IN PATIENTS WITH FUNCTIONAL GASTROINTESTINAL DISORDERS

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Introduction: Irritable Bowel Syndrome (IBS) is a heterogenous disorder characterised by recurrent abdominal pain combined with alteration in bowel habit. It is associated with reduced quality-of-life and significant economic cost to society. IBS sufferers also have elevated scores for anxiety and depression which have been speculated to be part of the disease etiology [1]. Indirect evidence for the role of mood in IBS prevalence comes from studies showing that a proportion of patients show improvement in abdominal symptoms with antidepressants [2] but also in response to psychological therapies including cognitive behaviour therapy (CBT) [3]. Newer forms of CBT including internet-delivered CBT (iCBT) have shown similar effect sizes to conventional CBT in patients with mood disorder [4]. iCBT provides access to therapy for patients who are geographically or culturally isolated from qualified psychologists and has been shown to be cost-effective [5]. The eCentreClinic at Macquarie University (Australia) has developed a transdiagnostic model of CBT which is applied via distance mode, remote delivery via internet but an initial telephone.

Aims & Methods: This study sought to pilot a new form of iCBT designed for chronic health conditions, including functional gastrointestinal disorders, with respect to: 1. Reduction in abdominal symptom burden, anxiety and depression 2. Identify the risk of psychological factors that correlate with improvements in abdominal symptom burden. These aims were addressed using a single arm design with measurements of psychological factors and symptoms pre, mid and post-therapy. n=27 individuals from across Australia were recruited at the eCentreClinic at Macquarie University (Australia) which specialises in online psychological therapies. Abdominal symptoms were assessed using the Gastrointestinal Symptom Rating Scale (GSRS) while anxiety was measured via the GAD-7 and depression via the PHQ-9. Aim 1 was addressed via correlating change in GSRS scores with change in anxiety, depression and pain catastrophising scores. Results: Of 27 patients who commenced therapy 22 completed the entire course and a post-therapy feedback survey was done. There was no difference in baseline measures for any measure between completers and non-completers. Scores for both abdominal symptom and psychological traits were substantially and statistically significantly improved at the end of therapy (Table 1).

At end of therapy 77% of patients had reduced GSRS scores and 95% reported the program was worth the effort expended. The percentage change in GSRS scores was positively correlated with percentage change in pain catastrophising (r=0.53, p=0.01) and to a lesser extent with change in anxiety (r=0.36, p=0.1). Conclusion: Based on this pilot trial, a transdiagnostic iCBT program developed specifically for functional gastrointestinal disorders shows considerable promise with improvements in both gastrointestinal symptoms as well as psychological functioning. The correlation between change in both mood scores and catastrophizing with change in abdominal symptoms opens avenues for further understanding of the mechanisms by which iCBT improves the gastrointestinal sufferings of these patients. The low cost of iCBT compared with conventional face-to-face therapy is attractive given challenges to public health budgets and its modality makes therapy accessible to potential patients who are not able to travel to a psychologist. Further, the transdiagnostic model on which this particular iCBT treatment is based is readily adaptable to other functional somatic syndromes so offers hope to a wide range of disorders.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OPI19 DYSBIOSIS INDUCES GUT INFLAMMATION AND DEPRESSIVE-LIKE BEHAVIOR ASSOCIATED WITH BRAIN BIOCHEMICAL AND FUNCTIONAL ALTERATIONS WHICH ARE RESTORED BY PROBIOTIC TREATMENT

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Introduction: The gut-brain axis has been indicated as major substrate of pathophysiological mechanisms in psychiatric comorbidities associated with chronic inflammatory bowel disorders. In particular, intestinal microbial alterations have been speculated to play a role in the development of symptoms between these two systems. However, the communication between these two systems is not yet fully understood and probably involves multiple mechanisms.

Aims & Methods: In the present study we examined the presence of gut inflammation and depressive-like behaviour associated with brain biochemical and functional alterations in an antibiotic-induced dysbiosis animal model. Young male mice received a mixture of nonabsorbable antimicrobials (ampicillin, streptomycin and cyclodextrin), which has been associated to the microbiota composition alteration2, for 2 weeks. Afterwards, animals were treated with probiotic (Lactobacillus Casei DG, 107 cells) or vehicle up to 7 days. Whereupon, various behavioral testing were performed. After sacrifice, mice intestine was cut in segments (duodenum, jejunum, ileum and colon) and expression of pro-inflammatory markers (IL-1β,
TNFα and IL-1β) was evaluated by Western blot analysis. Extracellular recording from CA3 regions of dorsal hippocampus was performed. Astrocytes and microglial cells markers (GFAP and iNOS, respectively) expression was evaluated by immunohistochemistry.

**Results:** Biochemical evaluations indicated that dysbiosis induced an overall gut immune response characterized by a significant increase in IL-1β, TNFα and iNOS expression, accompanied with a depressive-like behavior and a reduced social interaction. Altered behavior was accompanied by significant changes CA3 pyramidal neurons firing activity. Moreover, the number of GFAP and iNOS positive cells was significantly dysbiotic. Very interestingly, probiotic treatment significantly decreased IL-1β, TNFα and iNOS expression, normalized mice behavior, restored the spontaneous ongoing activity of CA3 pyramidal neurons and reduced the GFAP and iNOS positive cells number.

**Conclusion:** We found that, in mice, dysbiosis induced gut inflammation and sickness behaviors associated with biochemical and electrophysiological alterations in hippocampus. Probiotic treatment counteracted the gut inflammation and restored the behavioral phenotype as well as the biochemical and functional changes occurring in the brain of diabetic mice. These data suggest that intestinal dysbiosis, via the gut-brain axis, might contribute to the psychiatric comorbidity in patients with bowel disorders associated with an altered microflora and that probiotic treatment may improve this condition.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

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*OP102 QUORUM SENSING MOLECULES OF GUT MICROBIOTA AFFECT INTESTINAL TASTE RECEPTORS AND ANOREXIGENIC PEPTIDES TO CONTROL SATIETY IN THE HOST*

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**Introduction:** Accumulating evidence suggests that the gut microbiota controls host satiety and hunger (1). Even if quantitative modifications of the gut microbiota have been described in obesity, bacterial derived soluble factors are likely involved in host dietary habits.

**Aims & Methods:** In this study we investigated the role of quorum sensing molecules (the autoinducers, AI) used for communication within gut microbial communities (2), in modifying food intake in the host. Adults CD1 male mice were fed a high-fat diet (HFD, 35% energy by fat) or a normal diet (4% energy by fat) for 4 weeks. Two weeks later we determined: a) gut microbiota composition by quantitative PCR (qPCR) on fecal DNA; b) enteroendocrine cells (EECs) density in colonic mucosa by immunohistochemistry (IHC) for synaptotagmin; c) mRNA levels specific for taste receptors and for anorectic or orexigenic peptides by qRT-PCR on colon and hypothalamus; d) food intake, body weight gain, oral glucose tolerance test.

**Results:** In HFD-fed mice rectal administration of AHL-12 or PQS restored the gut microbiota composition and normalized the density in colonic mucosa, altered by fat diet. AI administration increased the mRNA levels of Tas2r5, Tas2r28 and Tas2r105 whereas it did not affect Tas2r131 and Tas1r3 allics variables of bitter taste receptors. Moreover, AHL-12 and PQS significantly increased mRNA levels of anorectic peptides namely Cholecystokinin, Leptin and Neurotensin in the gut and Brain-Derived Neurotrophic Factor in the hippocampus. Probiotic treatment counteracted the gut inflammation and restored the behavioral phenotype as well as the biochemical and functional changes occurring in the brain of diabetic mice. These data suggest that intestinal dysbiosis, via the gut-brain axis, might contribute to the psychiatric comorbidity in patients with bowel disorders associated with an altered microflora and that probiotic treatment may improve this condition.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References**


*OP12 ACOTIAMIDE-SENSITIVE IMPAIRED RECEPTIVE RELAXATION OF LOWER ESOPHAGEAL SPHINETER IN PATIENTS WITH ESOPHAGOESOPHAGEAL JUNCTION OUTFLOW OBSTRUCTION*

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**Introduction:** The pathogenesis and treatment of esophageal junction outflow obstruction (EGJOO) are not fully understood. The lower esophageal sphincter (LES) pressure is suppressed by swallowing and pharyngeal water stimulation (PWS) (Mittal, *J Gastroenterol* 1996;111:378–384); PWS-induced LES relaxation appears to be analogous to gastric receptive relaxation. We have previously reported that acotiamide was effective for patients with EGJOO.

**Aims & Methods:** This study aimed to evaluate the physiologic characteristics of acotiamide-sensitive LES relaxation in patients with EGJOO. High-resolution manometry was performed according to a standard protocol with the participant in the supine position, while swallowing ten 5-mL liquid boluses. 13 patients with EGJOO (mean age 65.5 ± standard deviation 4.1 years, eight of whom were women) and 19 participants with normal esophageal pressures (mean age 50.0 ± 3.0 years, 11 of whom were women) were enrolled. Basal LES pressure (BLES) and the integrated relaxation pressure (IRP) were measured. The extent of PWS-induced LES relaxation (mmHg) was calculated as the difference between BLES and the mean LES pressure in the 5-s period before PWS.

**Results:** There was no difference in BLES between normal subjects (34.6 ± 2.1 mmHg) and patients with EGJOO (32.7 ± 1.8 mmHg), but IRP was significantly higher in patients with EGJOO (20.3 ± 1.4 mmHg) than normal subjects (10.8 ± 0.6 mmHg). In normal subjects, LES pressure immediately declined from 34.6 ± 2.1 mmHg to 25.6 ± 1.4 mmHg when the fluid bolus stimulated the mouth and pharynx on the first swallow. Mean PWS-induced LES relaxation was observed in normal subjects, but was absent in patients with EGJOO.
The mean LES pressure induced by PWS was 33.0 ± 1.6 mmHg, and did not differ significantly from the baseline (32.7 ± 1.6 mmHg). Acetamide normalized impaired receptive LES relaxation and substantially improved symptoms.

Conclusion: Esophageal strictures have receptive LES relaxation, but this is impaired in EGJOO. Acetamide normalizes impaired receptive LES relaxation and substantially improved symptoms.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

MONDAY, OCTOBER 17, 2016 15:45–17:15
ENDOSCOPIC MANAGEMENT OF UPPER GASTROINTESTINAL CANCER – ROOM L7

OP123 EFFICACY AND SAFETY OF ESD FOR SUPERFICIAL CANCER OF THE CERVICAL ESOPHAGUS
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Introduction: It is a difficult to observe a lesion in the cervical esophagus because of the difficulty in spreading the lumen. It is a challenge not only to find esophageal cancers at an early stage, but also to successfully treat them by ESD compared with lesions located at the thoracic esophagus.

Aims & Methods: The aim of this study was to clarify the safety and efficacy of ESD for superficial cancer located at the cervical esophagus. Patients who met the following criteria (case group) were enrolled in this retrospective study: (1) ESD was performed from January 2006 to December 2015; (2) the lesion was located at the cervical esophagus; and (3) squamous cell carcinoma (SCC) was proven histologically. Forty-five patients met those criteria. As a control group, 379 patients with 405 lesions of SCC which were located at the middle thoracic esophagus were enrolled. The lesions with entire circumferential mucosal defect, recurrent lesions after radiotherapy, and the lesions located near the scar were excluded from both groups. We evaluated the complications including stricture and pneumonia, procedure time, en bloc resection rate, and frequency of local recurrence.

Results: In the case group, the average age was 67.3 years old, and the male-to-female ratio was 38:7. The average maximum size of lesions was 20.7 mm, and the histological depth of invasion was EP/LPM, MM, and SM2 in 39, 5, and 1 cases, respectively. The en bloc resection rate and R0 resection rate was 100% and 91.1%, respectively, and the mean procedure time was 57 min. ESD was performed for general anesthesia in 32 patients (71.1%). Damage of the muscular layer during treatment was observed in 5 patients, for which clipping was performed in 2 patients. Esophageal stricture was observed in 9 patients (41%), for which local injection of steroid was administered in 6 patients. No post-ESD bleeding was observed. Although perforation was identified in one patient, he recovered with conservative treatment. Chemoradiotherapy as additional treatments were conducted in Ipatient. No local recurrence was observed during an average duration of follow-up of 34.1 months. In the control group, the average age was 65.9 years old, and the male-to-female ratio was 338:45. The average maximum size of lesions was 24.2 mm, and the histological depth of invasion was EP/LPM, MM, and SM2 in 306, 67, and 32 cases, respectively, and the mean procedure time was 54 min. ESD was performed under general anesthesia in 45 patients (11.1%). Damage of the muscular layer during treatment was observed in 91 patients (22.5%), for which clipping was performed in 38 patients. Esophageal stricture was observed in 14 patients (6.6%) of 213 patients with more than half of mucosal defect, for which local injection of steroid or PGA sheet were administered in 38 patients. No post-ESD bleeding was observed. Although perforation was identified in three patients, they recovered with conservative treatment.Surgery or chemoradiotherapy as additional treatments were conducted in 19 or 49 patients respectively. Local recurrence was observed in one patient during an average duration of follow-up of 41.8 months.

Conclusion: Safe ESD for superficial esophageal cancer in the cervical esophagus could be achieved under an appropriate management and successful local control was also confirmed. The stricture after ESD in the cervical esophagus developed significantly higher than those in the middle esophagus.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP124 SUBMUCOSAL TUNNELING ENDOSCOPIC RESECTION VS. THORACOSCOPIC SURGERY FOR LARGE SYMPTOMATIC SUBMUCOUS TUMORS IN THE ESOPHAGUS AND ESOPHAGOGRASTIC JUNCTION
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Introduction: Small gastrointestinal submucosal tumors (SMTs) are asymptomatic and undetectable, while patients with larger tumors have symptoms, and require intervention. Previously, thoracoscopic submucosal tunneling endoscopic resection (STER) was reported to be the treatment of choice for large esophageal tumors and the resection of upper gastrointestinal SMTs. Recently, reports about STER are increasing. However, it is unclear whether STER is feasible for large SMTs. Moreover, studies about comparison of STER and surgery for upper gastrointestinal SMTs are still little. The aim of this study is to compare the clinical outcomes of STER and thoracoscopic surgery for large symptomatic SMTs in esophagus and esophagogastrectic junction, as well as to analyze the clinicopathological factors that affect the feasibility of STER. Patients with large SMTs of the esophagus and the esophagogastric junction were enrolled in the retrospective study between May 2011 and December 2013. The clinicopathological data of a total of 145 patients were collected and analyzed.

Aims & Methods: The aim of this study is to compare the clinical outcomes of STER and thoracoscopic surgery for large symptomatic SMTs in esophagus and esophagogastrectic junction, as well as to analyze the clinicopathological factors that affect the feasibility of STER. STER was performed in 2 patients. Esophageal stricture was observed in 9 patients during an average duration of follow-up of 34.1 months. The lesions with entire circumferential mucosal defect, recurrent lesions after radiotherapy, and the lesions located near the scar were excluded from both groups. We evaluated the complications including stricture and pneumonia, procedure time, en bloc resection rate, and frequency of local recurrence.

Results: In the case group, the average age was 67.3 years old, and the male-to-female ratio was 23:4. On endoscopy, all patients were found to have atrophic gastritis. Among the 145 patients, 84 (57.8%) were IIc, 26 (17.9%) were IIb, 4 (2.8%) were Ila, 1 (0.7%) was Ila-c, and 2 (1.4%) were IIa. The male-to-female ratio was 170:75. The average maximum size of lesions was 24.2 mm, and the histological depth of invasion was EP/LPM, MM, and SM2 in 306, 67, and 32 cases, respectively, and the mean procedure time was 54 min. ESD was performed for general anesthesia in 45 patients (11.1%). Damage of the muscular layer during treatment was observed in 5 patients, for which clipping was performed in 2 patients. Esophageal stricture was observed in 9 patients (41%), for which local injection of steroid was administered in 6 patients. No post-ESD bleeding was observed. Although perforation was identified in one patient, he recovered with conservative treatment. Chemoradiotherapy as additional treatments were conducted in Ipatient. No local recurrence was observed during an average duration of follow-up of 34.1 months. In the control group, the average age was 65.9 years old, and the male-to-female ratio was 338:45. The average maximum size of lesions was 24.2 mm, and the histological depth of invasion was EP/LPM, MM, and SM2 in 306, 67, and 32 cases, respectively, and the mean procedure time was 54 min. ESD was performed under general anesthesia in 45 patients (11.1%). Damage of the muscular layer during treatment was observed in 91 patients (22.5%), for which clipping was performed in 38 patients. Esophageal stricture was observed in 14 patients (6.6%) of 213 patients with more than half of mucosal defect, for which local injection of steroid or PGA sheet were administered in 38 patients. No post-ESD bleeding was observed. Although perforation was identified in three patients, they recovered with conservative treatment. Surgery or chemoradiotherapy as additional treatments were conducted in 19 or 49 patients respectively. Local recurrence was observed in one patient during an average duration of follow-up of 41.8 months.

Conclusion: Safe ESD for superficial esophageal cancer in the cervical esophagus could be achieved under an appropriate management and successful local control was also confirmed. The stricture after ESD in the cervical esophagus developed significantly higher than those in the middle esophagus.

Disclosure of Interest: All authors have declared no conflicts of interest.

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antibiotics. There were no treatment-related deaths. On pathological examination, 20 were tubular adenocarcinomas, and 11 were tubular adenomas. Histologically, curative resection was obtained in 26 of the 31 lesions (83.9%). There were no differences in gross type (elevated type/frat and depressed type), tumor size, or histology between primary and metastatic lesions. However, locally advanced carcinoma (LNM) was significantly different (P = 0.029). Furthermore, there were significant differences in U/M (P = 0.016) and U/L (P = 0.014). There was a slightly higher frequency of metastatic lesions in the U area.

Conclusion: Metachronous lesions tended to develop in the U area. These results suggest that it is important to carefully observe the U area by surveillance endoscopy after ESD for gastric neoplasms.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP126 A SIMPLE SCORING SYSTEM TO STRATIFY CURABILITY AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION FOR EARLY GASTRIC CANCER WHICH HAS PATHOLOGICAL FACTORS HIGHLY RELATED WITH LYMPH NODE METASTASIS: DEVELOPMENT AND VALIDATION OF “ECURA SYSTEM”


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Introduction: According to the European and Japanese guidelines for endoscopic submucosal dissection (ESD) of early gastric cancer (EGC), radical surgery is recommended for patients after ESD that does not meet the curative criteria because of the potential risk of lymph node metastasis (LNM). However, as LNM occurs in only 5–10% of patients who undergo radical surgery, this recommendation may be overestimated.

Aims & Methods: This multicenter study aimed to establish a scoring system (eCura system) for deciding the potential risk of LNM after ESD with pathological factors related with LNM. Of the 15,785 consecutive patients who underwent ESD for EGC from January 2000 to August 2011, we retrospectively reviewed 2,006 patients who did not meet the curative criteria for ESD of EGC. This study consisted of two stages. First, the risk-scoring system for LNM was developed using multivariate logistic regression analysis in 1,101 patients who underwent radical surgery after having failed to meet the curative criteria. The estimated factors were tumor size (>30 mm), tumor depth (submucosal invasion ≥500 μm: SM2), histopathological type (undifferentiated-type), lymphatic invasion, venous invasion, ulceration (scar), and positive vertical margin. We then validated the risk-scoring system in patients who underwent radical surgery, and the estimated factors were tumor size (30 mm), tumor depth (submucosal invasion >30 mm), lymphatic invasion, venous invasion, ulceration (scar), and positive vertical margin.

Conclusion: This scoring system predicted cancer-specific survival, which may be helpful to value the risk of LNM in patients after ESD that does not meet the curative criteria.

Disclosure of Interest: All authors have declared no conflicts of interest.


OP128 LONG-TERM OUTCOME OF THE INCIDENCE RATE OF METACHRONOUS GASTRIC CANCERS AFTER HELICOBACTER PYLORI ERADICATION – A FOLLOW-UP AND ANALYSES OF JAPAN PICY STUDY GROUP ENROLLED PATIENTS

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Introduction: The author and Japan Gast Study Group (JGSG) reported that the eradication of Helicobacter pylori reduced the incidence of metachronous gastric cancers (GC) after endoscopic mucosal resection significantly in the Lancet study [1] and also in our study [2].

Aims & Methods: We analyse long-term outcomes of the incidence rate of metachronous GC for JGSSG enrolled patients at Yamagata Prefectural Central Hospital. Out of 89 enrolled patients, 6 patients died by other diseases and 43 patients were introduced to other clinics and hospitals, therefore 40 patients (the eradication group 21, the non-eradication group 19) were followed-up at Yamagata Prefectural Central Hospital. After this Lancet study, non-eradication patients were recommended to receive an eradication therapy. Patients have been followed-up once a year endoscopically. Among 40 patients, the last follow-up case is in 15th observation year. A long-term incidence rate of metachronous GC was analysed and compared between the two groups.

Results: Out of the eradication group, 1 metachronous GC was detected (9 years 7 months after the enrollment). Out of the non-eradication group, 4 metachronous GC were detected (5 years 3 months, 6 years 7 months, 10 years 2 months, 13 years 10 months after the enrollment). When these 4 lesions were detected, 3 cases were not eradicated and 1 case was eradicated unsuccessfully. The incidence rate of metachronous GC of the eradication group was 4.8% but that of the non-eradication group was 21.1%.

Conclusion: The incidence rate of metachronous GC of the non-eradication group was about four times higher that of the eradication group even in 15th observation year. All 4 cases of metachronous GC of the non-eradication group were persistent infected cases. The earlier eradication of Helicobacter pylori is recommended.

Disclosure of Interest: All authors have declared no conflicts of interest.

MONDAY, OCTOBER 17, 2016

**OP129 THE EFFECT OF PASIREOTIDE IN CYST REDUCTION OF ASPIRATION SCLEROTHERAPY IN PATIENTS WITH LARGE SYMPTOMATIC HEPATIC CYSTS, A RANDOMIZED CONTROLLED TRIAL**

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**Introduction:** Aspiration sclerotherapy is a therapeutic option for large symptomatic hepatic cysts. However, inadequate cyst reduction is frequently reported. Somatostatin analogues are able to curtail cyst volume. We hypothesized that combining the long-acting somatostatin analogue pasireotide (SOM230) with aspiration sclerotherapy would enhance hepatic cyst reduction.

**Aims & Methods:** Our aim was to test whether pasireotide could improve the efficacy of aspiration sclerotherapy of large symptomatic hepatic cysts. We conducted a single-center, randomized (1:1 ratio), double-blind, placebo-controlled trial with patients with a large (> 5 cm) symptomatic hepatic cyst. All patients underwent aspiration sclerotherapy. In addition, we randomized patients between two arms: (1) pasireotide 60 mg long-acting release (LAR) injection or (2) placebo (saline) injection. Injections were administered two weeks prior and two weeks after aspiration sclerotherapy. Primary endpoint was proportional cyst diameter reduction after six weeks, as measured by ultrasonography. Secondary outcomes included long-term diameter reduction at 26 weeks, symptomatic change at 26 weeks, and safety during the study. Symptomatic change was evaluated using the polycystic liver disease-questionnaire (PLD-Q) that assesses frequency and severity of 14 disease-specific symptoms leading to a total PLD-Q sum score.

**Results:** Thirty-four patients (32 females (94%); mean age 53.6 ± 7.8 years) were randomized between pasireotide (n = 17) and placebo (n = 17). Pasireotide did not improve efficacy of aspiration sclerotherapy at six weeks compared to controls (23.6% [IQR 9.6–31.8%] versus 21.8% [IQR 9.6–31.8%], respectively; p = 0.96). Long-term cyst diameter reduction was similar in both groups (49.1% [IQR 27.0–73.6%] and 45.5% [IQR 29.2–59.6%]; p = 0.90). Mean PLD-Q scores improved significantly in both groups (p < 0.01) indicating symptomatic relief, but there were no differences between groups (p = 0.92). Transient hyperglycaemia was seen in all patients allocated to pasireotide.

**Conclusion:** Aspiration sclerotherapy is a highly effective treatment option of large symptomatic hepatic cysts, spiking with pasireotide does not further improve efficacy.

**Disclosure of Interest:** J.P.H. Drenth: Novartis provided the study drug and partially funded this investigator-initiated study. Novartis did not have any influence on the execution of the trial or the preparation of the manuscript.

All other authors have declared no conflicts of interest.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**OP130 A STUDY TO INVESTIGATE THE EFFECT OF PASIREOTIDE ON CYST REDUCTION OF ASPIRATION SCLEROTHERAPY WITH LARGE SYMPTOMATIC CYSTS**

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**Introduction:** Knowledge of pathogenic spectrum for cholangitis is important for adequate empiric therapy. *Enterococcus* species, which come well equipped with a variety of intrinsic antibiotic resistances, are sometimes isolated. However, little is known of risk factors for this organism’s isolation in patients with cholangitis. We conducted a study to investigate them on the basis of single-center experience in Japan.

**Aims & Methods:** Consecutive 191 hospitalized patients with cholangitis with positive bile and/or blood culture between January 2009 and October 2015 were enrolled. Diagnosis of cholangitis was based on clinical symptoms, blood chemistry and radiological imaging. Potential risk factors for *Enterococcus* species isolation such as patient attributes (Age, sex, underlying conditions, and past history) were retrospectively investigated. Univariate and multivariate analyses to identify risk factors were performed using a proportional hazards model.

**Results:** 127 patients were men (67%). The average age was 74.2 (34–97) years. *Enterococcus* species were isolated in 128 episodes from bile and/or blood culture. Age over 75 years old (OR 5.895; 95% CI 1.301–26.71; P = 0.001), presence of device in biliary tract (OR 5.895; CI 1.301–26.71; P = 0.001), and biliary reconstruction (OR 5.895; CI 1.301–26.71; P = 0.001) were independent risk factors for *Enterococcus* species isolation in cholangitis.

**Conclusion:** We found prior endoscopic sphincterotomy and biliary reconstruction were independent risk factors for *Enterococcus* species isolation in cholangitis. We should consider empirical therapy with anti-enterococcal antibiotics when managing patients with these attributes.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**OP131 MENOPAUSAL HORMONE THERAPY AND RISK OF BILIARY TRACT CANCER**

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**Introduction:** The risk of developing biliary tract cancer, including cancers of the gallbladder and extrahepatic bile ducts, may be influenced by estrogen...
Introduction: Hepatopulmonary syndrome (HPS) is a severe pulmonary complication of liver disease for which no medical treatment is available. In rats, common bile duct ligation (CBDL) has been documented as a model for human HPS, which is characterized by pathological pulmonary angiogenesis. Studies in genetically modified mice could offer opportunities for further research. However, in this species the development of pulmonary angiogenesis in biliary cirrhosis has not been outlined yet.

Aims & Methods: We aimed to elucidate the temporal changes in proangiogenic signature of hepatic and pulmonary vascular bed after CBDL in mice and in addition identify potential proangiogenic factors contributing to the pathogenesis of HPS. Male Swiss mice underwent CBDL or sham surgery and were sacrificed at a weekly basis for 6 consecutive weeks. Pulmonary inflation was studied by cytology on broncho-alveolar lavage fluid, myeloperoxidase assay and lung wet-to-dry ratio.

Results: CBDL progressively induced liver fibrosis from week 1 (F0−1) to week 6 (F4). This was accompanied by a gradual increase in hepatic immunopositivity for Endoglin and von Willebrand Factor, two markers of endothelial cell activation (P < 0.0001). Hepatic and pulmonary vascular growth factor (VEGF), VEGF receptor 1 and 2 were significantly increased at week 6, whereas placental growth factor (PIGF), which is exclusively involved in pathological angiogenesis, was already upregulated at week 2 (P = 0.0001). In the pulmonary compartment, CBDL resulted in neutrophil infiltration and increased pro-inflammatory mediators from week 2 to 6 (all P < 0.0001). Pulmonary immuno-reactivity for Endoglin and von Willebrand Factor progressively increased from week 4 to 6, while PIGF was already increased from week 2 onwards (all P < 0.0001). Scanning electron microscopy revealed regions of abnormal vascular architecture, mainly located at the pleural side, decreased intercapillary distance (P < 0.0001) and increased capillary density (P < 0.0005) in lungs of cirrhotic mice.

Conclusion: CBDL in mice is associated with pathological pulmonary angiogenesis and may represent a model for human HPS. In addition, we point to PIGF as an early indicator of pathological hepatic and pulmonary angiogenesis.

Disclosure of Interest: S. Raevens: Sarah Raevens is sponsored by the Research Foundation Flanders (FWO14/ASP/200). S. Lefer: Sander Lefer is sponsored by the Research Foundation Flanders (FWO15/ASP/146). X. Verhelst: Xavier Verhelst is sponsored by the Research Foundation Flanders (170021/IN). H. Van Vlierberghe: Hans Van Vlierberghe is senior clinical investigator of the Research Foundation Flanders. All other authors have declared no conflicts of interest.
polyps and the attribution of neoplastic polyps and nonneoplastic polyps was calculated. For the evaluation of prevalence of gallbladder polyps, we obtained the total number of cholecystectomies between 2003–2013 from PALGA.

**Results:** In total 220,612 cholecystectomies were performed over the period 2003–2013. The PALGA search identified 4532 excerpts, representing 4549 patients. A total of 337 patients were excluded due to primary non-gallbladder surgery, leaving 4012 unique cholecystectomies. In 2083 cholecystectomies (0.9%), a polyloid lesion was present. Which results in a calculated prevalence of polyps in 944,100,000 patients who undergone cholecystectomy. Of the polyps, 1172 (36.8%) were adenomatous polyps, 57 (13.3%) adenocarcinomas, and 57 (2.7%) other malignancies. Nineteen hundred and ten (43.7%) polyp were nonneoplastic; 375 (18%) cholesterol polyps, 334 (16%) adenomyoma’s, 70 (3.7%) hyperplastic polyps, 54 (2.6%) mucosal polyps, 42 (2%) inflammatory polyps, 18 (0.9%) papilloma’s and 17 (0.8%) other types of polyps.

**Conclusion:** Approximately one percent of gallbladders contain a polyp on histopathological assessment after cholecystectomy. Fifty-six percent of the polyps after cholecystectomy are neoplastic.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References:**

**MONDAY, OCTOBER 17, 2016 15:45–17:15 MECHANISMS OF LIVER CANCER AND PORTAL HYPERTENSION – ROOM 1.06

**OP135 CHANGES IN CIRCULATING MICRORNA AFTER TREATMENT: MICRONORA SIGNATURES TO PREDICT THERAPY RESPONSE AND DISEASE FREE SURVIVAL IN HEPATOCELLULAR CARCINOMA**

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**Aims & Methods:** Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death worldwide. Although treatment options have improved in the past 30 years, prognosis remains unfavorable in many patients. The lack of effective models for outcome prediction prevents the opportunity for individualised treatment. The potential role of microRNAs (miRNAs) as prognostic biomarker has witnessed an increasing interest, owing to the non-invasive nature of miRNA-based screening assays. While many studies have suggested several miRNAs as biomarker candidates, dynamic variations over extended time periods have been assessed until now.

**Aims & Methods:** To identify potential circulating miRNA signatures for the prediction oftherapy response and patient follow-up. Methods: 15 consecutive patients with early-intermediated stage HCC were enrolled and treated according to the ESSL/AASLD practice guidelines. Patients were staged (CT scan and/or MRI) at time 0 (T0, before treatment), 1 month (T1) and 6 months (T6) from the starting of the therapy. Pax-gene Blood RNA tubes and Vacuette tubes were used to collect the circulating miRnome remained significant in all time points indicating a persistent p-mTOR and up-regulated Beclin-1/Vps34 proteins were detected in the intra-hepatic Treg cells. In HBV-infected mouse models, the intra-hepatic HMGB1, was indispensible to maintain Foxp3, CTLA-4, IL-10 and TGF-beita mRNA expression and increased intracellular mass of lysosomes. The mean fluorescence intensity (MFI) of lysosomes in Treg cells significantly and positively correlated with the following

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References:**

**Disclosure of Interest:** All authors have declared no conflicts of interest.
OP138 RIOCIGUAT, A STIMULATOR OF THE GUANYLYL CYCLASE, REDUCES LIVER FIBROSIS AND PORTAL PRESSURE IN CIRRHOTIC RATS

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Introduction: Intrahepatic nitric oxide (NO) signaling including activation of its receptor, guanylyl cyclase (GC) is impaired in cirrhosis. The GC stimulator riociguat (RIO) is approved for treatment of pulmonary hypertension. Experimental studies suggest anti-fibrotic effects of RIO. We investigated the effects of RIO in cirrhotic rats with portal hypertension (PHT).

Methods: Male Wistar rats were studied. 15 of which were left untreated and 39 received b.i.d. alcohol (7.5% w/v) or ethanol infusion with balloon catheter in a pig model. Acta Radiol 2005; 46: 344–52.

Results: PV-CV and lobule area showed no significant difference between E and Cont at d0, but were lower in E than in Cont at w2, w4 or w6 (P < 0.001). Hepatocyte number was not significantly reduced in E at d0 and w2 but was reduced in E at w4 and w6 (P < 0.001). Hepatocyte activity was higher E in Cont at d0 and w4. LC3 staining peaked in E at w2, with no significant difference between E and Cont at w4 and w6. GS and CYP2E1 areas in E at w2, w4 and w6 were narrower than those in Cont.

Conclusion: Our morphological study focused on changes in the lobules over time, and we observed two distinct phases of liver atrophy following portal blood flow disruption. The first (the autophagic phase) was characterized by cellular shrinkage without hepatocytic loss and high LC3 expression, and lasted for the first two weeks following PTPE. The second phase, termed the apoptotic phase, was characterized by reduced hepatocyte number without reduced lobular size but with reduced LC3 expression and increased TUNEL staining, and lasted 2–4 weeks.

Disclosure of Interest: All authors have declared no conflicts of interest.

References


received TAA for 16 weeks, 46% (11/24) developed liver fibrosis with a Desmet score of 1–3 (group 16w/fib) and 54% (12/22) had liver cirrhosis as a Desmet score of 4 (group 16w/cir). The untreated rats (15/54) served as control group (con group). Mean portal vein showed no significant differences among all groups. However mean portal flow velocity was reduced by 15% in group 12w/fib, 11% in group 16w/fib and 9% in group 16w/cir compared to group con. In contrast mean portal flow volume per body weight was significantly lower than that of group fib. Thus flow volumes were adjusted according to the body weight in order to eliminate weight-induced changes in hemodynamics. Mean aortal flow volume per body weight showed no significant differences among all groups. In contrast mean portal flow volume per body weight was significantly reduced in group 12w/fib by 23% compared to group con. On the other hand, in group 16w/fib and group 16w/cir there was no further reduction of mean portal flow volume per body weight compared to group fib so that in the majority of TAA-induced liver injuries the development of fibrosis is sufficient to cause a significant decrease in portal flow volume. There were no significant differences between group 12w/fib and 16w/fib in terms of all parameters, in particular portal flow volume.

Contact: The non-invasive test technique can be a reliable diagnostic tool to investigate the hepatic hemodynamics in different experimental models of liver injury. In this particular animal model even the TAA-induced liver fibrosis led to a significantly reduced portal perirusion. The molecular mechanisms of a left need to be further investigated.

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 08:30-10:00

OPTIMISING ANTI-TNF THERAPY – ROOM G

OP141 CORRELATION OF ENDOSCOPIC FINDINGS WITH SERUM DRUG CONCENTRATIONS AND NEED FOR RESCUE THERAPY: SUBANALYSIS OF THE TROUGH CONCENTRATION ADAPTED INFLIXIMAB TREATMENT (TAXIT) TRIAL

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Introduction: The Trough Concentration Adapted Infliximab Treatment (TAXIT) randomized controlled trial [1] showed that patients' infliximab trough concentrations to a 3–7 μg/mL window resulted in a more efficient use of the drug in patients with inflammatory bowel disease. Following dose optimization, continued concentration-based dosing was not superior to clinically-based dosing for achieving clinical and biochemical remission (primary endpoint) after 1 year maintenance treatment. This subanalysis of TAXIT aims to explore the correlation between drug level-based dosing and endoscopic healing.

Aims & Methods: This was a retrospective analysis of all endoscopies performed at the end of TAXIT. For Crohn's disease (CD), mucosal healing was defined as absence of ulcerations (complete mucosal healing) or clear improvement in ulcerations (partial mucosal healing) when compared to baseline. Following dose optimization, continued concentration-based dosing was not superior to clinically-based dosing for achieving clinical and biochemical remission (primary endpoint) after 1 year maintenance treatment. This subanalysis of TAXIT aims to explore the correlation between drug level-based dosing and endoscopic healing.

Results: Of the 226 patients completing the TAXIT maintenance phase, 125 (55%) underwent endoscopy after one year (33 in arm 1; 55 in arm 1 and concentration-based dosing arm 2) and infliximab trough concentrations were correlated to the degree of healing.

Conclusion: The primary endpoint of TAXIT, clinical and biochemical remission, combined with endoscopic healing. Similar rate of mucosal healing were observed in patients after clinically-based dosing compared to concentration-based dosing. A trend towards less mucosal healing was seen if rescue therapy was needed during TAXIT. Mean serum trough concentrations during the maintenance phase of TAXIT were not significantly different from baseline. However, mean portal flow velocity per body weight was significantly lower than that of group fib. Thus flow volumes were adjusted according to the body weight in order to eliminate weight-induced changes in hemodynamics. Mean aortal flow volume per body weight showed no significant differences among all groups. In contrast mean portal flow volume per body weight was significantly reduced in group 12w/fib by 23% compared to group con. On the other hand, in group 16w/fib and group 16w/cir there was no further reduction of mean portal flow volume per body weight compared to group fib so that in the majority of TAA-induced liver injuries the development of fibrosis is sufficient to cause a significant decrease in portal flow volume. There were no significant differences between group 12w/fib and 16w/fib in terms of all parameters, in particular portal flow volume.

Contact: The non-invasive test technique can be a reliable diagnostic tool to investigate the hepatic hemodynamics in different experimental models of liver injury. In this particular animal model even the TAA-induced liver fibrosis led to a significantly reduced portal perirusion. The molecular mechanisms of a left need to be further investigated.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference
Table (OP144): Clinical and serological evolution after dose de-escalation

<table>
<thead>
<tr>
<th>T-1 (n = 33)</th>
<th>T0 (n = 43)</th>
<th>T1 (n = 43)</th>
<th>T2 (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) time from T0</td>
<td>18.0 weeks (13.5–26.1)</td>
<td>14.0 weeks (12.3–19.0)</td>
<td>30.5 weeks (26.8–34.5)</td>
</tr>
<tr>
<td>Median (IQR) serum albumin</td>
<td>44.5 g/L (9.3–14.3)</td>
<td>7.5 g/mL (5.8–9.8) p &lt; 0.001</td>
<td>7.2 g/mL (5.4–8.6) p &lt; 0.001</td>
</tr>
<tr>
<td>Median (IQR) PRO2 UC</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
</tr>
<tr>
<td>Median (IQR) ADA serum level</td>
<td>11.6 µg/mL (9.1–15.1)</td>
<td>11.5 µg/mL (9.3–14.3)</td>
<td>11.5 µg/mL (9.3–14.3)</td>
</tr>
<tr>
<td>Median (IQR) CRP level</td>
<td>11.5 mg/L (9.1–15.1)</td>
<td>7.5 g/mL (5.8–9.8) p &lt; 0.001</td>
<td>7.2 g/mL (5.4–8.6) p &lt; 0.001</td>
</tr>
<tr>
<td>Median (IQR) albumin</td>
<td>44.5 g/L (42.6–47.0)</td>
<td>44.1 g/L (42.2–47.0)</td>
<td>43.7 g/L (41.6–47.2)</td>
</tr>
</tbody>
</table>

p-values: relative to T0, Wilcoxon Signed Rank test: IQR: interquartile range

Aims & Methods: In this retrospective cohort analysis, the outcome of dose de-escalation (ADM 40 mg every other week) in patients with inflammatory bowel disease (IBD) who are in clinical remission. Dose de-escalation may not only have beneficial economic repercussions, it may possibly also decrease the occurrence of adverse events.

Conclusion: In our study, dose de-escalation was widely used to optimise biological therapy in case of clinical relapse, less is known about possibilities to de-escalate ADM every other week, which was initiated a median of 28 months prior to dose de-escalation. Median PRO2 was 0, and median CRP level 1.4 mg/L. Reasons for dose de-escalation were ADM associated adverse events (AE, n = 1), serum levels above 2 µg/mL (n = 9), or a combination of both (n = 33). Most frequently reported AE were skin manifestations (52%), arthralgia (24%) and recurrent infections (21%). While ADM serum level dropped significantly 4 and 8 months after dose de-escalation, CRP levels remained stable (Table). In patients with CD a significant increase in PRO2 was observed.

Disclosure of Interest: S. Vermeire: Grants from MSD, Takeda and Abbvie, lecture fees from Abbvie, MSD, Falk, Tillotts, Ferring, Centocor, Takeda, Hospira; consultancy for Ferring, Abbvie, Shire, Genentech/Roche, Celgene, Janssen, MSD, Takeda, Galapagos, Hospira, Mundipharma, Pfizer.

All other authors have declared no conflicts of interest.

OP145 Efficacy and safety of biosimilar infliximab after one-year: Results from a prospective nationwide cohort


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Disclosure of Interest: All authors have declared no conflicts of interest.
Introduction: Biosimilar infliximab CT-P13 received positive CHMP recommendation in June 2013 for all indications of the originator product. It has been previously shown that CT-P13 is effective and safe in inducing remission in inflammatory bowel disease (IBD). However, prospective, long-term data on the efficacy and safety of the biosimilar infliximab in IBD are lacking.

Aims & Methods: A prospective, nationwide, multicentre, observational cohort was designed to examine the efficacy and safety of CT-P13 infliximab biosimilar in the maintenance treatment of Crohn’s disease (CD) and ulcerative colitis (UC). Demographic data were collected and a harmonized monitoring strategy was applied. Clinical remission, response and biochemical response were evaluated at week 14, 30 and 54. None of the patients had received infliximab within 12 months prior to initiation of the biosimilar infliximab. Safety data were registered.

Results: 291 consecutive IBD (184 CD and 107 UC) patients were included in the present cohort, of which 100 patients reached the week 54 endpoint. The age at disease onset was 23/28 years in CD/UC patients, respectively. 32/49% of CD patients had colonic/ileocolonic disease location, 41% had complicated disease behaviour, 35% had perianal disease and 23% had gone through previous surgery. 83/77/58% of UC patients had proctitis/left-sided colitis/extension colitis. 25/14% of patients had received previous anti-TNF therapy in CD and UC, respectively. 60/52% of CD/UC patients received concomitant immunosuppressives at baseline. 55, 57 and 47% of CD patients achieved clinical remission by week 14, 30 and 54. Clinical response was 83, 77 and 58%, respectively. 59, 46 and 53% of UC patients reached clinical remission by week 14, 30 and 54. Clinical response was 78, 69 and 64%, respectively. Previous anti-TNF exposure was associated with lower response and remission rates (p < 0.001). The mean CRP decreased from 14(±4.05) and p < 0.001 to 3.2(±1.3) and p < 0.01 for CD and from 18.6(±5.7) to 5.0(±1.8) and p = 0.004 for UC at weeks 14, 30 and 54. Mean CRP decreased significantly both in CD and UC patients by week 14, which was maintained throughout the 1-year follow-up. (CRP level decreased from 18.6 to 5.0 in CD and from 18.6 to 5.0 in UC; p = 0.006). 23 (7.9%) patients had infliximab reactions, 23 (7.9%) patients had infections and 1 death occurred. Conclusion: This prospective nationwide cohort shows that CT-P13 is effective and safe in inducing and maintaining remission in both CD and UC. Efficacy was influenced by previous anti-TNF exposure.

Disclosure of Interest: All authors have declared no conflicts of interest.

Introduction: Biosimilar infliximab (Inflectra®) is a cost-effective alternative to the originator infliximab for the treatment of luminal CD, and it may contribute to increasing the affordability of biological treatments throughout Europe.

Aims & Interest: F. Rencz received funding from Hospitaled Pfizer. P. B. Brosdzky: V. Brosdzky received funding and support for research on biosimilars from EGIS Pharma, and Hospira Pfizer. P. Bajj: P. Bajij received funding and support for research on biosimilars from Biosimilars, and Hospira Pfizer. M. Pentek: M. Pentek received funding and support for research on biosimilars from EGIS Pharma, and Hospira Pfizer. L. Gulacsi: L. Gulacsi has been paid as a consultant by Celltrion and received speaker’s honoraria from Celltrion, EGIS and Pfizer/Hospira and received speaker’s honoraria from Celltrion, EGIS and Pfizer/Hospira and unrestricted research funding from Pfizer/Hospira. All other authors have declared no conflicts of interest.

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All authors have declared no conflicts of interest.

Disclosure of Interest:
All authors have declared no conflicts of interest.
treatment produced extensive cell injury and reduced RGM1 cell viability by

A. Lanas5

Results: the quantitative expression of MT1 and MT2 in gastric epithelial and submucosal using Calcein AM live cell tracking dye and MTT assay; 3) cell proliferation were assessed: 1) cell injury under confocal microscopy, 2) survival and apoptosis of cultured rat gastric epithelial cells against indomethacin-induced protection of cultured rat gastric epithelial cells against indomethacin-induced gastric mucosal injury and whether it affects the expression of MT1 and -2, survivin, IGF-1 and IGFR-1 in these cells. In vitro study, the cultured normal rat gastric mucosal epithelial cells (RGM1) were pretreated with vehicle or melatonin (10 µM) for 24 hr and then exposed to either: medium alone (controls), or indomethacin (IND 0.25 mM) for 4 hr. In these cells the following were assessed: 1) cell injury under confocal microscopy, 2) survival and apoptosis using Calcein AM live cell tracking dye and MTT assay; 3) cell proliferation using BrdU assay; 4) quantitative expression of MT1 & 2, and survivin, IGF-1 and IGFR-1 by Western blotting and immunoassay.

For comparison, the relative expression of MT1 and MT2 in gastric epithelial and submucosal structures from full thickness wall specimens of a normal rat stomach was evaluated.

B. Marce´n

4) Rat gastric mucosa expressed both MT1 and MT2 (1.8-fold more MT1 than MT2, survivin, IGF-1 and IGFR-1 in these cells. In vitro study, the cultured normal rat gastric mucosal epithelial cells (RGM1) were pretreated with vehicle or melatonin (10 µM) for 24 hr and then exposed to either: medium alone (controls), or indomethacin (IND 0.25 mM) for 4 hr. In these cells the following were assessed: 1) cell injury under confocal microscopy, 2) survival and apoptosis using Calcein AM live cell tracking dye and MTT assay; 3) cell proliferation using BrdU assay; 4) quantitative expression of MT1 & 2, and survivin, IGF-1 and IGFR-1 by Western blotting and immunoassay.

Conclusion: 1) Melatonin directly protects the gastric mucosal epithelial cells against IND- induced injury and this effect is independent of systemic and neural factors, 2) rat gastric epithelial RGM1 cells express melatonin receptors MT1 and MT2 that are co-localized with survivin, IGF-1 and IGFR-1 indicating a protective role during and after the effect of melatonin derived from pineal gland, this indoleamine can protect the gastric epithelial cells possibly due to its local autocrine and paracrine actions and interactions with survivin, IGF-1 and its receptor.

Disclosure of Interest: All authors have declared no conflicts of interest.

OPI49 RISK OF REBLEEDING, VASCULAR EVENTS AND DEATH AFTER GASTROINTESTINAL BLEEDING IN ANTICOAGULANT AND/OR ANTIPLATELET USERS

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Introduction: Patients who develop gastrointestinal (GI) bleeding during anticoagulant (AC) and/or antiplatelet (AP) therapy represent a clinical challenge. Considering the higher risk of either long-term interruption or administration of these treatments will have important clinical implications concerning the risk of vascular, GI bleeding and death events. Differences on the risks between AP or AC users after drug resumption are not well established.

Aims & Methods: We aimed to determine the rate of rebleeding, vascular events and death in a cohort of patients treated with AP or AC agents who developed a major GIB (upper or lower) event. To compare these risks depending on the treatment adopted after the GIB event.

Methods: Retrospective long-term observational cohort study of patients who developed GIB while on AP and/or AC treatment from March 2008 to August 2013. Drug use information was prospectively collected during the GIB event. Data concerning the follow-up period, which extended until December 31st 2013 were obtained from databases of different Spanish Health care areas. Primary outcomes were vascular event, GI rebleeding and death from any cause. Statistical analyses were performed using SPSS software version 22.0.

Results: Rebleeding events were included (mean age 78.7 ± 8.9; 56.6% males; 52.8% (409/774), 38.5% (298/774), 8.7% (67/774) were on AP, AC or AP+AC therapy respectively. 22.6% of patients presented rebleeding, 17.1% ischemic event and 26.0% death during the follow up (median 23 months). Following the index GIB, rebleeding event was interrupted in 101 (13.1%) of patients, although 80.1% (572/ 714) resumed afterwards (median time 6 days (1–370). Resumption of therapy was associated with higher risk of rebleeding (3.5% vs 24%/p < 0.001) but lower risk of death (43.7% vs 19.9%/p < 0.001). Early resumption of therapy (<7 days vs ≥7 days) was associated with a higher rate of rebleeding (p < 24%/p < 0.001), with no statistical differences in GI events. AC users had higher death risk (OR 1.5; 95%CI: 1.1–2.2) compared to AP users. Dual AP users had higher risk of ischemic events (OR 2.1; 95%CI: 1.3–3.7). Rebleeding event rates were 85 and 120 events per 1000 pt-year with AP and AC users respectively. The corresponding event rates were 71 and 82 per 1000 pt-year for vascular events, and 93 and 144 respectively for deaths.

Conclusion: Nearly 40% of patients presented a new adverse event related with AP/AC treatment during the follow-up. The risk of death is higher in patients on AC therapy compared with AP users. Resumption of AC/AP therapy is associated with higher risk of rebleeding and lower risk of death without any influence on ischemic events. Results suggest that AC/ AP agents for more than 7 days is associated with significant higher risk of ischemic events.

Disclosure of Interest: A. Lanas: Professor Lanas has been an advisor for AstraZeneca, Bayer and Pfizer. All other authors have declared no conflicts of interest.

OPI50 NOVEL 4-THIAZOLIDINONE DERIVATIVES AS CYTOPROTECTIVE AGENTS AGAINST NSAID-INDUCED INJURY

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Introduction: Hydrogen sulfide (H2S) and prostaglandins are an important mediator of mucosal defense and suppression of its synthesis by NSAIDs leads to increased susceptibility to enteropathy. H2S also exerts a number of anti-inflammatory effects. Thus, the ability of H2S to promote the healing of the damage tissue and to resolution of inflammatory response has been exploited in the development of novel therapeutic agents.

Aims & Methods: The purpose of our study was to investigate the role of 4-thiazolidinone derivatives (compounds Les-5044 [5-(3,5-Di-tert-butyl-4-hydroxy-benzylidene)-2-thioxo-thiazolidin-4-one] and Les-5053 [3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-mercapto-acrylic acid]) as a novel H2S donors in promoting the resolution of inflammation and injury in small intestine. The study was conducted on 40 white rats weighing 180–250 g according to the ethical requirements concerning the work with the laboratory animals. Animals were divided into 4 groups: I – control; II – small intestinal injury produced by indomethacin (IM) in the ulcerogenic dose (35 mg/kg, subcutaneously) per 72 h; III, IV – compounds Les-5044 and Les-5053 were administered three times per 72 h intragastrically at a single dose 10 mg/kg on the background of NSAID- induced injury. Then the rats were sacrificed and in small intestinal mucosa were measured the MOS and arginase activity, concentration of nitrite and nitrate and MDA, activity of enzymes of the antioxidant protection system (SOD and catalase) and MPO activity; the concentration of L-arginine and H2S in blood plasma.

Results: IM injection manifested by erosions and hemorrhages and leads to the following changes: the activity of INOS increased more than threefold (P < 0.01) as well as the content of nitrite enhanced in two times while arginase activity decrease more than 4 fold (P < 0.01); enhanced activity of lipid peroxidation process manifested by increase of MDA concentration for 5.3 fold (P < 0.01), MPO activity enhanced more than 4 fold (P < 0.01) and catalse activity – by 32% (P < 0.01). Compound Les-5044 displayed significant cytoprotective effect and decreased the total area of hemorrhagic lesions for 63% (P < 0.01). The administration of Les-5054 on the background of IM decreased the activity of iNOS for 35% (P < 0.01), and activity of eNOS increased for 52% (P < 0.01), MDA concentration declined for 32% (P < 0.01), H2S concentration increased for 24% (P < 0.05) as compared with indices of the second group. Compound Les-5055 decreased the total area of hemorrhagic lesions for 71% (P < 0.05) as compared with independent action of indomethacin. Parameters of NO-synthetic system in Les-5055-treated group showed the same tendency as under the effect of Les-5054.

Conclusion: Administration of 4-thiazolidinone derivatives on the background of indomethacin induced injury reduce the activity of iNOS, myeloperoxidase, intensity of lipid peroxidation and increase generation of H2S, that may be linked with the structure of this compounds. However compound Les-5054 showed more efficacious effect and antioxidant properties than compound Les-5055. Thus, the novel 4-thiazolidinone derivatives, particularly compound

United European Gastroenterology Journal 4(5S)
Introduction: There was considerable individual variability in NSAID-induced small intestinal injury in previous studies on healthy subjects. Several studies reported that several single nucleotide polymorphisms (SNPs) were associated with gastrointestinal bleeding and ulceration. However, the studies investigated only a few candidate SNPs in the enzymes of metabolizing NSAIDs and arachidonic acid cascade. Therefore, a comprehensive analysis was necessary to identify other unknown SNPs having a stronger effect on NSAID-induced small intestinal injury than the reported SNPs.

Aims & Methods: The aim of the study was to identify the SNP most significantly involved with NSAID-induced small intestinal mucosal injury. One-hundred fifty healthy subjects were enrolled from an RCT which compared standard 16 days with five or more mucosal breaks (severe injury group) after 14-day treatment between coxib mono-therapy and concomitant treatment with loxoprofen and lansoprazole. Details of the RCT were reported by Fujimori S et al (1). After the RCT, subjects were divided into three groups on the basis of numbers of increasing small intestinal mucosal breaks after NSAIDs treatment with zero (No injury group), one to four (Mild injury group), and five and more mucosal breaks (Severe injury group). A genome-wide association study (GWAS) was conducted among the three groups to detect the SNP which was the most associated with NSAID enteropathy.

Results: After RCT and GWAS analysis, 70 subjects receiving the lansoprazole treatment and 69 subjects receiving the coxib treatment were determined to be eligible for analysis. The minimum p-value was detected in the analysis between 16 cases with five or more mucosal breaks and the reported SNPs. In the GWAS, five SNPs in bactericidal/permeability-increasing fold-containing family B member 4 (BPIFB4) gene showed the lowest p-value (p = 2.69 x 10^{-7} with an odds ratio of 40.91). Among the five SNPs, four were nonsynonymous SNPs (rs2070325: V268I, rs2889732: T230N, rs1169909: F527L, rs11696307: T533I, rs11696316: intronic).

Conclusion: Although SNPs that surpassed the genome-wide significance level (p < 5 x 10^{-8}) were identified through GWAS, results seemed to indicate that the SNPs of BPIFB4 were associated with NSAID-induced small intestinal mucosal injury. (UMIN: 00007936) The GWAS was financially supported by grants from the Project for Development of Innovative Research on Cancer Therapeutics and from the Tailor-made Medical Treatment Program (BioResource Bank of Japan) funded by Ministry of Education, Culture, Sports, Science and Technology of Japan.)

Disclosure of Interest: S. Fujimori: Dr. Fujimori has received grant/research support from Astellas Pharma Inc., Covidien Co. Ltd., Daich-Sankyo Co. Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Pfizer Japan Inc., and, Zenra Co., Ltd. K. Iwakiri: Dr. Iwakiri has received grant/research support from Astellas Pharma Inc., Daich-Sankyo Co. Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Takeda Co., Ltd., and, Zenra Co., Ltd. C. Sakamoto: Dr. Choitsu Sakamoto has received speaker fees from Pfizer, Astellas, and AstaZeneca. All other authors have declared no conflicts of interest.

Reference

Disclosure of Interest: All authors have declared no conflicts of interest.

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Disclosure of Interest: All authors have declared no conflicts of interest.

Disclosure of Interest: All authors have declared no conflicts of interest.

Disclosure of Interest: All authors have declared no conflicts of interest.
Aims & Methods: We aimed to study (1) the rate of AEs and (2) factors associated with occurrence of AEs in patients undergoing POEM. Methods: Patients who underwent POEM for the treatment of achalasia and SEDs at 12 tertiary-care centers (5 US, 4 Europe, 2 Asia and 1 Australia) between 2011 and 2015 were used in a case-control study. Cases were defined by the occurrence of any AEs related to POEM procedure. Control patients were selected for each AE case by matching for age, gender, disease classification (type I/II vs. type III/SEDS). All pertinent data including AEs were collected and their severity was graded according to the ASGE lexicon’s severity grading system.

Results: A total of 1826 patients underwent POEM during the study period. Overall, 153 AEs occurred in 137 patients (7.5%). A total of 48 inadvertent mucosotomies occurred and represented the most common AE of POEM (31% of all AEs, overall incidence 2.8%). Mild, moderate and severe AEs occurred in 102 (74.5%), 26 (19%) and 9 (6.5%) patients, respectively. Among the 9 severe AEs, 2 were esophageal leaks, 1 perforation, 1 aspiration pneumonia, 1 empyema, 1 pneumomediastinum, 1 cardiac arrhythmia and 2 delayed bleeding. There were no deaths related to POEM. When patients with AEs were compared with a control group (case-control analysis), there was no difference between the 2 groups in terms of Charlson comorbidity index/ASA class, prior therapy, sigmoid esophagus, operator specialty, direction of myotomy (anterior vs. posterior), type of knife used, extent and length of myotomy, and operator experience. However, time of procedure was significantly longer in cases compared to controls (123 min ± 90 min vs. 103 min ± 38, p < 0.002). Length of stay was significantly higher in patients who experienced AEs (4.9d vs. 2.7d, p < 0.001).

Conclusion: POEM as a safe alternative to Heller Myotomy. However, the safety of POEM is still debated since comprehensive analysis of adverse events (AEs) associated with POEM in large cohort studies has not been performed.

References
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Table (OP154)

<table>
<thead>
<tr>
<th>Age ≤ 50 50–64 65–79 &gt; 80</th>
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<tr>
<td>Aspirin Group (n = 254,887)</td>
</tr>
<tr>
<td>24,067 (9.4%)</td>
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<tr>
<td>121,671 (47.4%)</td>
</tr>
<tr>
<td>57,690 (11.7%)</td>
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<td>232,319 (47.2%)</td>
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| Sex – Male | 136,534 (53.8%) |
| Duration of Aspirin Prescribed 1 month to < 6 months 6 months to < 3 years 3 years to < 5 years 5 years to < 10 years 10 years or more |
| 48,591 (19.1%) | 44,516 (17.5%) | 34,013 (13.3%) | 49,451 (19.4%) | 78,316 (30.7%) |

*Not Applicable for the Patients in Non-Aspirin Group.

POEM (n = 1) and Heller myotomy (n = 2) and clinical response was noted in 2 of them. Of 171 patients with available data, 24% of patients reported reflux symptoms after POEM. Reflux esophagitis was noted in 26 patients of 144 (18%) who had EGD after POEM. 15% of asymptomatic patients had reflux esophagitis.

**Conclusion:** POEM is safe and provides high initial clinical success and excellent long-term outcomes. Less than 10% of patients who had clinical response at 6 months had recurrent symptoms at 2 years. History of prior pulmonary delay is associated with clinical failure. Post-POEM symptomatic reflux occurs in quarter of patients, and esophagitis is found in 15% of asymptomatic patients.

**Disclosure of Interest:** S. Roman: Sabine Roman is a consultant for Medtronic and Sandhill Scientific
F. Mion: Francois Mion is a consultant for Medtronic
M. Kashah: Mounesh Kashah is a consultant for Boston Scientific
All other authors have declared no conflicts of interest.

**OP155 MAJOR PERI-OPTERATIVE ADVERSE EVENTS OF PERORAL ENDOSCOPIC MYOTOMY (POEM): 5 YEARS’ EXPERIENCE, 1680 PATIENTS**

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**Introduction:** Peroral endoscopic myotomy (POEM) is now a widely used treatment for esophageal achalasia, supported by several large cohort studies. Although major perioperative adverse events (mAE) are rare, in-depth investigations of related risks and preventive measures are lacking.

**Aims & Methods:** Hence, mAE during POEM were systematically assessed in terms of incidence, risks, prevention, and management. This retrospective single-center analysis included all patients (N = 1680) undergoing POEM between August, 2010 and July, 2015 at our facility. Major adverse events were defined as follows: vital-sign instability, required ICU stay, hospital readmission, conversion to open surgery, invasive postoperative procedure, blood transfusion, or hospitalization > 5 days due to functional impairment.

**Results:** A total of 55 patients (3.3%, 95% confidence interval [CI] 2.5–4.2%) suffered mAE, distributed as follows: delayed mucosal barrier failure, 13 (0.8%, 95% CI 0.4–1.3%); delayed bleeding, 3 (0.2%, 95% CI 0.4–0.6%); hydrothorax, 8 (0.5%, 95% CI 0.2–0.9%); pneumomediastinum, 25 (1.5%, 95% CI 1.0–2.2%); and miscellaneous, 6 (0.4%, 95% CI 0.1–0.6%). Four patients (0.2%) required ICU admissions. No surgical conversions occurred, and 30-day mortality was zero. In stepwise multivariate regression, experience < 1 year (OR = 3.85, 95% CI 1.49–9.95), air insufflations (OR = 3.41, 95% CI 1.37–9.50), and mucosal edema (OR = 2.01, 95% CI 1.14–3.55) were identified as related risk factors. After introducing CO2 insufflation, mAE rate declined to 1.9% (95% CI 1.2–2.7%) and seemed to plateau after 3.3 years at ~1%.

**Conclusion:** In general, POEM is a safe procedure. Major adverse events are rare and usually may be prevented or anticipated and conservatively managed.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References**

Conclusion:
Prior PD (OR 3.36, p = 0.01) were significantly associated with clinical failure.

Disclosure of Interest:
94%, p = 0.02). Mean post-POEM ES was also higher in the HM group (2.09 vs. 1.7; p = 0.009). Two patients underwent complications related to the procedure: one was a bleeding due to an ulceration along the tunnel path (coagulation necrosis) treated by endoscopy, while the other was a renal insufficiency and was transferred to intensive care unit; the second had a secondary perforation of an acute gastric ulcer, which was managed endoscopically by a naso-cystic drain and fasting, with excellent outcomes. All the other patients could be refeed at POD2-3, and discharged at POD5-6, with PPI treatment.

Conclusion: Per-oral endoscopic pyloromyotomy seems to be an effective approach for treating patients with severe refractory gastroparesis. This procedure is also highly reproducible, when applying some tips to increase the technical success rate, and safe with complication that could be managed endoscopically. It could be a new hope for a many patients whom have a poor quality of life. More data, especially in prospective studies are needed to confirm these very promising results.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:

TUESDAY, OCTOBER 18, 2016 08:30–10:00
LIVER FIBROSIS: FROM MECHANISM TO THERAPY - ROOM 1.61/1.62

OP59 EXPRESSION OF CONSTITUTIVELY ACTIVE IKK2 LEADS TO LIVER FIBROSIS AND INCREASED CARCINOGENESIS IN THE BACKGROUND OF LIVER SPECIFIC TRP53 DELETION
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Introduction: Liver carcinoma is of particular importance, since it is a leading cause of cancer-related deaths worldwide. Most frequently liver tumors are arising in the context of inflammatory and consequent sequence of liver fibrosis which primarily develops subsequently due to chronic liver diseases. Another circumstance contributing to liver cancer formation is the disruption of the p53 signaling pathway. In human liver tumors, p53 mutations are associated with a poor prognosis. In this study, we analyzed the cooperation between loss of p53 and inflammatory response in the liver.

Aims & Methods: To investigate the sequence of inflammation and Trp53 deletion, we combined two transgenic mouse models. For modulation of an inflammatory response, we used an inducible mouse model (Tet-Off system) with a permanent expression of a constitutively active IKK2 isoform (CAIKK2). The expression of CAIKK2, starting from birth, leads to a continuous activation of the NF-kB pathway, simulating chronic inflammation. For the modulation of a p53 deletion, the inducible Cre transgenic mouse expressing line AlfpCre-ERT2 was crossed with a conditional Trp53 knockout mouse. Tamoxifen treatment at the age of four weeks induces liver-specific deletion of Trp53.

Results: Expression of the constitutively active IKK2 isoform leads to liver fibrosis development, increased proliferation in the liver and elevated expression of inflammatory markers independent of the p53 status. During ageing, the CAIKK2 expression and the inflammatory response decreased, the liver fibrosis was reversible. The tumor incidence at the age of 9-12 month in CAIKK2/Trp53Δ/Δ mice is significantly higher (67%) compared to CAIKK2 mice with wild-type Trp53 (25%). Mice with induced liver-specific Trp53 deletion did not exhibit liver tumor formation at the same age. The majority of liver tumors in CAIKK2/Trp53Δ/Δ mice show intrahepatic cholangiocarcinoma (ICC) (81%) next to hepatocellular carcinoma (2%) and combined HCC/ICC (17%). In contrast, CAIKK2 mice with wild-type Trp53 developed mainly HCC (50%), but also ICC (25%) and HCC/ICC (25%) at lower level.

Conclusion: The study shows that liver-specific Trp53 deletion in combination with an inflammatory background results in elevated tumor incidence and leads to an increased occurrence of ICCs in the liver.

Disclosure of Interest: All authors have declared no conflicts of interest.
OP160 EXPRESSION OF CD161 ON CD4+ T CELLS PROMOTES HBV-RELATED LIVER FIBROSIS THROUGH ACTIVATION OF SPHINGOMELINASE AND CD161-LECTIN-LIKE TRANSCRIPT-1 INTERACTION

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Introduction: Hepatitis B virus (HBV)-related liver fibrosis always progresses from inflammation to fibrosis. CD4+ T cell immune responses play a pivotal role in the process. Recently, CD161 is considered to be a costimulatory molecule on T cells and an important phenotypic marker of human Th17 cells.

Aims & Methods: This study was designed to investigate the roles of CD161 in the pathogenesis of HBV-related liver fibrosis. Methods: A total of 54 CHB patients who underwent liver biopsy and 20 healthy controls (HC) were enrolled. CHB patients were further categorized according to the disease phase: immune-tolerant (IT, n = 12), immune-active (IA, n = 30), or inactive CHB (n = 12). Peripheral blood mononuclear cells (PBMCs) and flow cytometry sorted CD4+ CD161+ and CD4+ CD161- T cells were prepared for further flow cytometric and real-time PCR analyses. Flow cytometry sorted CD4+ CD161+ and CD4+ CD161- T cells were also cultured alone or co-culture with primary hepatic stellate cells (HSCs) in vitro experiments.

Results: Compared to HC, the percentage of CD4+ CD161+ T cells significantly increased among IA patients while dramatically decreased among IT patients, but there was no significant difference between inactive CHB patients and HC. Besides, CD161 showed a positive correlation with histological grades and advanced histological fibrosis stages. In the PBMCs of CHB patients, CD4+CD161+ T cells exhibited a CD45RO+ memory phenotype and secreted more interferon-γ (IFN-γ) and TNF-alpha, IL-17, IL-21 and IL-4 whereas produced less IL-10 and IL-22 than CD4+ CD161- T cells. In comparison with CD4+ CD161+ T cells, in vitro culture of CD4+CD161+ T cells revealed that CD161 expression increased the activity of acid Sphingomyelinase (aSM) and subsequent PI3K/Akt, MAPK and mTOR pathways of CD4+ T cells. Both knocking down of CD161 and using imipramine to inhibit aSM could down-regulate CD4+ T cell-proliferation and production of IFN-γ and IL-17, especially for IL-17. HSCs express lectin-like transcript-1 (LLT1), the only ligand of human CD161 on CD4+ T cells. In our in vitro experiments, after co-culture with primary HSCs (HUVECs and immortalized HSCs) CD4+ CD161+ T cells revealed that CD161 expression increased the activity of acid Sphingomyelinase (aSM) and subsequently PI3K/Akt, MAPK and mTOR pathways of CD4+ T cells. Both knocking down of CD161 and using imipramine to inhibit aSM could down-regulate CD4+ T cell-proliferation and production of IFN-γ and IL-17, especially for IL-17.

Conclusion: Our data revealed that the expression of CD161 on CD4+ T cells might promote HBV-related liver fibrosis through CD161-LLT1 interaction to activate HSCs and through raising aSM to enhance the proinflammatory functions of CD4+ T cells.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

TUESDAY, OCTOBER 18, 2016
08:30-10:00
FREE PAPER SESSION: NOVEL DIAGNOSTIC TOOLS: GOING DEEPER AND DEEPER INTO THE BOWEL – ROOM N2

OP161 FULL SPECTRUM ENDOSCOPY (FUSE) IN THE DETECTION OF INFLAMMATORY BOWEL DISEASE NEOPLASIA (FUSION): A RANDOMIZED CROSSOVER TANDEM STUDY VERSUS CONVENTIONAL COLONOSCOPY

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Introduction: Inflammatory bowel diseases (IBD) are the most significant acute phase reactants and therefore inflammation is widely expanded. Conventional forward-viewing colonoscopy (FVC), however, lacks acceptable sensitivity in IBD dysplasia identification and the addition of dye-based chromoendoscopy is recommended. Full Spectrum Endoscopy (FUSE) is a novel colonoscope that incorporates 2 additional cameras to the forward camera and provides 330-degree panoramic view of the colonic mucosa.

Aims & Methods: This study aims to evaluate FUSE versus FVC in dysplasia surveillance in an IBD population. The dysplasia yield of targeted versus random colonic biopsies will also be assessed. Methods: A prospective, single-center, randomized-order, back-to-back tandem colonoscopy study was conducted comparing FVC versus FUSE in an IBD surveillance population. Cohn’s disease (CD) and ulcerative colitis (UC) subjects were recruited from the IB Sydney Cohort population-based database, all of whom met the inclusion criteria of published IBD surveillance guidelines. Subjects not due surveillance colonoscopy were excluded. The primary outcome was the per-dysplasia miss rate of the first colonoscopy identified by the second colonoscopy with chromoendoscopy. Secondary outcomes were per-subject dysplasia miss rate, mean dysplasia lesions found, procedural times, and dysplasia yield of targeted versus random colonic biopsies. The trial was registered with the Australia New Zealand Clinical Trials Registry (ACTRN12616000074973).

Results: In total 104 tandem (52-paired) colonoscopies were conducted with 27 subjects randomized to FVC first and 25 to FUSE first. Both arms were not statistically significantly different for age, IBD duration, CD versus UC, and additional dysplasia risk factors. The dysplasia prevalence rate of the cohort was 30.8%. The dysplasia miss rates for FVC and FUSE were 71.4% versus 46.4% (P = 0.08), respectively. (P = 0.08). Targeted biopsies increased dysplasia identification (26/163, 16.0%) versus random biopsies (12/757, 1.6%, P < 0.0001). Chromoendoscopy identified 10/28 (35.7%) of dysplastic lesions. The total colonoscopy times were similar (21.2 minutes versus 19.1 minutes, P = 0.32) but colonoscopy withdrawal time was significantly longer (15.8 minutes versus 12.0 minutes, P = 0.03) for FUSE and FVC respectively.

Conclusion: Full Spectrum Endoscopy outperformed conventional forward-viewing colonoscopy in inflammatory bowel disease subjects undergoing dysplasia surveillance. A high dysplasia prevalence was identified most likely due to multiple colonoscopy passes and the use of multiple advanced imaging modalities comprising white-light colonoscopy, FUSE and chromoendoscopy. Improved dysplasia identification rates may reduce colorectal cancer mortality and increase interval colonoscopies. Improved dysplasia yield of targeted biopsies versus random colonic biopsies was confirmed.

Disclosure of Interest: R. W. Leong: Endochoice USA investigator-initiated study. All other authors have declared no conflicts of interest.

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Introduction: Optical biopsies of colonic polyps < 10 mm in size could potentially replace standard histological assessment. WaxStat version 4 is a novel optical biopsy system designed by Spectrascience Inc, San Diego, California, USA, for prediction of histology based on laser induced autofluorescence spectroscopy.

Aims & Methods: The primary aim of this study was to demonstrate the accuracy of WaxStat version 4 in characterizing colorectal polyps < 10 mm that can be removed and discarded (or left in situ) without adverse clinical impact. The secondary aim was to compare the real time diagnostic performance of WaxStat version 4 with NBI and a combination of endoscopic and WaxStat assessments. Patients attending the endoscopy unit for lower gastrointestinal endoscopy as requested by their responsible physician were approached to participate in the study. Adult patients aged above 18 years were included.

Table (OP162): Diagnostic performance of WaxStat, E4 optical assessment and combined алгоритмical assessment for characterization of colorectal polyps less than 10 mm in size and prediction of surveillance intervals

<table>
<thead>
<tr>
<th>WaxStat alone</th>
<th>WLE+NBI assessment</th>
<th>Combination of WaxStat + endoscopic assessment (algorithmic approach)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>97.6% (95% CI 0.88-0.95)</td>
<td>85.0% (95% CI 0.77-0.89)</td>
</tr>
<tr>
<td>Specificity</td>
<td>46.9% (95% CI 0.44-0.48)</td>
<td>77.2% (95% CI 0.61-0.82)</td>
</tr>
<tr>
<td>NPV</td>
<td>96.8% (95% CI 0.85-0.91)</td>
<td>91% (95% CI 0.73-0.84)</td>
</tr>
<tr>
<td>PPV</td>
<td>54.7% (95% CI 0.28-0.77)</td>
<td>66% (95% CI 0.44-0.79)</td>
</tr>
<tr>
<td>Surveillance interval (%) of patients coded correctly</td>
<td>81.2%</td>
<td>97%</td>
</tr>
<tr>
<td>Surveillance interval (%) of patients called earlier</td>
<td>18.8%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Patients known to have inflammatory bowel disease or colonic cancer were excluded from the study. Polyps sized <10 mm were assessed in real time by high definition white light, NBI and WavSTATversion 4 optical biopsy forces. Standard techniques were used for polypectomy. Histopathological specimens were read separately by two expert GI pathologists blinded to the results of the WavSTAT assessments. The primary outcome measure was the negative predictive value in distinguishing adenomatous from non-adenomatous colorectal polyps. The secondary outcome measure was the accuracy of on-site recommended surveillance intervals.

Results: 50 polyps were <10 mm and 10 were >10 mm) were found in 70 patients (Males-44, females-27). Average age of the patients was 65 years (range 29–95 years). 16 polyps were not included in the final analysis due to discrepancy in histological analysis between two pathologists. We failed to retrieve 5 polyps. 26 patients were excluded from the study (No polyps seen in 17 patients, polyps <10 mm were not seen in 3 patients, and device failure in 4 patients). A total of 126 polyps <10 mm were included in final analysis. The diagnostic performance for WavStat version 4 and endoscopic assessment is detailed in the table. Wavstat4 had a NPV of 96% and was more specific. Since the specificity of WavSTAT was poor mainly for hyperplastic recto-sigmoid polyps we evaluated an algorithmic approach combining Wavstat4 and endoscopic assessment had a NPV of 91% and was more specific. Since the specificity of WavSTAT was poor mainly for hyperplastic recto-sigmoid polyps we evaluated an algorithmic approach combining Wavstat4 and endoscopic assessment had a NPV of 91% and was more specific.

Conclusion: Wavstat4 prediction was as accurate as an adenomatous polyp classification only if Wavstat4 prediction was as accurate as an adenomatous polyp classification. This combined algorithmic approach met the PIVI recommendations only if Wavstat4 prediction was as accurate as an adenomatous polyp classification. This combined algorithmic approach met the PIVI recommendations only if Wavstat4 prediction was as accurate as an adenomatous polyp classification. This combined algorithmic approach met the PIVI recommendations only if Wavstat4 prediction was as accurate as an adenomatous polyp classification. This combined algorithmic approach met the PIVI recommendations only if Wavstat4 prediction was as accurate as an adenomatous polyp classification. This combined algorithmic approach met the PIVI recommendations only if Wavstat4 prediction was as accurate as an adenomatous polyp classification. This combined algorithmic approach met the PIVI recommendations only if Wavstat4 prediction was as accurate as an adenomatous polyp classification. This combined algorithmic approach met the PIVI recommendations only if Wavstat4 prediction was as accurate as an adenomatous polyp classification. This combined algorithmic approach met the PIVI recommendations only if Wavstat4 prediction was as accurate as an adenomatous polyp classification. This combined algorithmic approach met the PIVI recommendations only if Wavstat4 prediction was as accurate as an adenomatous polyp classification.
colonic cancer microbiome using mass spectrometry imaging in a prospective cohort of CRC patients.

**Aims & Methods:** A prospective, multi centre observational study was performed on patients undergoing elective resections for colorectal cancer at Imperial Healthcare NHS Trust and the Royal Marsden Hospital. Fresh mucosal tissue was collected using a cedarwood swab under aseptic conditions from cancers and adjacent normal tissue and frozen at −80 °C. Using 16s rRNA sequencing analysis of corresponding tissue samples (performed in Mothur and Stamp), target bacteria including *Fusobacterium spp.*, *E.Coli* and *Bifidobacteria* were identified. A chemical database was constructed using Rapid Evaporative Ionisation Mass Spectrometry (REIMS) from pure cultures of the target microbes. Desorption Electrospray Ionisation Mass Spectrometry (DESI-MSI) was then performed to provide a spatially resolved map of the mucosal microbial lipidome. This was mapped onto the nuclei for using chemical spectra identified by REIMS. Candidate microbial lipids were validated using cell co-culture experiments and analysis with REIMS. Multivariate analysis was performed using Matlab (Mathworks) and R. Both unsupervised Principle Component Analysis and Supervised Linear Discriminant Analysis were used to perform statistical analysis of single lipid species.

**Results:** 26 patients with sporadic colorectal cancer were recruited (17 women, median age 68, range 35–84, median BMI 27.1 kg/m²). Eight tumours were right sided, eleven were left sided and seven were rectal. Two patients had neo-adjuvant chemoradiotherapy. Histology showed six adenomas, one T1, six T2, ten T3 and three T4 cancers. Using DESI-MSI it was possible to geographically identify distinct anatomical regions based on co-registration of the chemical data with independently validated H+E stained tissue. Using leave one patient out cross validation, DESI-MSI was able to diagnose cancer from normal colonic mucosa with ROC AUC = 97.3%. Increased long chain fatty acids were seen in malignant tissues and phospholipids were seen in healthy mucosa (both p < 0.0001). Target spectra just specific to the mucosa were then extracted for analysis. This revealed 102 lipid species that differentiated colon cancer from normal adjacent mucosa, including 24 attributable to taxon-specific markers for *Clostridia*, *Bifidobacteria* and *Enterobacteria*. These were positively validated using cell culture REIMS.

**Conclusion:** Chemical mapping of the colonic lipidome permits spatially resolved analysis of the cancer microbiome and its metabolic functions, and this has diagnostic value. DESI-MSI provides a completely novel methodology for studying microbial-host interactions critical to the aetiology of inflammation and cancer.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**OP0166 UNSUPERVISED TRANSCRIPTOMICS-BASED CLUSTERING OF ULCERATIVE COLITIS PATIENTS REVEALS MARKED HETEROGENEITY THAT RELATES TO ANTI-TNF TREATMENT RESPONSE**

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**Contact E-mail Address:** rahul.kalla@jaclab.com

Introduction: Heterogeneity in IBD patient populations is widely cited as the main barrier to efficient clinical trials and development of therapies with high clinical efficacy. We and others hypothesize that phenotypic heterogeneity is a direct result of molecular heterogeneity in disease-driving molecular pathways. We and others have hitherto not extensively explored the concept of defining molecular heterogeneity in a manner independent of known biology.

**Aims & Methods:** Whole-genome transcriptomic data was generated for colonic biopsies from 463 patients (152 CD, 159 UC, 26 IBD-U) using the Ion AmpliSeq RNA Expression platform (Ion Torrent, Thermo Fisher Scientific). Whole-genome transcriptomic data was then filtered to identify genes expressed in both UC and CD biopsies. Next, a multi-organ transcriptome and proteome profiling in newly diagnosed IBD, we can gain an understanding into the molecular mechanisms that may be relevant in disease.

**Results:** Analysis of the cancer microbiome and its metabolic functions, and this has diagnostic value. DESI-MSI provides a completely novel methodology for studying microbial-host interactions critical to the aetiology of inflammation and cancer.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

Table 1 (OP168): Demographics, procedural outcomes, bowel cleanliness and adenoma detection.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>WE N = 408</th>
<th>WI N = 408</th>
<th>AI N = 408</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, n (%)</td>
<td>184 (45.1)</td>
<td>185 (45.3)</td>
<td>183 (44.9)</td>
<td></td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>224 (54.9)</td>
<td>223 (54.7)</td>
<td>225 (55.1)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>61.4 (6.2)</td>
<td>61.0 (6.3)</td>
<td>60.9 (6.2)</td>
<td>0.261 ( \text{+}) 0.173 ( \text{+}) 0.822 ( \text{+}) 0.350</td>
</tr>
<tr>
<td>Body Mass Index, mean (SD)</td>
<td>26.4 (4.1)</td>
<td>26.4 (4.4)</td>
<td>26.6 (4.4)</td>
<td>0.751 ( \text{+}) 0.473 ( \text{+}) 0.696 ( \text{+}) 0.775</td>
</tr>
</tbody>
</table>

**Indications for colonoscopy, n (%)**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>WE</th>
<th>WI</th>
<th>AI</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted right colon ADR, n (%)</td>
<td>63 (25.9)</td>
<td>32 (17.2)</td>
<td>26 (13.7)</td>
<td>0.0007</td>
</tr>
<tr>
<td>At BBPS 3 (right colon)</td>
<td>242 (59.3)</td>
<td>242 (59.3)</td>
<td>222 (54.4)</td>
<td>1 ( \text{+}) 0.157 ( \text{+}) 0.157 ( \text{+}) 0.263</td>
</tr>
<tr>
<td>At BBPS 9–8 (entire colon)</td>
<td>18 (4.4)</td>
<td>19 (4.7)</td>
<td>19 (4.7)</td>
<td>0.365 ( \text{+}) 0.863 ( \text{+}) 1 ( \text{+}) 0.982</td>
</tr>
<tr>
<td>Family history of colorectal cancer</td>
<td>47 (11.5)</td>
<td>47 (11.5)</td>
<td>45 (11.0)</td>
<td>0.823 ( \text{+}) 0.823 ( \text{+}) 0.968</td>
</tr>
<tr>
<td>Primary colonoscopy</td>
<td>101 (25.4)</td>
<td>100 (25.4)</td>
<td>122 (29.9)</td>
<td>0.920 ( \text{+}) 0.099 ( \text{+}) 0.084 ( \text{+}) 0.143</td>
</tr>
</tbody>
</table>

**Procedural outcomes**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>WE</th>
<th>WI</th>
<th>AI</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecal intubation rate (final), n (%)</td>
<td>402 (98.5)</td>
<td>400 (98.0)</td>
<td>399 (97.8)</td>
<td>0.590 ( \text{+}) 0.435 ( \text{+}) 0.807 ( \text{+}) 0.734</td>
</tr>
<tr>
<td>Cecal intubation time, mean (SD), min</td>
<td>10.1 (5.4)</td>
<td>9.4 (5.7)</td>
<td>9.7 (6.7)</td>
<td>0.050 ( \text{+}) 0.364 ( \text{+}) 0.390 ( \text{+}) 0.188</td>
</tr>
<tr>
<td>Withdrawal time without polypectomy, mean (SD), min</td>
<td>9.5 (3.2)</td>
<td>9.5 (3.6)</td>
<td>8.9 (3.1)</td>
<td>0.870 ( \text{+}) 0.074 ( \text{+}) 0.128 ( \text{+}) 0.084</td>
</tr>
<tr>
<td>Total procedure time, mean (SD), min</td>
<td>24.8 (11.7)</td>
<td>24.6 (12.0)</td>
<td>23.3 (11.0)</td>
<td>0.842 ( \text{+}) 0.039 ( \text{+}) 0.098 ( \text{+}) 0.128</td>
</tr>
<tr>
<td>Withdrawal endoscopists’ correct guesses of insertion method</td>
<td>119 (29.2)</td>
<td>135 (33.1)</td>
<td>116 (28.4)</td>
<td></td>
</tr>
<tr>
<td>Overall Boston Bowel Preparation Scale (BBPS) score, mean (SD)</td>
<td>7.9 (1.5)</td>
<td>7.4 (1.6)</td>
<td>7.5 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Right colon BBPS score (SD)</td>
<td>7.5 (1.6)</td>
<td>7.5 (1.7)</td>
<td>7.5 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Infused water during insertion, median (range), mL</td>
<td>550 (50–6500)</td>
<td>400 (50–2000)</td>
<td>0 (0–1000)</td>
<td></td>
</tr>
<tr>
<td>Aspirated water during insertion, median (range), mL</td>
<td>500 (0–6500)</td>
<td>50 (0–1000)</td>
<td>0 (0–1000)</td>
<td></td>
</tr>
</tbody>
</table>

**Adenoma detection**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>WE</th>
<th>WI</th>
<th>AI</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ADR, n (%)</td>
<td>201 (49.3)</td>
<td>177 (43.4)</td>
<td>165 (40.4)</td>
<td>0.395 ( \text{+}) 0.011 ( \text{+}) 0.092 ( \text{+}) 0.036</td>
</tr>
<tr>
<td>Overall advanced adenoma detection rate, n (%)</td>
<td>79 (19.4)</td>
<td>70 (17.2)</td>
<td>58 (14.2)</td>
<td>0.413 ( \text{+}) 0.049 ( \text{+}) 0.249 ( \text{+}) 0.145</td>
</tr>
<tr>
<td>Right colon ADR, n (%)</td>
<td>98 (24.0)</td>
<td>78 (19.1)</td>
<td>69 (16.9)</td>
<td>0.089 ( \text{+}) 0.012 ( \text{+}) 0.413 ( \text{+}) 0.034</td>
</tr>
<tr>
<td>Right colon ADR (primary adenoma)</td>
<td>79.9 (1.2)</td>
<td>79.7 (1.2)</td>
<td>79.1 (1.3)</td>
<td>0.265 ( \text{+}) 0.991 ( \text{+}) 0.245 ( \text{+}) 0.365</td>
</tr>
</tbody>
</table>

**At BBPS 9–8 (entire colon)**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>WE</th>
<th>WI</th>
<th>AI</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>WE N = 275</td>
<td>148 (53.8)</td>
<td>94 (41.4)</td>
<td>88 (38.8)</td>
<td></td>
</tr>
<tr>
<td>WI N = 227</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI N = 227</td>
<td></td>
<td></td>
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</tbody>
</table>

**At BBPS 3 (right colon)**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>WE</th>
<th>WI</th>
<th>AI</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>WE N = 243</td>
<td>63 (25.9)</td>
<td>32 (17.2)</td>
<td>32 (13.7)</td>
<td>0.0007 ( \text{+}) 0.0005 ( \text{+}) 0.566 ( \text{+}) 0.004</td>
</tr>
<tr>
<td>WI N = 186</td>
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<tr>
<td>AI N = 190</td>
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</tbody>
</table>

**Disclosure of Interest:**

All authors have declared no conflicts of interest.

References


SD, standard deviation; FIT+, positive at fecal immunochromatographic test; FOBT+, fecal occult (guaiac-based) blood test; Advanced adenomas: adenomas ≥10 mm in diameter, or high grade dysplasia, or with ≥20% villous components. \( \text{Chi-squared}\); \( \text{t test}\); ANOVA, analysis of variance.
Conclusion: found (6.1% vs. 3.2%, P = 0.001) with the use of Endocuff. The advanced adenoma detection rate increased by 15% (55% vs. 40%, OR = 2.3, 95% CI 1.6–6.0, p = 0.001). After adjusting for age and gender, distal location (OR 3.1, 95%–66.0% male) were all independent predictors for advanced histopathology. The odds of growing up- or downwards. We conducted a logistic regression analysis to identify predictors for advanced histopathology, defined as high-grade dysplasia adenoma (29.8%), high-grade dysplasia adenoma (37.1%), early colorectal cancer (17.1%), sessile serrated adenoma/polyp (6.6%), hyperplasia (8.8%), and traditional serrated adenoma (0.5%). Sessile-LNPCPs more often contained advanced histopathology than LST-LNPCPs (61.5% vs. 34.9%, p < 0.001). We previously trained all endoscopists (9 faculty and 14 trainees) at Maastricht UMC+ on detection, diagnosis and endoscopic resection of colorectal neoplasms using a stepwise training program: Phase 1: Training on detection and diagnosis of colorectal neoplasms, with special attention for non-polyloid (flat and depressed) colorectal neoplasms using lectures, videos and individual feedback. Phase 2: Training in endoscopic resection techniques using videotraining and hands-on training with experienced colonoscopists. Then, we embarked in a prospective study of all consecutive colonoscopies performed at our institution from February 2008 to February 2012. Quality indicators (colonic intubation rate, adenoma and polyp detection and resection rate) were monitored. We recorded patient characteristics (age, gender) and lesion characteristics, i.e. location, size, shape using Paris classification (including photo documentation) and histopathology. We defined LNPCPs as large (>20 mm) non-pedunculated (i.e. sessile, flat, depressed, combinations) colorectal neoplasms (Rutter et al, Gut 2015). We paid special attention to laterally spreading tumors (LSTs), defined as superficially growing lesions along the mucosa instead of growing up- or downwards. We conducted a logistic regression analysis to identify predictors for advanced histopathology, defined as high-grade dysplasia or early colorectal cancer (pT1).

Results: A total of 7166 neoplasms were identified in 9353 patients (mean age 59.9 years, 46.0% male), of which 761 (8.5%) were in 176 (1.9%) patients (mean age 63.8 years, 56.3% male) were LNPCPs. The majority (65.9%) of LNPCPs were located in the proximal colon. Mean size was 30 mm (20–100 mm). Ninety-six LNPCPs (46.8%) were sessile and 109 (55.2%) LSTs. LNPCPs contained low-grade dysplasia adenoma (24.7%), high-grade dysplasia adenoma (17.1%), early colorectal cancer (17.1%), sessile serrated adenoma/polyp (6.6%), hyperplasia (8.8%), and traditional serrated adenoma (0.5%). Sessile-LNPCPs more often contained advanced histopathology than LST-LNPCPs (61.5% vs. 34.9%, p < 0.001). After adjusting for age and gender, distal location (OR 3.1, 95% CI 1.6–6.0, p < 0.001), size of lesion (OR 2.7 for LNPCP ≥40 mm compared to 20–29 mm, 95% CI 1.1–6.2, p = 0.023) and sessile shape (OR 2.3, 95% CI 1.2–4.4, p < 0.001) were all independent predictors for advanced histopathology. The odds of growing up- or downwards. We conducted a logistic regression analysis to identify predictors for advanced histopathology, defined as high-grade dysplasia or early colorectal cancer (pT1).

Conclusion: In this real-life prospective cohort, 1.9% of all patients undergoing a colonoscopy had a LNPCP. Lesion size, sessile shape and distal location were independent predictors of advanced histopathology. Careful case selection which considers both patient-related factors and endoscopic predictors for advanced histopathology is critical to optimize the outcomes of endotherapy for LNPCP.

Disclosure of Interest: S. Sanduleanu: Consultancy; Pentax Europe All other authors have declared no conflicts of interest.

Reference

OP172 HEALTH EFFECTS AND COSTS DUE TO POST-COLONOSCOPY COLORECTAL CANCER

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Introduction: Colorectal cancers (CRC) detected shortly after a colonoscopy are referred to as a post-colonoscopy colorectal cancer (PCCRC), and has been reported to represent 2–9% of all CRCs, depending on the definition, setting and methods for estimating its incidence. The delay in detection of the CRC might imply higher mortality, effect on the quality of life of the diagnosed individuals, and association with extra costs for health services.

Aims & Methods: The aim of this study was to estimate the loss of health and productivity due to CRC diagnosed after a colonoscopy in Sweden. A...
Aim & Methods: Colonoscopy and colonoscopy.

The aim of our study is to compare cumulative cost was estimated to be £1,922,000 less if the patients had been diagnosed at the time of the prior colonoscopy. The extra cost per case is £1,305.

Conclusion: Our simulation results imply that false negative colonoscopies cause significant loss of life-years and quality of life in the affected individuals. This, together with higher costs, motivates further efforts to improve the quality of colonoscopies.

Disclosure of Interest: All authors have declared no conflicts of interest.

OPIT3 COMPARISON OF COLONOSCOPY, SIGMOIDOSCOPY AND MULTIPLE ROUNDS OF FIT-BASED COLORECTAL CANCER SCREENING: LONG-TERM FOLLOW-UP


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Introduction: Several methods for colorectal cancer (CRC) screening are available, the most often used include colonoscopy, sigmoidoscopy and fecal immunochemical testing (FIT). To date, comparison between these screening methods was mainly focused on one-time endoscopic screening to one-time FIT screening. A fair comparison of diagnostic yield (DY) of FIT would comprise cumulative DY after multiple rounds of FIT screening. The aim of our study is to compare the DY of multiple rounds of FIT-screening to one-time screening by sigmoidoscopy and colonoscopy.

Aims & Methods: Demographic data of 30,007 randomly chosen individuals aged 50–74 were obtained from municipal populations. These participants were invited for FIT screening in 2010; of these, 15,046 were invited for four rounds of FIT, 8,407 for one-time sigmoidoscopy, and 6,600 for one-time colonoscopy screening. We compared 2 rounds of FIT to one-time sigmoidoscopy and 4 rounds of FIT to one-time colonoscopy.

Results: In total, 28,515 eligible persons (median age 60 years, IQR 55–66; 50% males) were invited. Cumulative participation was significantly higher for FIT (77%) than for sigmoidoscopy (31%; p < 0.001) and colonoscopy (24%; p < 0.001). Number of colonoscopies performed relative to eligible invitees was highest for colonoscopy (24%) compared to FIT (13%; p < 0.001) and sigmoidoscopy (3%; p < 0.001). For invitees the DY for advanced neoplasia (AN) was significantly higher after two rounds of FIT compared to one-time sigmoidoscopy (3.1% vs 2.3%; p < 0.001) and after four rounds of FIT compared to one-time colonoscopy (4.5% vs 2.2%; p < 0.001). For participants, DY for AN was significantly higher for endoscopic screening; 4.7% for 2 rounds of FIT compared to 7.3% for sigmoidoscopy (p < 0.001), and 6.1% for 4 rounds of FIT compared to 9.1% colonoscopy (p < 0.001).

Conclusion: In this population-based CRC screening cohort, we demonstrated that multiple rounds of FIT screening detects significantly more advanced neoplasia per invitee compared to one-time sigmoidoscopy and colonoscopy screening, and with significantly fewer colonoscopies needed. Colonoscopy detected more advanced neoplasia per participant. However, due to low participation in colonoscopy screening, FIT seems most effective in population-based CRC screening.

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 08:30–10:00

Surgery in IBD – Room L7

OPIT4 OUTCOMES OF EMERGENCY ADMISSIONS WITH CROHN’S DISEASE IN ADULTS IN ENGLAND BETWEEN 2004 AND 2014

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Introduction: Between 2006 and 2010, the UK national audit of adult inflammatory bowel disease admissions revealed a small but non-significant fall in mortality. John’s disease (CD) from 1.13 to 0.87, a fall in the rate of prescription of anti-TNF therapy on admission from 3.9 to 2.6% and a fall in surgery from 23 to 18%.

Aims & Methods: Hospital Episode Statistics (HES) is an administrative database of data on all elective and emergency care episodes in hospitals in England. Using HES, patients aged between 18 and 60 years coded with a first emergency admission with CD were identified. The influence of demographic factors, comorbidity and infused anti-TNF therapy on mortality, surgery and emergency readmissions was examined using multivariate logistic regression.

Results: Between 2004 and 2014, 24,830 patients (55% female, mean age of 35 (IQR 25–44)) were identified. Mortality was 0.22% at 30 days, 0.29% in hospital and 0.81% within 1 year. During admission, 19.2% of patients underwent surgery (median time to surgery 2 days (IQR 1–6)) and 1.9% received infused anti-TNF therapy. Surgery during admission rose from 16.1 to 22.9% (OR 1.52 (95% CI 1.32–1.75), p < 0.001) between 2004 and 2014, and infused anti-TNF therapy rose from 1.8% to 2.8% between 2006 and 2014. In-hospital and 1-year mortality fell from 0.53 and 1.05% in 2004 to 0.10 and 0.57% in 2013 (0.15% CI 0.04–0.77, p = 0.021 and 0.46 (0.23–0.91), p = 0.026 respectively). Patients aged 35–60 had a higher 30-day (3.99 (1.97–8.05), p < 0.001) and 1-year mortality (4.57 (2.34–8.89), p < 0.001) if they had a coexisting illness age 18–34. Increasing comorbidity (15.38

Table 1 (OPIT42): Logistic regression model adjusted for age and gender to identify predictors for advanced histopathology in LNPPCs. LGD: low-grade dysplasia; HGD: high-grade dysplasia; early CRC: early colorectal cancer (p<1).
OP175 IS THE ‘RESET’ SURGERY EFFECTIVE FOR CROHN’S DISEASE PATIENTS REFRACTORY TO ANTI-TNF THERAPY?

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Introduction: Anti TNF-alpha agents (anti-TNFa) are currently the most effective therapeutics for Crohn’s disease (CD). Some of CD patients under anti-TNFa therapy, however, need surgery because of disease progression. Surgical resection (‘Reset’) usually leads to the elimination of the intestinal regions with the most severe activity. However, little is known about whether retreatment with anti-TNFa is effective for patients who underwent ‘Reset’ surgery. The aim of this study was to evaluate the efficacy of anti-TNFa therapy for CD patients who underwent surgery due to the refractoriness to previous anti-TNFa.

Aims & Methods: From July 2005 to November 2015, 65 CD patients underwent intestinal resection at Okayama University Hospital. Of these, 34 patients received anti-TNFa therapy after surgery and 31 were refractory to preoperative anti-TNFa (TNFα-refractory group), and 15 anti-TNFα naïve (TNFα-naïve group). The efficacy of post-surgical treatment with anti-TNFa was compared according to the status of pre-operative anti-TNFa therapy. In addition, clinical factors predicting relapse in patients with anti-TNFa retreatment after precedent surgery were evaluated. The evaluated factors were clinical backgrounds, duration of TNFα therapy, concomitant medications before and after surgery, laboratory data before surgery, and the residual of the affected intestine after surgery, etc. as well as a deterioration in quality of life and disease activity at the moment of the interview which was seen more frequently after CRD. These findings can probably be revealed to be independent predictors of quality of life. Finally, minimally invasive surgery tended to be associated with a less frequently CD recurrence (p = 0.08).

Disclosure of Interest: All authors have declared no conflicts of interest.

OP177 CLOSE RECTAL DISSECTION VERSUS TOTAL MESORECTAL EXCISION IN PATIENTS UNDERGOING BOWEL DISEASE UNDERGOING PROCTECTOMY


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Introduction: Proctocolectomy or completion proctectomy in inflammatory bowel disease patients is frequently complicated by disturbed perineal wound healing and pre- and postoperative amputation. Close rectal dissection (CRD) has been recommended as an intensification of medical therapy, hospitalization, or surgery due to worsening of abdominal symptoms, CRP elevation with the evidence of endoscopic recurrence.

Results: Patients of the TNFα-naïve group showed significantly higher rate of total CGQL score compared to the TNFα-refractory group (12.19 (63%) vs. 3.15 (20%), p < 0.05). In the evaluation of factors predicting relapse in patients with retreatment of anti-TNFα after surgery, only the residual of the affected intestine after surgery, etc. as well as a deterioration in quality of life and disease activity at the moment of the interview which was seen more frequently after CRD. These findings can probably be revealed to be independent predictors of quality of life. Finally, minimally invasive surgery tended to be associated with a less frequently CD recurrence.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP176 IMPACT OF MINIMALLY INVASIVE SURGERY ON QUALITY OF LIFE AFTER SURGERY FOR CROHN’S DISEASE TERMINAL ILEITIS

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Introduction: Crohn’s disease (CD) is a chronic disease that interferes with the daily life of those affected. Surgical treatment is required in about 70% of CD patients during the course of disease and risk of surgery is among the highest rated concerns among them. Quality of life is often worsened by intestinal surgery.

Aims & Methods: The aim of the study is to assess the impact of minimally invasive surgery on quality of life after surgery for Crohn’s disease terminal ileitis. From June 2010 to December 2015, one hospital interviewed by telephone and responded to the generic European Global Quality of Life (CGQL) questionnaire and the Body Image Questionnaire (BIQ). Their disease activity was defined as Harvey-Bradshaw Index (HBI). Comparisons and correlations were carried out with non-parametric tests. Survival analyses were performed with log rank test.

Results: In our study group 46 patients had minimally invasive surgery for terminal ileum CD while 66 had open surgery for the same indication. Twenty seven patients had a recurrent CD. The total CGQL score and its single items (quality of life and disease activity) were significantly higher (and thus, better) in the laparoscopic group patients. Similarly, all the BIQ items were significantly better in patients who had a minimally invasive surgery compared to those who had open surgery. At univariate analysis, total CGQL score was directly correlated with minimally invasive surgery (-0.34, p = 0.001) and inversely correlated with disease activity at the moment of the interview (rho = -0.44, p = 0.001), the use of steroids (rho = -0.20, p = 0.02) and recurrent CD as indication for surgery (rho = 0.19, p = 0.05). At multivariate analysis, only the use of steroids was significantly correlated with minimally invasive surgery (rho = 0.35, p = 0.02) and recurrent CD as indication for surgery (rho = 0.39, p = 0.01).

Conclusion: Minimally invasive surgery was associated to a better quality of life and body image perception. This results is probably due in part to the beneficial effect of minimally invasive surgery on body image but also by the less severe disease of these patients (less recurrent CD as indication for surgery or simpler surgery). Quality of life is essentially predicted by current disease activity and minimally invasive surgery. Finally, minimally invasive surgery tended to be associated with a less frequent CD recurrence.

Disclosure of Interest: All authors have declared no conflicts of interest.
OP178 LONG-TERM FOLLOW-UP AFTER ILEORECTAL ANASTOMOSIS IN ULCERATIVE COLITIS (UC) A GETAID/GETAID CHIRURGIE MULTICENTER RETROSPECTIVE COHORT OF 343 PATIENTS


Introduction: Colectomy is frequently performed in ulcerative colitis (UC) patients. Although ileal pouch-anal anastomosis is recommended after colectomy, ileorectal anastomosis (IRA) is still performed. The main objective of our study was to determine the cumulative incidence of IRA failure and its prognostic factors.

Aims & Methods: This was a multicenter retrospective cohort study, which included patients with IRA for UC performed between 1960 and 2014. IRA failure was defined as secondary proctectomy and/or rectal cancer occurrence. Univariate and multivariable survival analyses were performed using a Cox-proportional hazards model.

Results: 343 patients from 13 French centers were included. Median follow-up after IRA was 10.6 years. IRA failure rates were estimated at 27.0% (95CI [22.3–32.1]) and 40.0% (95CI [33.4–47.1]) at 10 and 20 years, respectively. Median survival time without IRA failure was estimated at 26.8 years. Two-thirds of secondary proctectomies were performed for refractory proctitis, and 20% for rectal neoplasia. Univariate analysis identified factors associated with IRA failure: IRA performed after 2004, a longer duration of disease at the time of IRA and having received immunomodulatory agents prior to IRA. In multivariable analysis, treatment with both immunosuppressant (IS) and anti-TNF before colectomy was independently associated with IRA failure (HR = 2.9, 95CI [1.2–7.10]). Conversely, colectomy for severe acute colitis was associated with decreased risk of IRA failure (HR = 0.6, 95CI [0.41–0.97]).

Conclusion: Patients with UC have a high risk of IRA failure, particularly when receiving immunosuppressants. However, IRA could be discussed after colectomy for severe acute colitis, in patients naive to both IS and anti-TNF.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP179 THERAPY REFRACTORY UC PATIENTS MAY BENEFIT FROM APPENDECTOMY: EARLY RESULT FROM THE PASSION STUDY


Introduction: Appendectomy is frequently performed in ulcerative colitis (UC) patients. Although ileal pouch-anal anastomosis is recommended after colectomy, ileorectal anastomosis (IRA) is still performed. The main objective of our study was to determine the cumulative incidence of IRA failure and its prognostic factors.

Aims & Methods: This was a multicenter retrospective cohort study, which included patients with IRA for UC performed between 1960 and 2014. IRA failure was defined as secondary proctectomy and/or rectal cancer occurrence. Univariate and multivariable survival analyses were performed using a Cox-proportional hazards model.

Results: 343 patients from 13 French centers were included. Median follow-up after IRA was 10.6 years. IRA failure rates were estimated at 27.0% (95CI [22.3–32.1]) and 40.0% (95CI [33.4–47.1]) at 10 and 20 years, respectively. Median survival time without IRA failure was estimated at 26.8 years. Two-thirds of secondary proctectomies were performed for refractory proctitis, and 20% for rectal neoplasia. Univariate analysis identified factors associated with IRA failure: IRA performed after 2004, a longer duration of disease at the time of IRA and having received immunomodulatory agents prior to IRA. In multivariable analysis, treatment with both immunosuppressant (IS) and anti-TNF before colectomy was independently associated with IRA failure (HR = 2.9, 95CI [1.2–7.10]). Conversely, colectomy for severe acute colitis was associated with decreased risk of IRA failure (HR = 0.6, 95CI [0.41–0.97]).

Conclusion: Patients with UC have a high risk of IRA failure, particularly when receiving immunosuppressants. However, IRA could be discussed after colectomy for severe acute colitis, in patients naive to both IS and anti-TNF.

Disclosure of Interest: All authors have declared no conflicts of interest.

Disclosure of Interest: All authors have declared no conflicts of interest.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP180 THE RISK OF CLOSTRIDIUM DIFFICILE INFECTION IN PATIENTS WITH PERNICIOUS ANAEMIA: A RETROSPECTIVE COHORT STUDY USING PRIMARY CARE DATABASE

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Introduction: Previous studies have shown an association between proton pump inhibitor use and Clostridium difficile infection1. One suggested mechanism of this association is the low stomach acid levels caused by these drugs, since gastric acid is an important host defence against ingested pathogens. If acid suppression is the true cause of Clostridium difficile infection in patients receiving proton pump inhibitors, then this effect should be manifested in patients with achlorhydria (no acid production), a condition associated with pernicious anaemia. Elucidating this association would provide a clear understating of the acid-suppression hypothesis underlying the increased risk of infection in patients who have received gastric acid suppressive therapy.

Aims & Methods: The aim of this study was to determine the risk of Clostridium difficile infection in patients with pernicious anaemia. We conducted a population based cohort study using English linked primary (Clinical Practice Research Datalink) and secondary (Hospital Episode Statistics) care records (1998–2012). The exposed group consisted of patients with a diagnosis of pernicious anaemia who had been treated with vitamin B12 therapy. Each exposed patient was matched by age (within 5 years), gender and general practice to non-pernicious anaemia patients, with the follow-up start date of the control being their matched exposed patient. Cox regression analysis was used to estimate the hazard ratio (HR) and 95% confidence interval for the association between Clostridium difficile infection and pernicious anaemia, adjusted for potential confounders.

Results: We identified 20,058 patients with pernicious anaemia receiving vitamin B12 therapy and 196,895 controls. The crude incidence rate of Clostridium difficile infection was 3.3/1000 person-years for those with pernicious anaemia while it was 1.7/1000 person-years for controls. Patients with pernicious anaemia had a greater risk of Clostridium difficile infection than controls (adjusted HR 1.52, 95% confidence interval 1.33 to 1.73).

Conclusion: Individuals with pernicious anaemia have an increased risk of Clostridium difficile infection. This study supports severe hypochlorhydria as the mechanism for the increased Clostridium difficile infection in people who have received long-term acid suppression medication.

Disclosure of Interest: F. Othman: This study has been carried out as part of my PhD program at University of Nottingham-UK, funded by Scholarship Award from King Saud bin Abdulaziz University for Health Sciences Saudi Arabia. There is no other potential conflicts of interest. All other authors have declared no conflicts of interest.

Reference

OP181 CONSISTENT AND REPRODUCIBLE PRODUCTION OF A MICROBIOTA-BASED DRUG FOR RECURRENT C. DIFFICILE INFECTION: APPLICATION OF A NOVEL DIAGNOSTIC FOR DYSBIOSES

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Introduction: Antibiotics are the first-line treatment for C. difficile infection (CDI). However, the most commonly prescribed antibiotics for CDI are associated with high recurrence rates. Antibiotics have been shown to disrupt the intestinal microbiota. Restoration of the intestinal microbiota to its pre-disease state protects against recurrence. There is an unmet need for a standardised, reproducible microbiota-based therapy for recurrent CDI. RBX2600, a...
microbiota-based drug candidate targeted at recurrent CDI, is sourced from human-derived microbes from extensively colonized donors and manufactured using standardized, quality-controlled processes.

Aims & Methods: To compare the bacterial abundance in the source material for RBX2660 (DS) with the bacterial abundance in the finished drug product (DP) used in the Phase 2B/PUNCH CD 2 study. A total of 70 DS samples sourced from 17 unrelated donors (mean age 27; range 18 to 57 years; 94% male) from August 2014 to February 2016 were compared with 70 matched DP samples using the GA-map Dysbiosis Test (GA-test), Genetic Analysis AS, Oslo, Norway. The GA-test used 54 probes targeting V3 to V7 of the bacterial 16S rRNA gene to characterize and identify bacteria present. Approximately 300–400 bacteria at different taxonomic levels are covered, providing for an assessment of the microbial community using multiple variable regions. The GA-test enables serial assessment of the faecal bacterial abundance profile as well as potentially clinically relevant alterations in the microbiome over time. These capabilities of the GA-test were used to assess the production processes for RBX2660. The differences in bacterial abundance between the DP and DS were calculated from log2-abundance values (DP/DS), averaging the differences.

Results: The GA-test found that the bacterial abundance in the RBX2660 DP was lower than in the DS in 38 of the 54 probes; equal in number in 6 of the probes; and higher in 10. More specifically, Firmicutes and Actinobacteria showed reduced signal strength in the DP compared with the DS. Bacteroidetes showed increased signal strength in the DP compared with the DS, while Proteobacteria demonstrated equal signal strength in both samples. The comparative abundance in the DP vs. the DS is shown in Table 1. Accuracy was as high as 83.4% at cross-validation. Principal component analysis found that the bacterial profiles in the RBX2660 DP, though lower than in the donor source material, were largely kept intact during the production process for all 17 donors.

Table 1: Comparative Signal Strength of Bacteria

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Signal Strength in DP vs. DS</th>
<th>Mean Difference (95% CIM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroidetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>Increased</td>
<td>0.07 (0.03, 0.11)</td>
</tr>
<tr>
<td>Parabacteroides</td>
<td>Increased</td>
<td>0.12 (0.07, 0.17)</td>
</tr>
<tr>
<td>Allstipes</td>
<td>Increased</td>
<td>0.17 (0.11, 0.23)</td>
</tr>
<tr>
<td>Firmicutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lachnospirae</td>
<td>Decreased</td>
<td>-0.13 (-0.15, -0.11)</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>Decreased</td>
<td>-0.16 (-0.20, -0.13)</td>
</tr>
<tr>
<td>Negativicutes</td>
<td>Increased</td>
<td>0.03 (0.01, 0.06)</td>
</tr>
<tr>
<td>Clostridia</td>
<td>Decreased</td>
<td>-0.18 (-0.20, -0.16)</td>
</tr>
<tr>
<td>Actinobacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bifidobacterium</td>
<td>Decreased</td>
<td>-0.33 (-0.38, -0.28)</td>
</tr>
<tr>
<td>DP = drug product</td>
<td>DS = drug source</td>
<td>CIM = confidence interval of mean</td>
</tr>
</tbody>
</table>

Conclusion: GA-test analysis confirmed that RBX2660 can be manufactured in a consistent and reliable manner with the preservation of key bacterial diversity believed critical for protection from recurrent CDI.

Disclosure of Interest: C. Jones: Employee of RebiotiX Inc., Roseville, MN USA

References:

OP182 A METHYL DONOR MOLECULES-SUPPLEMENTED DIET ERADICATES E. COLI POPULATION AND METHYLATES CEACAM6 PROMOTER DECREASING ITS EXPRESSION IN COLON EPITHELIAL CELLS IN MICE

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Introduction: Adhesion-invasive E. coli are clearly involved in triggering and maintaining ileal CD. AIEC bacteria adhere to the enterocytes through high affinity interaction between their variant type one pili and abnormally expressed CEACAM6 protein on host cells. We previously reported an original mechanism of CEACAM6 regulation, depending on DNA methylation parameters such as CpG island hypermethylation at the HIF-1 binding site (HRE, Hypoxia responsive element) in the promoter of the gene. We observed that an unmethylated HRE site allows HIF-1 to bind the promoter and to induce CEACAM6 expression in intestinal epithelial cells (IEC). Decreasing CEACAM6 expression in CD intestinal cells is one strategy that could prevent AIEC bacteria colonization of the intestinal mucosa and subsequent inflammation. This work aims at studying the effect of a methyl donor enriched diet (HMD: High Methyl Diet). Aims & Methods: CEABAC10 female mice were fed a HMD (supplemented in folate, biotin, B12 vitamin, zinc, methionine) for 2 weeks before pregnancy. After weaning, the colonic epithelial cells from offspring were purified using EDTA. A range of different parameters such as CIMP (Cancer immune methylator phenotype), AIEC bacteria population was quantified using a qPCR approach. DNA methylation was measured at a global level and on the CEACAM6 promoter using bisulfite-sequencing. qPCR was used to quantify CEACAM6 mRNA. RNA-seq data was used to highlight transcriptomic changes in colonic cells in the both conditions tested.

Results: We observed that mice fed a HMD show a significant decrease in basal lipocalin-2 level in stools compared to mice receiving a conventional diet suggesting a beneficial effect on gut inflammation. No significant changes were observed on histological sections following HMD. Microbiota analysis revealed a 1000-fold decrease in E. coli population in mice fed HMD compared to mice receiving a conventional diet. As expected, global DNA methylation was also decreased in a global hypermethylated strain used in mice fed a HMD compared to mice fed a conventional diet. Bisulfite sequencing revealed a hypermethylation of the CEACAM6 promoter, especially on the HRE sites. This hypermethylation of the promoter was associated with a significant decrease in CEACAM6 expression as measured by qPCR and Western-blot. RNA-seq data confirmed the decrease in CEACAM6 expression and highlighted many mis-regulated genes following HMD, among them, many genes involved in adaptive immunity. Conclusion: This work shows that the addition of a few vitamins and oleo-elements to the diet could interfere with the DNA-methylation metabolism leading to changes in genes expression such as a decrease in CEACAM6 and modify microbiota composition leading to eradication of the E. coli population in the intestine. A diet-based strategy could help decreasing AIEC colonization in CD patients by modulating CEACAM6 expression.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP183 COMPARATIVE GENOMICS AND SINGLE NUCLEOTIDE POLYMORPHISM DISTRIBUTION BETWEEN ADHERENT-INVASIVE ESCHERICHIA COLI (AIEC) AND NON-AIEC STRAINS FROM THE HUMAN INTESTINE

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Introduction: The molecular basis of Adherent-invasive Escherichia coli (AIEC) pathogenicity, a pathotype associated with Crohn’s disease, still needs to be well resolved. Nowadays the identification of the pathotype is performed with time-consuming techniques based in phenotypic screening of cultured bacteria; obtaining new molecular tools would therefore be of great significance.

Aims & Methods: Our aim was to identify putative genetic elements involved in AIEC phenotype to gain insight into the mechanisms of its pathogenicity and to find molecular targets for its identification. To achieve this objective we performed comparative genomics of three E. coli strain pairs consisting in one AIEC and one non-AIEC of identical pulsed field gel electrophoresis fingerprint. Each pair belonged to a distinct phylogroup. This approach was designed in order to increase the chance of finding sequences AIEC-specific and not strain-specific. The six strains’ genomes were sequenced de novo by combing paired-end libraries of HiSeq Illumina and PacBio. Two different approaches for comparative genomics were used: i) assembly with Velvet and genome comparison of AIEC with non-AIEC, ii) SPAdes- Kraken taxonomy and comparative genomics between pairs in relation to a genome of reference (AIEC UMI146) with Mauve. Only non-synonymous Single Nucleotide Polymorphisms (SNPs) in coding regions were selected. Sanger sequencing was performed to confirm the presence of SNPs and to evaluate the distribution of the SNPs in a collection of 22 AIEC and 29 non-AIEC isolates. Nucleotides for each SNP were analysed taking into account AIEC phenotype, adhesion and invasion indexes of isolates by χ² test or ANOVA as required.

Results: Genome sizes of Velvet assemblies for AIEC strains ONT-HNT-D, O6:H1-B2 and O22:H7-B1 were 4.86, 5.16 and 4.79Mb respectively. When SPAdes were used, they presented +95,362bp, +47,933bp and +30,178bp respectively. Comparative genomics of the first approach reported 114, 80 and 31 SNPs, whereas the second resulted in 19, 27 and 31 SNPs respectively. Six SNPs were found with both strategies. From all, 23 SNPs were confirmed by Sanger and analysed among the study collection. These SNPs were comprised in 14 genes from which 3 were involved in metabolic processes, 2 in stress tolerance and 2 in adhesion and invasion pathways. Most of the SNPs were strain-specific, except from one found in a gene putatively implicated in adhesion/invasion, that was differentially distributed among AIEC and non-AIEC strains (p = 0.029). Interestingly, this SNP plus other 3 SNPs positions located in the same gene were associated with invasion (p = 0.024) and one of them also with adhesion (p = 0.04).

Conclusion: To conclude, we have detected SNP variations in a single gene that could be associated with AIEC phenotype. However, further studies with site-specific mutations are needed to confirm the implication of this gene in the AIEC pathogenicity and the SNP effects. Our study indicates that there is not an AIEC-specific genetic marker and widely distributed in all AIEC.

Disclosure of Interest: All authors have declared no conflicts of interest.
Aims & Methods: CDI on patients’ mortality and other outcomes among patients with Crohn’s disease.

Conclusion: Among the carbohydrates tested, only mannose specifically limited the adhesion of EHEC to ileal biopsies and reduced the number of hemorrhagic Peyer’s patches and M cells, indicating that expression of lpfA1 or/and lpfA2 genes is essential in EHEC infections and use of antibiotics remains controversial. Probiotic yeast could be an alternative strategy.

Aims & Methods: The objectives of the study were to investigate the role of Lpf in EHEC tropism to Peyer’s patches, and to explore the influence of probiotic yeasts on EHEC interactions with intestinal mucosa. The expression of lpf genes (encoded by two lpf operons) of EHEC O157:H7 strain EDL933 was analyzed using in vitro models of the human or murine gastrointestinal tract and large intestine. To investigate the involvement of Lpf in the ability of EDL933 to target Peyer’s patches, we generated the DlplfA1, DlplfA2, DlplfA1-DlplfA2 isogenic mutants and pre-treated them with Lpf genes. Lpf interaction with M cells was measured using an in vitro model of specialized M cells.

In vivo interactions of EHEC with murine Peyer’s patches were analyzed in ileal loop assays. Mice were infected with a mixture of two bacterial strains, and the number of Peyer’s patches-interacting bacteria were determined using a competitive index analysis. To investigate the effect of probiotic yeasts, mice were given the probiotic for 7 days before ileal loops assays were conducted with O157:H7 wild type.

Results: Lpf isogenic mutants (i) were not able to interact with ileal biopsies compared with the wild type strain in competitive colonization assays and (ii) translocated across M cells at levels significantly lower than those observed for the wild type strain. Trans-complementation of the mutants with the cloned lpf genes restored their ability to interact with Peyer’s patches, indicating that expression of lpfA1 and/or lpfA2 genes is required for interactions with Peyer’s patches. Bloodshot Peyer’s patches were macroscopically observed following EHEC infection of murine ileal loops. We showed that pre-treatment with yeasts significantly inhibited O157:H7 interaction with Peyer’s patches and reduced the number of hemorrhagic Peyer’s patches in murine ileal loops. Since yeast cell surface is rich in mannose, the role of carbohydrates in EHEC interactions with Peyer’s patches was investigated. Among the carbohydrates tested, only mannose specifically limited the interaction of EHEC with Peyer’s Patches.

Conclusion: We conclude that Lpf is involved in the interactions of EHEC with murine Peyer’s patches and are needed for an active translocation across M cell monolayer. Tropism of EHEC to Peyer’s patches can be limited by probiotic yeasts and carbohydrates.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP185 CURRENT OR PAST CLOSTRIDIUM DIFFICILE INFECTION IS ASSOCIATED WITH INCREASED MORTALITY, MORBIDITY AND RESOURCE UTILIZATION AMONG PATIENTS HOSPITALIZED FOR CROHNS’ DISEASE: RESULTS OF A NATIONWIDE ANALYSIS

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Introduction: Multiple factors have been associated with an acute flare of Crohn’s disease, including cigarette smoking and non-steroidal anti-inflammatory drug use. Recently, Clostridium difficile infection (CDI) has been added to this list. CDI can become chronic or recurrent in 20% of patients. To date, the impact of CDI on patients’ mortality and other outcomes among patients with Crohn’s disease has not been investigated.

Aims & Methods: The aim of this study is to explore the impact of past or current CDI on mortality, morbidity and resource utilization among patients hospitalized for Crohn’s disease. This was a retrospective cohort study using the 2012 National inpatient sample, the largest publically available inpatient database in the United States. The inclusion criteria were: 1- a principal diagnosis of Crohn’s disease 2- A principal diagnosis of intestinal hemorrhage, obstruction, fistula, or abdominal abscess with a secondary diagnosis of Crohn’s disease. There were no exclusion criteria. The primary outcome was in-hospital mortality. The secondary outcomes were morbidity as measured by shock, intensive care unit (ICU) admission, colectomy or intestinal resection rate and resource utilization as measured for Crohn’s disease. For patients with CDI, hospital region, rural location, size and hospital teaching status.

Results: 74,515 patients with Crohn’s disease were included in the study, 1,465 (2%) of whom had CDI. The mean age was 43 years, 44% were female. Patients with CDI had higher mortality rate (adjusted odds Ratio (OR): 1.05; 95% confidence interval: (CI): 1.79–19.07, p = 0.01) and higher morbidity compared with patients without CDI. Looking at morbidity, patients with CDI had similar a colectomy rate (OR:1.16, CI: 0.75–1.77, p = 0.5), ICU admission rate (OR: 2.77, CI: 0.93–8.29, p = 0.07) and shock rate (OR: 3.06, CI: 0.94–9.97, p = 0.06) but a lower intestinal resection rate (OR: 0.26, CI: 0.80–0.82, p=0.02) compared with patients without CDI. When resource utilization was examined, patients with CDI had lower LOS (mean: 2.54 days, CI: 1.78–3.30 days, p < 0.01), higher TPN use (OR: 2.71, CI: 1.92-3.82, p = 0.02), higher total hospitalization charges (mean: $14,250, CI: $8,473–$20,026, p < 0.01) and similar abdominal CT scan use (OR: 1.41, CI: 0.78–2.59, p = 0.25) compared with patients without CDI.

Conclusion: Current or past CDI is associated with increased mortality among hospitalized patients with Crohn’s disease. However, patients with CDI have similar colectomy rates, shock or ICU admission rate compared with patients without CDI. Finally, CDI has a profound effect on resource utilization with longer length of stay, increased TPN use and substantially higher total hospitalization charges.

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 08:30–10:00

COLON CANCER: FROM SCREENING TO PALLIATION – ROOM 186

OP186 SELF-EXPANDABLE METALLIC STENT AS BRIDGE TO SURGERY IS MORE SUPERIOR THAN TRANSKAL ILEAL DRAINAGE TUBE AT QUALITY OF LIFE FOR THE PATIENTS WITH PRIMARY MALIGNANT COLORECTAL OBSTRUCTION

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Introduction: Self-expandable metallic stents (SEMS) or transanal drainage tube (TDT) is endoscopic decompression for malignant colorectal obstruction. SEMS is said to be superior to TDT at quality of life (QOL) for the patients, but the comparison between SEMS and TDT for malignant colorectal obstruction was few reported include the clinical efficiency, safety and prognosis.

Aims & Methods: The aim of this study is to evaluate QOLs, clinical efficiency and safety between SEMS and TDT for the patients with malignant colorectal obstruction. We retrospectively analyzed 69 patients who underwent SEMS or TDT insertion for malignant colorectal obstruction from April 2009 to March 2016 on the basis of single-center experience in Japan. SEMS was inserted for bridge to surgery (BTS) or palliation, and TDT was inserted for BTS or bridge to SEMS insertion.

Results: There were 27 patients in SEMS group (male 37.0%, median age 73±17.0years) and 42 patients in TDT group (male 54.8%, median age 65±15.2 years). Technical success rate was 100% of SEMS group and 95.2% of TDT group (p = 0.15). The endoscopic decompression as BTS for primary colorectal cancer was performed in 57.1% of SEMS group and 85.7% of TDT group (p = 0.02). Among these patients, the duration for surgery after decompression was longer in SEMS group (14.9±7.9 days vs 10.5±6.6 days, p = 0.04), because the rate of temporary discharge was significantly higher in SEMS group (41.7% vs 0.0%, p < 0.001). No significant difference was shown about the hospitalization in both group (36.1±23.5 days vs 46.4±36.0 days, p = 0.36). The oral intake (at least solid foods) was significantly higher in SEMS group (89.2% vs 25.0%, p < 0.001). The Colonic Stent Safe Procedure Research Group ColonRectal Obstruction Scoring System (CROSS) score before decompression was not significantly different in both group (1.1±0.9 vs 1.2±0.7, p = 0.49), but CROSS score after decompression was significantly improved in SEMS group (3.7±0.8 vs 2.3±0.5, p < 0.001). The complications after procedure, such as perforation, migration, re-obstruction, had no significant difference in both group.

Table: Patients characteristics and results

<table>
<thead>
<tr>
<th>SEMS (n = 27)</th>
<th>TDT (n = 42)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>10 (37.0%)</td>
<td>23 (54.8%)</td>
</tr>
<tr>
<td>Age (median, years)</td>
<td>73±17.0</td>
<td>65±15.2</td>
</tr>
<tr>
<td>Age &gt; 85years</td>
<td>9 (33.3%)</td>
<td>7 (17.1%)</td>
</tr>
<tr>
<td>Obstructed location (left side)</td>
<td>23 (85.2%)</td>
<td>38 (90.5%)</td>
</tr>
<tr>
<td>Primary colorectal cancer</td>
<td>21 (77.8%)</td>
<td>28 (70.0%)</td>
</tr>
<tr>
<td>-BTS</td>
<td>12 (44.4%)</td>
<td>24 (57.1%)</td>
</tr>
<tr>
<td>-Bridge to SEMS insertion</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>-Palliation</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>-Emergent surgery</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>-Metastatic colorectal cancer</td>
<td>6 (22.2%)</td>
<td>12 (30.0%)</td>
</tr>
<tr>
<td>-BTS</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>-Bridge to SEMS insertion</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>-Palliation</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>-Emergent surgery</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>-Technical Success</td>
<td>27 (100%)</td>
<td>40 (95.2%)</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Perforation</td>
<td>2 (7.4%)</td>
<td>6 (14.3%)</td>
</tr>
</tbody>
</table>

(continued)
Aims & Methods: This study aimed to clarify the clinical factors associated with the technical difficulty of SEMS placement for malignant colonic obstruction. We established the Colonic Stent Safe Procedure Research Group to provide instructions on how to safely perform SEMS placement, and we then conducted its prospective, observational, single-arm, multicenter clinical trial between March 2012 and October 2013 in Japan. Forty-six facilities participated in this study. An uncoaxed WallFlex Expandable Colonic Stent (Boston Scientific Corporation) was placed in each patient. Technically difficult cases of SEMS placement were defined as those that had a procedure time longer than 45 min (i.e., 1.5-fold longer than the median procedure time). We evaluated the clinical data and extracted risk factors associated with the technical difficulty of SEMS placement by using univariate and multivariate analyses.

Results: A total of 518 consecutive patients were enrolled in this study. Seven patients were excluded and the remaining 511 patients constituted the per-protocol population. There were 333 men (70%) and 178 women (30%) with a mean age of 70 years. Three hundred eleven patients (61%) underwent stenting as a bridge to surgery, and 200 (39%) underwent stenting for palliation. Technical success was achieved in 497 patients (98.3%). The median procedure time in the cohort with technical success was 30 min (IQR, 4–170 min). One hundred thirty-six patients (27%) were defined as technically difficult cases of SEMS placement. Clinical risk factors independently associated with the technical difficulty of SEMS placement were metastasis of peritoneal carcinomatosis (odds ratio [OR], 2.24; 95% confidence interval [CI], 1.26–3.96; p < 0.01), a Colorectal Obstruction Scoring System (CROSS) score of 0 before SEMS placement (OR, 2.00; 95% CI, 1.18–3.40; p < 0.01), tumor site in the right colon (OR, 3.33; 95% CI, 2.06–5.42; p < 0.001), strictures length > 5 cm (OR, 1.65; 95% CI, 1.01–2.70; p = 0.04), the placement of > 1 stent (OR, 5.96; 95% CI, 1.39–29.27; p = 0.02), and a length > 6 cm for the first stent (OR, 2.21; 95% CI, 1.38–3.56; p < 0.01). However, the clinical risk factors independently negatively associated with technical success were a history of chemotheraphy before SEMS placement (OR, 0.47; 95% CI, 0.22–0.98; p = 0.04), digestive tract decompression (OR, 0.45; 95% CI, 0.25–0.81; p < 0.01), and a diameter of 25 mm for the first placed stent (OR, 0.32; 95% CI, 0.12–0.76; p = 0.02).

Conclusion: This large-scale study demonstrated the high technical success rate of SEMS placement for malignant colorectal obstruction. However, clinicians should perform this procedure very carefully in cases with metastasis of peritoneal carcinomatosis, severe stenosis with a CROSS score of 0, and/or long strictures treated as a first stent.

RESULTS

Overall survival in this observational cohort did not differ significantly from that of Belgian colon cancer patients in the same period (p = 0.14). One-, five- and ten-year survival was not statistically different in both groups (95.9% vs 79.0%; 54.7% vs 51.2%; 41.0% vs 35.6% respectively). Additionally, for tumour stage II, III and IV no statistical differences between both cohorts were found (p = 0.21, p = 0.58, p = 0.10 respectively). Technical success rate was 94.8%. Seventy patients did not experience any complication. Stent migration occurred in 9 patients, whereas stent-related micro- and macro perforations were observed in 14 patients, without influencing survival. Incidence rates of perioperative mortality did not differ significantly between patients with and without any type of perforation (22.2% vs 15.2% respectively, p = 0.47). On average, surgery took place 16.6 days after colonic stenting, ranging from an operation on the same day as the endoscopic procedure, to an interval of maximal 124 days. In 82.5% of these a laparoscopic resection of the tumor was performed. Five point two per cent of the patients got only primary surgery. In 5.2% of the patients a laparoscopic procedure was converted to laparotomy, because of adhesions or peritonitis. Stoma rates were low (5.2%).

CONCLUSION: We used a observational study design to evaluate the outcomes of screening colonoscopies in average risk population is 50–55 years, but there is no upper age limit. Many patients are addressed for screening in advanced age. Although the prevalence of neoplastic lesions increases with age, life expectancy decreases. The aim of or study was to evaluate the outcomes of screening colonoscopies in population over 70 years of age.

Aims & Methods: The data from all screening colonoscopies performed in one non-university gastroenterology center from January 2012 to December 2015 were recorded in our database. In total 12365 screened patients were included. Data regarding indication for and before the screening colonoscopy, and perioperative mortality and complications were documented. The main endpoints of this study were to evaluate the outcomes of screening colonoscopies in average-risk patients.

DISCLOSURE OF INTEREST: All authors declared no conflicts of interest.

OP190 IMPACT OF MORTALITY FROM SURGICAL ADENOMA REMOVAL ON THE EFFECTIVENESS OF COLORECTAL CANCER SCREENING

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INTRODUCTION: Implementation of colorectal cancer (CRC) screening programs results in an increase in the number of adenoma diagnoses. Some of the advanced adenomas (AADs) cannot be endoscopically removed and patients may then be referred for surgery. However these surgical resections have an associated mortality as well as a negative impact on the effectiveness of CRC screening.

METHODS: We used the MISCAN-Colon microsimulation model to simulate the Dutch population, aged 50 years and older in 2013 and followed them through lifetime. The population was offered biennial FIT (FOB-Gold at a cut-off of 46 mg/g feces) screening between ages 55 and 75. Gradual roll-out was simulated from 2014 to 2020 according to implementation. To assess the impact of perioperative mortality in relation to AAD removal, we simulated a scenario with and without perioperative mortality within the screening program. In the scenario with perioperative mortality, we assumed that 3.9% of all AADs diagnosed during diagnostic colonoscopy need to be surgically removed, based on findings with perioperative mortality per year, the number of prevented CRC deaths, life years gained (LYG), quality adjusted life years (QALYs) and costs. Sensitivity analyses were performed with a mortality risk of 0.05% and 0.11% for every AAD diagnosis. The primary outcomes were the size of perioperative mortality in relation to AAD removal on the effectiveness of CRC screening.

CONCLUSION: We used the MISCAN-Colon microsimulation model to simulate the Dutch population, aged 50 years and older in 2013 and followed their lifetime. The population was offered biennial FIT (FOB-Gold at a cut-off of 46 mg/g feces) screening between ages 55 and 75. Gradual roll-out was simulated from 2014 to 2020 according to implementation. To assess the impact of perioperative mortality in relation to AAD removal, we simulated a scenario with and without perioperative mortality within the screening program. In the scenario with perioperative mortality, we assumed that 3.9% of all AADs diagnosed during diagnostic colonoscopy need to be surgically removed, based on findings with perioperative mortality per year, the number of prevented CRC deaths, life years gained (LYG), quality adjusted life years (QALYs) and costs. Sensitivity analyses were performed with a mortality risk of 0.05% and 0.11% for every AAD diagnosis. The primary outcomes were the size of perioperative mortality in relation to AAD removal on the effectiveness of CRC screening.

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DISCLOSURE OF INTEREST: All authors declared no conflicts of interest.
Table 1: Prevalence of anaemia at diagnosis and 1-year follow up.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Eastern Europe</th>
<th>Western Europe</th>
<th>Eastern Europe</th>
<th>Western Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia - overall</td>
<td>43%</td>
<td>26%</td>
<td>29%</td>
<td>13%</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>6%</td>
<td>3%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Anaemia of chronic disease</td>
<td>9%</td>
<td>3%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Mixed anaemia</td>
<td>6%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Other anaemia</td>
<td>6%</td>
<td>4%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Unclassified</td>
<td>14%</td>
<td>16%</td>
<td>16%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Conclusion: In this unselected, population-based inception cohort the frequency of anaemia was high at the time of diagnosis, especially for CD, but decreased during the first year of follow-up. More Eastern than Western European patients remained anaemic after 1 year of follow-up. These geographic differences could be caused by differences in awareness of anaemia or they might reflect differences in global care and inflammation control of IBD patients in Europe. Geographic variations in the use of biological therapy might contribute to the observed differences in anaemia frequency.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OPI93 INCIDENCE AND RISK FACTORS OF SERIOUS VIRAL INFECTIONS IN INFLAMMATORY BOWEL DISEASE

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Introduction: Use of immunosuppressants in IBD is associated with an increased risk of serious infections that varies considerably according to infection and immunosuppressant subtypes. This study aimed to determine the incidence rate and risk factors for serious viral infection (SVI) according to drug exposure and IBD activity in patients with IBD.

Aims & Methods: Using MICISTA registry, a prospective observational cohort of IBD patients treated at our tertiary care hospital, we identified between Jan 2005 and Dec 2014 patients who developed SVI as defined by need for hospitalization, definite organ damage or disabling sequelae. Cases of CMV colitis without systemic manifestations were excluded. We first estimated incidence rates of SVI, overall and according to maximal yearly treatment. Additionally, we performed a case-control study (4 controls for 1 case matched for age, gender, IBD subtype and duration) assessing risk of SVI according to IBD drug use and IBD clinical activity in the 3 months preceding the SVI (data extracted from individual health records).

Results: We identified 31 patients with SVI among 2645 patients, followed for a median period of 6.2 years and a total observational time of 16922 patient-years. We identified 13 cases of CMV systemic infection (primary infection (n = 6), reactivation (n = 7)). 10 cases of EBV infection (primary infection (n = 6) including 2 haemophagocytic syndromes, reactivation (n = 4)). 5 cases of VZV infection (varicella (n = 3), shingles (n = 2) and 3 cases of HSV infection (severe esophagitis, facial nerve paralysis, severe refractory cutaneous manifestation). Most patients required hospitalization (94%) and received IV anti-viral therapy (75%). The incidence rate of SVI in patients with IBD was 1.83 per 1000 patient-years. Table 1 shows the incidence rate of SVI according to the maximal treatment received during the year. In the case control study, risk of SVI was associated with exposure to thiopurines (adjusted odds ratio (aOR) 5.1; 95% CI, 1.9–13.4; p = 0.001) and methotrexate (aOR, 4.1; 95%CI, 1.0–16.8; p = 0.05), and active clinical disease (aOR, 3.2; 95% CI, 1.3–8.1; p = 0.02). Odds-ratios for corticosteroids and anti-TNF did not reach statistical significance (1.1 and 1.2, respectively).

Table 1: Exposure to medication (patients-years) Incidence rate for SVI (per 1000 patients-years) 95% Confidence interval

<table>
<thead>
<tr>
<th>Medication</th>
<th>Exposure to medication</th>
<th>Incidence rate for SVI (per 1000 patients-years)</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment or 5ASA</td>
<td>7922</td>
<td>0.50</td>
<td>ref 0.01–1.00</td>
</tr>
<tr>
<td>Steroids</td>
<td>1582</td>
<td>0.63</td>
<td>0.68 0.87</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>6236</td>
<td>3.2</td>
<td>0.0002 1.80–4.61</td>
</tr>
<tr>
<td>Anti-TNF ± immunomodulators</td>
<td>5173</td>
<td>1.16</td>
<td>0.31 2.3–20.9</td>
</tr>
</tbody>
</table>

Conclusion: SVI are rare events in patients with IBD who do not receive immunosuppressants. Exposure to thiopurines or methotrexate, and IBD clinical activity increases substantially the risk. Among 100 patients treated with thiopurines for 10 years, 3 will develop SVI.

Disclosure of Interest: All authors have declared no conflicts of interest.

OPI94 COLORECTAL CANCER RISK IN A NATIONALWIDE INFLAMMATORY BOWEL DISEASE COHORT WITH LOW GRADE DYSPLASIA

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Introduction: Patients with long-standing colonic inflammatory bowel disease (IBD) bear an increased colorectal cancer (CRC) risk. Endoscopic surveillance allows early detection and removal of precancerous lesions, like low-grade dysplasia (LGD), and may subsequently prevent CRC. However, the long-term sustainability of surveillance and the consequent risk to develop CRC remains uncertain.

Disclosure of Interest: All authors have declared no conflicts of interest.
since most available studies are small and cover a relatively short follow-up period. Aims & Methods: We published a study examining a history of LGD to 1) determine the cumulative CRC incidence, and 2) identify risk factors for developing CRC.

Aims & Methods: We performed a logistic multiple regression expressing the risk in terms of Odd Ratio. Finally, the diagnostic accuracy was tested by a ROC curve.

Results: We identified 1177 IBD patients with colonic LGD with a median follow-up time of 9.8 years per patient after LGD diagnosis (total follow-up time: 11741 patient years). 825 (70.1%) patients had ulcerative colitis, 216 (18.4%) Crohn's disease and 136 (11.6%) indeterminate colitis. Hundred nine out of 1177 (9.3%) patients underwent colectomy. CRC developed in 86 out of 1177 patients resulting in a cumulative incidence of 2.9%, 5.8%, 11.1%, and 18.7% after respectively 5, 10, 15 and 20 years. Patients with an IBD duration of more than 5 years before LGD development had a significantly higher cumulative CRC incidence (14.7% after 15 years) compared to those with a shorter IBD duration (9.4% after 15 years; log rank p = 0.002). Furthermore, patients with recurrent LGD had a higher CRC risk compared to patients with single LGD (10.5% after 15 years versus 4.5% after 15 years; log rank p = 0.026). Multivariable Cox regression identified both a longer IBD duration (hazard ratio [HR] 2.5; 95% confidence interval 1.5-4.3) and recurrent LGD (hazard ratio 1.9, 95% confidence interval 1.1-3.4) as independent factors associated with increased CRC risk.

Conclusion: We showed a cumulative CRC risk of 18.7% after 20 years in a large national cohort of IBD patients with a history of LGD. Both a longer IBD duration and recurrent LGD were identified as independent risk factors for CRC development following LGD. These findings may aid in risk stratification following a diagnosis of LGD in IBD patients.

Disclosure of Interest: All authors have declared no conflicts of interest.
Table 1: Time-dependent cox-regression analysis of baseline FIT of advanced neoplasia.

<table>
<thead>
<tr>
<th>Baseline cox conc.</th>
<th>Univariate HR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Multivariate HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>1.7</td>
<td>1.3–2.3</td>
<td>&lt;0.001</td>
<td>1.7</td>
<td>1.3–2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.1</td>
<td>1.0–1.1</td>
<td>0.01</td>
<td>1.07</td>
<td>1.0–1.1</td>
<td>0.019</td>
</tr>
<tr>
<td>Baseline hB conc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5 g Hb/g</td>
<td>Ref.</td>
<td>&lt;0.001</td>
<td>Ref.</td>
<td>1.1</td>
<td>1.0–1.2</td>
<td>0.0007</td>
</tr>
<tr>
<td>&gt;5-10 g Hb/g</td>
<td>1.8</td>
<td>1.3–2.4</td>
<td>0.001</td>
<td>1.7</td>
<td>1.3–2.2</td>
<td>0.0005</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>High</td>
<td>Ref.</td>
<td>0.08</td>
<td>1.01</td>
<td>0.73–1.3</td>
<td>0.478</td>
</tr>
<tr>
<td>Average</td>
<td>1.6</td>
<td>1.0–1.3</td>
<td>0.73</td>
<td>1.01</td>
<td>0.73–1.3</td>
<td>0.737</td>
</tr>
<tr>
<td>Low</td>
<td>0.6</td>
<td>0.4–1.0</td>
<td>0.19</td>
<td>0.64</td>
<td>0.4–1.0</td>
<td>0.273</td>
</tr>
</tbody>
</table>

Conclusion: Among FIT negative screeners, baseline hB concentration is an independent predictor for the risk of future AN. Moreover, hB concentrations of ≤0.6 g Hb/g and >5-10 g Hb/g are strong predictors of the risk of AN with up to a 14-fold risk increase. These findings suggest a role for hB in personalized screening strategies in population-based screening policies. In addition, the use of hB of negative FITs may permit alteration of screening intervals. Such strategies could decrease unnecessary burden for screenee and optimize the use of program related resources.

Disclosure of Interest: All authors have declared no conflicts of interest.

Disclosure of Interest: All authors have declared no conflicts of interest.
Conclusion: The present study does not suggest unfavorable short-term consequences in health behavior after getting a negative CRC screening test result.

Aims & Methods: The aim of our study was to compare patient demographics, tumor site, stage and survival between patients with screen-detected CRCs (SD-CRC) and non-screen-detected CRCs (non-SD-CRC). Between 2006 and 2014, 4,073 asymptomatic persons aged 50 to 74 were invited to take part in four consecutive biennial FIT-screening rounds. CRC cases were identified through linkage with the Netherlands Cancer Registry and were classified into four groups: SD-CRC, FIT interval cancers (diagnosed between screening rounds after negative FIT), colonoscopy interval cancers, and CRCs detected after negative colorectal after a positive FIT and CRC in non-participants (the latter three representing non-SD-CRC). Information on gender, age, socioeconomic status (SES), tumor site, stage and survival were collected and compared between patients in the four CRC groups using Chi-square-test.

Result: A total of 27,340 people were invited for FIT-screening, of whom 18,752 (68.6%) participated at least once. Median follow-up time was 46 months (IQR 18.5–72.4). Among participants, 3,009 (16%) had a positive FIT in one of the 4 screening rounds. In total, 265 patients were diagnosed with CRC: 116 were SD-CRC, 27 FIT interval CRCs, 13 colonoscopy interval CRCs and 109 CRCs detected in non-participants. There were no differences between the groups regarding age, gender and SES distribution. Screen-detected CRCs, FIT interval cancers and CRCs in non-participants were mostly located in the distal colon (70.7%, 63%, 61.5% of cases, respectively), whereas colonoscopy interval CRCs were mainly located in the proximal colon (69.2%)(p = 0.010). Stage distribution was significantly different between the four groups, with more favorable stages in patients with SD-CRCs (p < 0.001). Stage distribution in patients with FIT interval CRC and CRCs in non-participants was similar (p = 0.361). Survival rates were significantly higher among patients with SD-CRCs and FIT interval cancers compared to non-participants and patients with colonoscopy interval CRCs.

Conclusion: In this population-based CRC screening cohort, 0.14% of all participants were diagnosed with a FIT interval CRC during follow-up. The patients with SD-CRCs had the most favorable stages and highest survival rates. Our results support the effectiveness of FIT-screening programs.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP203 THE ADDED BENEFIT OF SURVEILLANCE IN COLORECTAL CANCER SCREENING

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Introduction: Although the impact of colorectal cancer (CRC) screening on CRC burden is well studied, the added benefit of surveillance in the context of an implemented screening programme is unclear.

Aims & Methods: Using the Adenoma and Serrated pathway to Colorectal Cancer model, we simulated the Dutch faecal immunochemical test (FIT) -based screening programme and combined this with a colonoscopy surveillance strategy based on the Dutch guideline. In this strategy, individuals considered at low risk return to screening after ten years whereas surveillance with a three or five-year interval is recommended for high- and intermediate-risk individuals, respectively. Furthermore, we evaluated three strategies in which the surveillance intervals as recommended in the Dutch guideline were prolonged to a) five years for all individuals at increased risk, b) five and ten years for respectively high- and intermediate-risk individuals and c) ten years for all individuals at increased risk. The comparator strategy was no screening and no surveillance. In addition, we simulated a screening only strategy without surveillance. Outcomes were CRC incidence and mortality, number of colonoscopies per detected CRC, life-years lived and costs per individual in the lifetime of 20,000,000 individuals.

Table (OP202)

<table>
<thead>
<tr>
<th>Screen-detected cancer</th>
<th>FIT interval cancer</th>
<th>Colonoscopy interval cancer</th>
<th>CRC in non-participants</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CRCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age diagnosis (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CRCs</td>
<td>116</td>
<td>27</td>
<td>13</td>
<td>109</td>
</tr>
<tr>
<td>50–59</td>
<td>24.1 (28) 43.1 (50) 32.8 (18)</td>
<td>22.6 (60) 40.7 (11) 37 (10)</td>
<td>7.7 (1) 61.5 (8) 30.8 (4)</td>
<td>19.3 (21) 45 (49) 35.8 (39)</td>
</tr>
<tr>
<td>60–69</td>
<td>0.55 to 70</td>
<td>0.55 to 70</td>
<td>0.55 to 70</td>
<td></td>
</tr>
<tr>
<td>Sex (male;% (n))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CRCs</td>
<td>62.9 (73)</td>
<td>59.3 (16)</td>
<td>53.8 (7)</td>
<td>63.3 (69)</td>
</tr>
<tr>
<td>Low–Average–High</td>
<td>11.2 (13) 70.7 (82) 18.1 (21)</td>
<td>7.4 (2) 77.8 (21) 14.8 (4)</td>
<td>15.4 (2) 76.9 (10) 7.7 (1)</td>
<td></td>
</tr>
<tr>
<td>Proximal–Distal–Unknown</td>
<td>29.3 (34) 70.7 (82) 0 (0)</td>
<td>37 (10) 63 (17) 0 (0)</td>
<td>69.2 (9) 23.1 (3) 7.7 (1)</td>
<td>34.9 (38) 61.5 (67) 3.6 (4)</td>
</tr>
<tr>
<td>Stage I–II–III–IV–Missing</td>
<td>51.7 (60) 13.8 (16) 31.9 (17)</td>
<td>29.6 (8) 22.2 (6) 33.4 (9) 14.8</td>
<td>35.5 (7) 7.1 (7) 7.1 (3) 38.5 (5)</td>
<td>7.7 (1)</td>
</tr>
<tr>
<td>Survival (% (n))</td>
<td>88 (102)</td>
<td>81.5 (22)</td>
<td>61.5 (8)</td>
<td>59.6 (65)</td>
</tr>
</tbody>
</table>

OP202 SCREEN-DETECTED AND NON-SCREEN-DETECTED COLORECTAL CANCERS AFTER FOUR ROUNDS OF FECAL IMMUNOCHEMICAL TEST-BASED COLORECTAL CANCER SCREENING

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Introduction: Fecal immunochemical test (FIT)-based colorectal cancer (CRC) screening aims to detect CRC in an early stage, thereby reducing morbidity and mortality from this disease. Whereas data on survival among patients with CRC detected via screening are available, few data exist on cancers in FIT-screening programs based on guaiac fecal occult blood testing are available in literature, as follows:

<table>
<thead>
<tr>
<th>Aims &amp; Methods:</th>
<th>The added benefit of surveillance in the context of an implemented screening programme is unclear.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results:</td>
<td>A total of 27,340 people were invited for FIT-screening, of whom 18,752 (68.6%) participated at least once. Median follow-up time was 46 months (IQR 18.5–72.4). Among participants, 3,009 (16%) had a positive FIT in one of the 4 screening rounds. In total, 265 patients were diagnosed with CRC: 116 were SD-CRC, 27 FIT interval CRCs, 13 colonoscopy interval CRCs and 109 CRCs detected in non-participants. There were no differences between the groups regarding age, gender and SES distribution. Screen-detected CRCs, FIT interval cancers and CRCs in non-participants were mostly located in the distal colon (70.7%, 63%, 61.5% of cases, respectively), whereas colonoscopy interval CRCs were mainly located in the proximal colon (69.2%)(p = 0.010). Stage distribution was significantly different between the four groups, with more favorable stages in patients with SD-CRCs (p &lt; 0.001). Stage distribution in patients with FIT interval CRC and CRCs in non-participants was similar (p = 0.361). Survival rates were significantly higher among patients with SD-CRCs and FIT interval cancers compared to non-participants and patients with colonoscopy interval CRCs.</td>
</tr>
<tr>
<td>Conclusion:</td>
<td>In this population-based CRC screening cohort, 0.14% of all participants were diagnosed with a FIT interval CRC during follow-up. The patients with SD-CRCs had the most favorable stages and highest survival rates. Our results support the effectiveness of FIT-screening programs.</td>
</tr>
</tbody>
</table>

Disclosure of Interest: All authors have declared no conflicts of interest.
Result: FIT screening without a surveillance programme reduced CRC incidence and mortality, respectively, 25.4% and 39.6% compared to surveillance and no surveillance strategy. CRC incidence and mortality reductions increased to 28.1% and 40.8% when surveillance based on the Dutch guideline was added to FIT screening. Prolonging surveillance intervals slightly reduced surveillance effectiveness (CRC incidence reductions 26.6%–27.2%, mortality reductions 39.6%–40.8% compared to no screening and no surveillance). In screening, 21 diagnostic colonoscopies were required to detect one CRC. The burden of surveillance was considerably higher; in the Dutch guideline strategy, 572 colonoscopies were required to detect one CRC. In the screening programme, we showed that this burden in substantially lowered, without substantial loss of effectiveness, if surveillance intervals are lengthened to five years.

Conclusion: Adding surveillance to FIT screening reduces CRC burden and is cost-effective compared to screening without surveillance. However, the colonoscopy burden is markedly higher than this burden in a surveillance programme. Through modelling, we showed that this burden can be substantially lowered, without substantial loss of effectiveness, if surveillance intervals are lengthened to five years.

Disclosure of Interest: All authors have declared no conflicts of interest.

Disclosure of Interest: M. Mandorfer: M.M. received honoraria for consulting from AbbVie, Gilead, MSD and Roche. K. Kozbial: K.K. received travel support from AbbVie, Bristol-Myers Squibb and Gilead. P. Schwabl: P.S. received payments for lectures from Roche and travel support from Janssen and Roche. C. Freissmuth: C.F. received travel support from Gilead and Janssen. S. Beinhart: S.B. received honoraria for consulting from AbbVie, payments for lectures from Bristol-Myers Squibb, Janssen and Roche. T. Reiberger: T.R. received payments for lectures from Roche, as well as travel support from Gilead, MSD and Roche. M. Trauner: M.T. received grants from MSD, honoraria for consulting from AbbVie, Gilead, Janssen and MSD, payments for lectures from Gilead, MSD and Roche, as well as travel support from Gilead and Roche. P. Ferenci: P.F. received grants from Gilead, MSD, and Roche, as well as honoraria for board membership and consulting from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Idexx, MSD and Roche. M. Mandorfer: M.M. received grants from Gilead, MSD and Roche, honoraria for board membership and consulting from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, and MSD, as well as payments for lectures from AbbVie, Boehringer Ingelheim. All other authors have declared no conflicts of interest.

OP204 SUSTAINED VIOLOGIC RESPONSE TO INTERFERON-FREE THERAPIES AMELIORATES HCV-INDUCED PORTAL HYPERTENSION


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Introduction: Portal pressure, assessed by hepatic venous pressure gradient (HVPG) measurement, drives the development of liver-related complications and mortality in patients with advanced chronic liver disease. Since a decrease in HVPG translates into a clinically meaningful benefit, it is an acceptable surrogate endpoint.

Aims & Methods: We aimed to investigate the impact of sustained virological response (SVR) to interferon (IFN)-free therapies on portal hypertension in patients with paired HVPG measurements. One hundred and four patients with portal hypertension (HVPG ≥ 6 mmHg) who underwent HVPG and transient elastography (TE) before IFN-free therapy (baseline [BL]) were retrospectively studied. The effect of SVR on portal pressure was investigated in patients with SVR who also underwent follow-up (FU)-HVPG and TE after IFN-free therapy (group A; n = 60). To determine the generalizability of our results, we included a second group (group B; n = 40), comprising all patients who achieved SVR and were included in the FU-HVPG measurement. In these patients, only information on FU-TE was available. Moreover, we also included 4 patients who did not achieve SVR.

Result: SVR to IFN-free therapies significantly decreased HVPG across all BL-HVPG strata. HVPG decreases of 6-9 mmHg (BL:7.3±0.28 vs. FU: 5.1±0.38 mmHg; P < 0.001), 10-15 mmHg (BL:12.2±0.4 vs. FU: 8.91±0.62 mmHg; P < 0.001) and >15 mmHg (BL:16.8±0.9 vs. FU: 12.5±0.9 mmHg; P < 0.05) were observed. The subgroup of patients with BL-HVPG of 6-9 mmHg, portal hypertension resolved in 63% (12/19), while no patient had an increase in HVPG at FU. Among patients with a BL-HVPG of 10-15 mmHg, portal hypertension resolved in 14% (3/21), 29% (6/21) had a FU-HVPG of 6-9 mmHg, while no patient showed a progression of portal hypertension at FU. Finally, in the subgroup of patients with a BL-HVPG of 16 mmHg, 5% (1/20) and 35% (7/20) of patients had a regression to a FU-HVPG of 6-9 mmHg or a FU-HVPG of 10-15 mmHg, respectively. However, portal hypertension did not resolve in any patient and 20% (4/20) of patients showed an increase in HVPG at FU. Patients with Child-Pugh stage B were less likely to have a HVPG decrease (HR:0.103; 95%CI:0.02–0.514; P = 0.066), when compared to Child-Pugh A patients. In the subgroup of patients with a BL-HVPG > 10 mmHg, the relative change in liver stiffness (per %; HR:0.972; 95%CI:0.945–0.999; P = 0.044) was a predictor of a HVPG decrease ≥10%.

Conclusion: Changes in liver stiffness, platelet count, and liver function tests were comparable between patients with and without fenofibrate. Prolonged follow-up HVPG and TE (group B), providing an argument for the generalizability of our results. Among the 4 patients without SVR, one patient underwent FU-HVPG and TE (HVPG increased from 18 to 20 mmHg; liver stiffness increased from 45 to 75 kPa), while 3 patients only underwent FU-HVPG (LVPG increased from 18 to 20 mmHg; liver stiffness increased from 45 to 75 kPa), 72 to 72 kPa and 10.2 to 15.5 kPa). Changes in liver stiffness, platelet count, and liver function tests were comparable between patients with and without fenofibrate.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference
OP207 COMBINATION THERAPY WITH DACLATASVIR AND ASUNAPREVIR IN CIRRHOTIC AND NON-CIRRHOTIC PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1B IN JAPAN


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Introduction: Combination therapy with dual NS5A-NS5B inhibitor (DCC; VSV inhibitor) and asunaprevir (ASV; second-generation HCV NS5A/NS3 protease inhibitor) was approved for patients with HCV genotype 1 in Japan since September 2014. Now, elderly patients and those with advanced hepatic fibrosis including chronic liver disease are preferred IFN-free therapy. This study's objective was to assess the efficacy and tolerability of DCV/ASV combination therapy in patients with hepatic cirrhosis.

Aims & Methods: In total, 153 consecutive patients with HCV 1 b initiating DCV/ASV therapy were enrolled. The cohort comprised 52 patients with compensated cirrhosis and 101 patients without cirrhosis. Treatment was given for 24 weeks. Efficacy evaluations were done using HCV-RNA NS5A RAVs. The primary end-point was sustained virological response (SVR12).

Results: SVR12 was achieved in 103/153 (67%). The rate of SVR12 was 94% (49/52) in patients with cirrhosis and 80% (54/67) in patients without cirrhosis. One patient died of hepatocellular carcinoma with a SVR12. Four patients had breakthrough infection with no treatment modification. The rapid viral response rate (HCV-RNA decrease to below the limit of detection) was 94% (47/50) in patients with cirrhosis and 92% (47/51) in patients without cirrhosis. No statistically significant difference in age, sex, IL28B genotypes, HCV viral load at baseline, ALT level, creatinine level, or NS5A RAVs between patients with and without cirrhosis was observed. The rate of breakthrough was not statistically significant between the two groups (4.0% vs. 2.7%).

Conclusion: DCV/ASV therapy achieved a high anti-HCV effect in patients both with and without cirrhosis. However, close monitoring is necessary in patients with cirrhosis.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OP208 EXPERIENCE IN THE MANAGEMENT OF DECOMPENESATED HCV CIRRHOTIC PATIENTS WITH LOW DOSE SOFOSBUVIR AND RIBAVIRIN COMBINED WITH DACLATASVIR

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Introduction: Direct-acting antiviral (DAA) therapy in the management of chronic active HCV, sustained response rates occurred in more than 95% of patients with compensated liver disease with improvement in their survival and the risk of decomposition that necessitates liver transplantation. The observation of reduced rates of sustained virological response in decompensated cirrhosis was explained by extensive portosystemic collaterals, advanced fibrotic parenchyma which are difficult to be penetrated, and provide dormant foci for viral reactivation. It was claimed that achieving SVR will improve MELD and CPT scores with improvement in clinically significant portal hypertension and hepatic venous pressure gradient.

Aims & Methods: Evaluation of the efficacy and safety of managing chronic active HCV in patients with decompensated cirrhosis and if SVR will improve HVPG measurement at baseline and three months after end of treatment (SVR12) was included. LS and HVPG were measured in a fasted, non-sedated state. Concomitant beta-blocker treatment was stopped for all measurements. Post-treatment liver biopsies were assessed by METAVIR score.

Results: Of 19 patients (56% male, age: 53.4 ± 6.7 years, 95% concomitant antiretroviral therapy), 16 received SOF/DCV, 2 SOF/ RBV, and 1 SOF/LDV. Seven (37%) patients were treated and experienced HCV (GT) distribution with GT1a: 12, GT1b: 2 and GT3a: 5. All patients had portal hypertension (HVPG >5 mmHg) and 14 patients (74%) presented with liver cirrhosis (LS ≥12 kPa). DAA treatment resulted in 100% SVR12. LS decreased significantly from 23.0 ± 16.5 to 16.9 ± 16.1 kPa (mean change (Δ): −6.1 ± 5.2 kPa; p < 0.001). Also, HVPG decreased from 10.4 ± 7.6 to 4.3 ± 4.3 mmHg (Δ: −7.2 ± 4.4 mmHg; p < 0.001). In patients with clinically significant portal hypertension (HVPG ≥10 mmHg, n = 9), HVPG decreased from 13.8 ± 3.0 to 10.9 ± 3.5 mmHg (Δ: −2.9 ± 2.3 mmHg; p = 0.015) − resulting in a hemodynamic improvement of 10% in 6/9 (66.7%) patients. In the subgroup of patients with baseline line HVPG <10 mmHg (n = 10), a reduction from 7.3 ± 1.3 to 4.6 ± 1.8 mmHg (Δ: −2.7 ± 2.2 mmHg; p = 0.003) was noted − resulting in cure of PHT (<5 mmHg) in 6/10 (60%). Post-treatment liver biopsies were available in 15 patients, all showing histological improvement in cirrhosis (METAVIR A0). 8 of 14 (57%) patients with cirrhosis at baseline, presented a post-treatment histological METAVIR <F3. Serum transaminases were normalized after therapy (AST: 66 ± 34 vs. 33 ± 20; p < 0.001; ALT: 115 ± 80 vs. 34 ± 15, p < 0.001), while hemoglobin, WBC and CD4 cell counts remained stable.

Conclusion: Virological response to IFN-free DAA therapies decreases LS and ameliorates portal hypertension. SVR12 seems to abolish histological necroinflammation in most DAA treated HCV infected patients. It remains to be explored if these improvements result in decreased liver-related mortality in the setting of HIV/HCV confection.

Disclosure of Interest: P. Schwabl: received payments for lectures from Roche and Böhringer Ingelheim, and travel support from AbbVie, Gilead, Jansen, and Roche
Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016
10:30–12:00
IMPROVING DETECTION AND TREATMENT OF COLONIC POLYPS – ROOM N2

OP210 RANDOMIZED, BACK-TO-BACK TRIAL OF NEW GENERATION OF NBI (HQ 290) FOR THE DETECTION OF COLORECTAL POLYPS

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Introduction: The benefits of narrow band imaging (NBI) for improving the detection of colorectal polyps remain questionable. The newly available second generation of NBI using 290 nm (290-NBI) provides an at least two folds brighter image compared with the previous version.

Aims & Methods: The aim of this study was to compare polyp miss rates between 290-NBI and high-resolution white light endoscopy (HR-WLE). Methods: From June 2015 to September 2015, 102 patients were randomized to undergo either HD-WLE or 290-NBI colonoscopy. In HD-WLE group, we performed colonoscopic examination as first inspection with HR-WLE followed by a second inspection with NBI. In 290-NBI group, colonoscopic examination were performed first inspection with NBI followed by a second inspection with HR-WLE. The primary outcomes were polyp miss rates. Result: A total of 127 polyps of 102 patients were detected. In HD-WLE group, 39 polyps were detected during the first inspection. A second inspection with NBI added 20 polyps, resulting in polyp miss rate of 33.9% with HR-WLE. In the NBI group, 54 polyps were detected during the first inspection. Subsequent inspection with NBI added 14 polyps, resulting in polyp miss rate of NBI of 20.6% (33.9% vs 20.6%, p = 0.006). In subgroup analysis, the polyp miss rates of flat type of HR-WLE and NBI showed significant difference (18.6% vs. 5.9%, p = 0.029).

Conclusion: New generation of NBI (HQ290) may reduce polyp miss rates and be more effective in reducing polyp miss rates of flat type.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OP212 ASSOCIATION OF CHROMOSOMAL INSTABILITY AND MICROSATELLITE INSTABILITY PATHWAYS WITH POSTCOLONOCY TO COLORECTAL CANCER IN A RETROSPECTIVE COHORT STUDY

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Introduction: Over 50% of the postcoloscopy colorectal cancer (PCCRCs) (i.e. CRC diagnosed after a colonoscopy that excluded cancer) originate from missed precursor lesions, in particular the subtle appearing non-polypoid (flat and depressed) adenomas and sessile serrated lesions. The biologic pathway of these lesions is unclear. We hypothesized that PCCRCs and subtle appearing precursors may share molecular features. In a retrospective, cohort study, we examined the occurrence of chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) in PCCRCs and prevalent CRCs.

Aims & Methods: We identified all PCCRCs diagnosed from 2001 to 2010 in a large gastroenterology practice from the Netherlands (le Clercq et al, Gut 2014). PCCRCs were defined as cancers occurring within 5 years after a complete index colonoscopy, which excluded CRC. We applied a clinical algorithm to assign the most likely explanation of PCCRC (incomplete colonoscopy/insufficient bowel preparation, missed lesion, incompletely resected lesion or new cancer). PCCRCs were then compared to prevalent CRCs (insufficient bowel preparation/ incomplete...
We report early experience with a prospective multi-center study on a modality for one-stage complete enteroscopy. None of these devices permits routine evaluation of the entire small intestine, which is mandatory for diagnosis or exclusion of deep enteroscopy-related criteria. If enrolled, informed consent was obtained. Under general anesthesia, two endoscopists (IMG and SB) performed all the colonoscopies (n = 21). They performed all colonoscopies (n = 21) with an average total procedure time of 66 minutes [range: 41–94]. A bleeding event requiring hospitalization occurred within 7 days of one of the procedures, but that was due to the underlying lesion rather than a complication of the procedure. No other significant adverse events were reported.

**Conclusion:** We present our initial experience of a safety and efficacy data trial for the motorized small bowel enteroscope. We were able to safely accomplish full enteroscopy in 71% of cases with a single antegrade deep enteroscopy using the motorized spiral enteroscope. This percent achievement of complete enteroscopy in a time typically reported for unidirectional deep enteroscopy suggests that this device is a significant development in design of small bowel enteroscopes. One patient experienced bleeding requiring hospitalization within 7 days of the procedure. This was a significant adverse event (SAE) by protocol. However on further review it was determined that the patient bled from a Meckel’s diverticulum, identified during deep enteroscopy. Subsequent surgery was curative.

**Disclosure of Interest:** S. Sanduleanu: Consulting for Olympus
D. Cave: Consulting and receipt of research funds from Olympus, Consulting for Medtronic
D. Demarco: Consulting for Spirus
All other authors have declared no conflicts of interest.

**Reference**

1. le Clercq CM, Bouwens MW, Rondagi EJ, Bakker CM, Keulen ET, de Ridder RJ, Winkens B, Masdee AA and Sanduleanu S. Postcolonoscopy capsule findings of a small bowel polyp.

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**OP214 THE AER-O-SCOPE COLONOSCOPE PROVIDES SUCCESSFUL ENDOSCOPIC THERAPY IN AN EX VIVO SWINE COLON MODEL**

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**S. Bezobchuk**

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**Introduction:** Three different platforms have been developed to perform deep enteroscopy; namely, single balloon, double balloon, and spiral enteroscopy. None of these devices permits routine evaluation of the entire small intestine, even with a combination of antegrade and retrograde enteroscopy. We report our early clinical experience with a motorized spiral enteroscope, which may provide a modality for one-stage complete enteroscopy.

**Aims & Methods:** We aimed to demonstrate the success of the self-propelled Aer-O-Scope colonoscopy in providing endoscopic therapeutic access. Therapeutic endoscopic access was a priori defined as the ability to reach a predefined target of interest, a pseudo-polyp, within an ex vivo swine colon and deliver "simulated" endoscopic therapy including: polypectomy with snare or biopsy forceps, submucosal injection, or thermal coagulation using argon plasma coagulation (APC). This was a prospective cohort study (n = 12 ex vivo swine colons housed in four different models that simulated variants of a human colon). Varying sized pseudo-polyps (n = 8 in each ex vivo swine colon) were created using colored thread and were randomly distributed throughout each ex vivo swine colon. Thus, n = 96 pseudo-polyps in total were created: 1 mm-3 mm (n = 78, 0%); 6 mm-9 mm (n = 13, 14%); ≥10 mm (n = 6, 6%). Following one day of Aer-O-Scope training for joystick utilization and endoscopic therapeutic access, two endoscopists (IMG and SB) performed all the colonoscopies (n = 12 colonoscopies per each endoscopist) on three separate procedure dates, in random order, and blinded to the type of colon model. The study's primary endpoint was a success rate of at least 90% in providing simulated endoscopic therapy and the study's secondary endpoint was endoscopist-perceived usability of the Aer-O-Scope for endoscopic therapy. We planned on performing a total of 240 simulated endoscopic therapies (n = 192 biopsy forceps, snare polypectomy, or combination injection/snare polypectomy and n = 48 APC applications). This sample size allowed up to a 10% pseudo-polyp miss rate with a two-sided...
statistical precision of 5%. This study protocol was reviewed and approved by an animal ethics committee.

Result: There were 5 (5.2%) pseudo-polyps disqualified, thus 235 simulated endoscopic therapies were able to be attempted. The success rate of the Aer-O-Scope colonoscopy simulated endoscopic therapy was: 234/235 = 99.6% (95%CI 0.976–1.00). The overall success rate was 234/240 = 97.6% (p < 0.001). The below Table shows the number of successful simulated endoscopic therapies per endoscopic tool. All endoscopic tools had a success rate >95%. There were only 2 failures, both during use of a polypectomy snare. Endoscopist-rated subjective usability of the Aer-O-Scope colonoscope simulated endoscopic therapy (easy to perform or only slightly complicated to perform) was very high (98%–100%) for all endoscopic tools.

Disclosure of Interest: S. Be zobchuk: I am a consultant for GI View Ltd. I.M. Granek: I am a consultant for GI View Ltd.

References

OP215 OUTCOME OF ENDOSCOPIC MUCOSAL RESECTION OF 424 LARGE SESSILE COLORECTAL POLYPS (≥20MM) OVER A 9 YEAR PERIOD: A SINGLE CENTRE EXPERIENCE AND ANALYSIS OF CHANGE WITH TIME

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Introduction: Endoscopic mucosal resection (EMR) has become the standard technique for resection of large sessile and flat colonic polyps. We aimed to assess the clinical outcome of colonic EMR of polyps ≥2cm and greater in size at University Hospital of Leicester NHS Trust and to assess changes over a 9-year period.

Aims & Methods: Data was collected for all sessile colonic polyps ≥20mm removed by EMR between 2006 and 2014 by 3 endoscopists (PW, JDC, RJR). Patient demographics, resection technique, completeness of initial resection, recurrence rate at first surveillance (SC1), polyp eradication at 2nd surveillance after at least year 1 (SC2) and complication rates were analysed.

Results: 364 patients were assessed for EMR, among which there were 424 completed EMRs (BSP 138, Symptomatic 26) by three operators. Of the 140 not proceeding to complete EMR, in 65 EMR was not attempted and patients were referred for surgical resection (cancer 31, technical difficulty 34). In a further 32 EMR was attempted but abandoned; all were referred for surgery (cancer 18, benign polyp 14). Finally, 43 had no intervention (13 declined, 22 non-adenomatous or pseudo polyps, 8 moved away). The mean age was 68.7 years (range 25–93), male 226 (53%), female 198 (47%). Mean polyp size was 33 mm (median 30 mm). Site of polyp was right colon 27%, transverse colon 5%, left colon 68% (rectum 58%, sigmoid 4%, descending 6%). Piecemeal EMR was done in 381 (90%), and ‘en bloc’ in 40 (10%). Of those who have undergone surveillance so far, recurrence was found in 56/284 (19.7%) at initial SC1 (mean 7 month; range 2–36) and was endoscopically treated in 53/56 (94.6%); 3/56 (5.4%) referred for surgical resection (cancer, 1 non lifting). Complete eradication after one year SC2 (mean 16 months, range 5–51) 211/234 (90.2%) with recurrence in 23 (9.8%) – but in 22/23 this was endoscopically resected. Overall complication rate 17/424 (4.0%, 14/424 (0.2%) post-caecal EMR required conservative medical treatment; post polypectomy pain syndrome 14/424 (3.3%) required admission for overnight conservative medical treatment. Delayed bleeding 2/424 (0.5%) required endoscopic therapy to achieve haemostasis. There were no procedure-related deaths. For each 3-year period (2006–8, 2009–11, 2012–14), there was a consistent reduction in number of polyps not treated endoscopically or requiring surgery (overall decrease of 15.7%), incomplete EMR referred for surgical resection (overall decrease of 2.3%) and recurrence rate at first SC1 (overall decrease 16.3%). There were increases in numbers of EMRs performed annually (overall increase 26.2%), mean polyp size resected (+7mm), level 3 & 4 polyps (3.7% and 7%) and complete eradication rate at SC1 (16.5%).

Conclusion: This is a large single-centre series of EMR of 424 sessile colonic polyps ≥2cm performed by 3 operators over a 9 year period; overall 20% had recurrence at initial surveillance, most managed endoscopically, with eradication rate at 1 year of over 90% (22/23 one year recurrences treated endoscopically). Examination of time trends over this period showed progressive reduction in recurrence and a trend for larger, more complex polyps to be resected endoscopically, with a corresponding drop in surgical management, demonstrating improvement in outcome with time.

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016

10:30-12:00

BARRETT’S ASSOCIATED NEOPLASIA – ROOM L7

OP216 DEVELOPMENT AND VALIDATION OF A CLASSIFICATION SYSTEM TO IDENTIFY BARRETT’S NEOPLASIA USING ACETIC ACID CHROMOENDOSCOPY: THE PREDICT CLASSIFICATION

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Introduction: Neoplasia in Barrett’s can be very subtle and difficult to identify. Acetic acid chromoendoscopy (AAC) has been demonstrated to highlight neo- plastic areas allowing for earlier treatment. Although the technique of AAC is very simple, lesion recognition with acetic acid (AA) remains a challenge and therefore hampering its widespread usage.

Aims & Methods: We aim to develop a simple and easy to use classification system for AAC to allow for identification of Barrett’s neoplasia. Three expert AAC endoscopists (PB, GLW, OP) formed a working group to identify AAC component criteria of non-dysplastic and dysplastic Barrett’s using a modified Delphi Method. Following this, a panel of 7 advanced endoscopists assessed the performance of each individual criterion by reviewing a bespoke online database of 40 images and 40 videos of non-dysplastic and dysplastic Barrett’s lesions. Finally, we assessed the diagnostic reproducibility of the validated criteria by asking 13 non-AAC expert endoscopists to complete an assessment tool of 40 images and 20 videos using this newly developed classification system.

Result: The component criteria identified by the expert AAC endoscopists were as follows: - Early focal loss of acetowhiteness: Present: Indicates presence of neoplasia - Absent: Indicates the absence of neoplasia - Surface pattern - Normal (Large uniformly distributed pattern) - Indicative of non-dysplastic Barrett’s - Abnormal (Compact, irregular or absent pits): Indicates neoplasia A total of 560 observations were undertaken to validate these criteria. The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) is shown in Table 1.

Table 1: Validation results of the classification criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of acetowhiteness</td>
<td>96.2%</td>
<td>91.8%</td>
<td>90.9%</td>
<td>97.5%</td>
</tr>
<tr>
<td>Normal</td>
<td>93.4%</td>
<td>97.9%</td>
<td>88.9%</td>
<td>94.8%</td>
</tr>
<tr>
<td>Abnormal</td>
<td>95.3%</td>
<td>99.4%</td>
<td>91.0%</td>
<td>94.1%</td>
</tr>
<tr>
<td>Surface pattern</td>
<td>77.0%</td>
<td>99.0%</td>
<td>91.4%</td>
<td>96.9%</td>
</tr>
<tr>
<td>Normal</td>
<td>69.7%</td>
<td>97.5%</td>
<td>88.4%</td>
<td>93.9%</td>
</tr>
<tr>
<td>Abnormal</td>
<td>99%</td>
<td>99.9%</td>
<td>99.0%</td>
<td>99.3%</td>
</tr>
</tbody>
</table>

When the AAC validated criteria are applied by the 13 endoscopists, the sensitivity, specificity, NPV and PPV of detecting neoplastic Barrett’s are 98.5%, 97.9%, 95% and 94% respectively.

Conclusion: We have developed and established the validity of a simple classification system to identify Barrett’s neoplasia using AAC. When non-AAC trained endoscopists apply these criteria, the sensitivity and NPV meet the recommended PPV threshold.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP217 STEPWISE DEVELOPMENT OF A VOLUMETRIC LASER ENDOMICROSCOPY PREDICTION SCORE FOR BARRETT’S NEOPLASIA USING MATCHED VOLUME IMAGING TOOLS OF ENDOSCOPIC RESECTION SPECIMENS

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Introduction: Endoscopic detection of early neoplasia in Barrett’s esophagus (BE) is difficult. Volumetric laser endomicroscopy (VLE) is an advanced imaging system incorporating 2nd generation optical coherence tomography in a balloon-based system, providing a 6-cm long circumferential scan of the esophageal wall up to 3 mm deep, with near-microscopic resolution. Several VLE features of early BE neoplasia have been determined previously (1,2).

Aims & Methods: Aims of this study were to determine (additional) VLE features of neoplasia, based on precise VLE-histology correlations ex vivo, and to develop and validate a VLE prediction score for early BE neoplasia.

A unique database of VLE images from endoscopic resection specimens and/or biopsy specimens of BE patients +/- neoplasia was used. Precise
VLE-histology correlation methodology has been described previously (5). In the orientation phase, VLE-histology images were compared with histopathological specimens and evaluated in an unbiased manner by a GI pathologist, BE endoscopist and VLE researcher. Features potentially predictive for early BE neoplasia were identified and subsequently discussed in consensus with 2 VLE experts. In the learning phase, VLE images corresponded with histological neoplasia (high-grade dysplasia (HGD) or early adenocarcinoma (EAC)); n = 10) and non-dysplastic (ND)BE tissue (n = 10) were scored by the 2 VLE experts – blinded to histology – for presence of neoplasia and VLE features identified in the orientation phase. After a consensus meeting, a predictive model was trained based on multinomial logistic regression analysis using learning phase results. This score was validated by expert scoring of 40 additional VLE images (20 HGD/EAC; 20 ND)E using area under receiver operating characteristic (ROC) curve (AUC) analysis.

Result: Four VLE features potentially predictive for BE neoplasia were identified: 1) lack of layering; 2) higher surface signal than subsurface signal; 3) presence of irregular, dilated glands; and 4) homogeneity. In the learning phase, features 1, 2, and 3 were significantly and independently associated with neoplasia. ROC analysis of the learning phase score was developed with: features 1, 2, and 3 (5 points), 2 (6 or 8 points for equal or higher surface signal) and 3 (5 points). ROC curve of this prediction score showed an AUC of 0.83 (95% CI 0.69–0.96) in the learning and 0.81 (95% CI 0.71–0.90) in the validation phase. A cut-off value of ≥3 was associated with sensitivity and specificity of 85% and 68% in the learning and 83% and 71% in the validation phase, respectively.

Conclusion: This study, using high-quality ex vivo VLE-histology correlation, confirms that the VLE features layering, surface signal, and irregular glands/ducts are independently and significantly associated with early BE neoplasia. Using these features, we developed and validated a VLE prediction score for BE neoplasia, with promising accuracy.

Disclosure of Interest: E. Tearney: Massachusetts General Hospital has a licensing arrangement with NinePoint Medical. Dr. Tearney has the rights to receive royalties from this licensing arrangement.


All other authors have declared no conflicts of interest.

References

OP218 DETECTION OF DYSPLASIA IN BARRETT’S OESOPHAGUS USING LECTIN-BASED NEAR INFRARED-RED MOLECULAR IMAGING: AN EX-VIVO STUDY ON HUMAN TISSUE


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Introduction: Detection of early neoplasia in Barrett’s oesophagus by white-light endoscopy is challenging due to the inopacuous nature of dysplasia. Molecular imaging using fluorescently labelled wheat-germ agglutinin (WGA) is a promising tool for detecting dysplasia as this topically applied imaging agent shows localization to pachydermic versus non-pachydermic oesophageal glandular mucosa (1). However in an endoscopy setting, the detection of fluorescence in the blue/green range is limited by high levels of tissue autofluorescence. This effect can be overcome by using near infra-red (NIR) imaging. Aims: To assess the feasibility of WGA-based NIR imaging for detection of dysplasia in Barrett’s. To this end, we studied patients with early Barrett’s-related neoplasia undergoing endoscopic mucosal resection (EMR). Freshly collected EMR specimens were sprayed with WGA-IR800CW (10μg/mL; 10 min, room temperature); washed with PBS buffer and then imaged with a high-sensitivity NIR camera (FluoeamTM). Planar fluorescence images were captured and up to two punch biopsies (2 mm diameter) were collected from each EMR specimen, underwent histopathology. The EMRs were then assessed in an ex-vivo model for dysplasia and fluorescence intensity. punch biopsies, taken from areas of interest within the EMR specimen, were also scored by the pathologist. The mean fluorescence intensity (MFI) of cells in dysplastic and non-dysplastic areas was compared by the Wilcoxon matched-pairs signed rank test. The MFI of punch biopsies taken from dysplastic and non-dysplastic areas was compared by the Wilcoxon matched-pairs signed rank test. The correlation between the fluorescent contrast and spatial extent of dysplasia was analysed by linear regression. Result: Ten patients were recruited at a single centre. We included in the analysis dysplasia associated with 16 benign lesions. In the whole EMR analysis, we found a significantly lower mean fluorescence intensity (MFI) in dysplastic versus non-dysplastic areas (P < 0.0001), in accordance with the reported reduced binding of WGA to neo- plastic Barrett’s epithelium (1). Similarly, the MFI of punch biopsies taken from dysplastic regions was significantly lower compared to that of non-dysplastic areas (P = 0.0002). Finally, we found that the fluorescent contrast between dysplastic and non-dysplastic areas was higher in EMRs with wider extent of neoplasia (R2 = 0.58; p = 0.0002).

Conclusion: WGA-based NIR imaging is an effective method for differentiating dysplastic from non-dysplastic Barrett’s mucosa ex vivo, which reduces the effects of tissue autofluorescence. In-vivo studies are now required to test the feasibility and potential clinical utility of this imaging tool for detecting dysplasia as this topically applied imaging agent shows rapid endoscopic identification of dysplasia in Barrett’s esophagus. Nat Med 2012; 18(2): 315-21.

OP219 RESULTS OF A PROSPECTIVE MULTICENTER REGISTRY OF RADIOFREQUENCY ABLATION FOR BARRETT’S ESOPHAGUS

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Introduction: Radiofrequency ablation (RFA), combined with endoscopic resection (ER) of visible lesions, can be used as a primary treatment for low-grade dysplasia (LGD), high-grade dysplasia (HGD) and early adenocarcinoma (EAC) in Barrett’s esophagus. In prospective multicenter controlled trials, high rates of complete remission of dysplasia (CR-D) and intestinal metaplasia (CR-IM) have been reported.

Aims & Methods: The aim of this study is to monitor outcome and efficacy of RFA in a setting of absence of reimbursement in a multicenter national prospective registry. Between February 2008 and August 2015, data from 7 centers performing RFA were collected in the Belgian RFA registry. All procedures were monitored for indication, treatment before RFA, short-/long-term complications and prospective long-term pathological outcome. Primary endpoint was CR-D and CR-IM. Secondary endpoints was safety.

Result: 388 RFA procedures were registered in 279 different patients (mean age 65; 84.5% men). In 60% a previous EMR/ESD was performed. Baseline histology prior to RFA (including ER) was: 2% SIM (5), 8% LGIN (22), 52% HGIN (146), 37% adenocarcinoma (102), 1% unknown (4). At the time of analysis, 181 patients were still under surveillance. In an intention to treat analysis (ITT), 83% (194/235) patients achieved CR-IM and 87% (204/235) CR-D after a median FU time of 670 days in an ITT and PP analysis. HGIN (146), 37% adenocarcinoma (102), 1% unknown (4). At the time of analysis, 181 patients were still under surveillance. In an intention to treat analysis (ITT), 83% (194/235) patients achieved CR-IM and 87% (204/235) CR-D after a median FU time of 670 days in an ITT and PP analysis. HGIN (146), 37% adenocarcinoma (102), 1% unknown (4). At the time of analysis, 181 patients were still under surveillance. In an intention to treat analysis (ITT), 83% (194/235) patients achieved CR-IM and 87% (204/235) CR-D after a median FU time of 670 days in an ITT and PP analysis.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference
OP22 LONG-TERM FOLLOW-UP RESULTS OF STEPWISE RADICAL ENDOSCOPIC RESECTION FOR BARRETT’S ESOPHAGUS WITH EARLY NEOPLASIA

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Introduction: Stepwise radical endoscopic resection (SRR) allows for complete endoscopic treatment of Barrett’s esophagus (BE) with early neoplasia. This approach has been shown very effective in reaching complete eradication of high-grade dysplasia (HGD) or early cancer (EC) (CE-neo) in 98% and all intestinal metaplasia (CE-IM) in 85% of patients.

Aims & Methods: The aim of this study was to report the long-term follow-up (FU) results after successful SRR for BE with early neoplasia. We screened all patients treated with SRR in two centers between 2001-2014, for BE ≤5 cm with HGD/EC, without signs of invasion. >T1m1, G3/G4 differentiation, lym-phovascular invasion or irradial deep resection margins in ER specimens. All patients who had reached endoscopic and histologically confirmed CE-neo and CE-IM after SRR were included for evaluation of long-term FU. All included patients from endoscopies and histological outcomes were collected and entered in a dedicated database. Duration of FU was calculated from last treatment till last FU endoscopy. Primary outcome: recurrence of HGD/EC and recurrence of IM combined with visible BE islands or tongues. Secondary outcomes: Barrett’s metaplasia (BB) in neoupsiious biopsies, and IM in biopsies obtained distal to the neo-z-line.

Result: Seventy-three patients were included (64 men, mean age 66 yrs, median BE 2(3)). Worst baseline pathology: HGD, n = 50; EC, n = 23. Median FU was 76 months (IQR 2(10) with a range (16) of 24 - 129 months). Recurrence of HGD/EC was observed in 1 patient (1.4%) after 129 months FU (T1N0M0 treated with curative surgery). Recurrence of IM in endoscopically visible BE was observed in 16 patients (of which 2 had LGD) after a median FU of 31 months. In all cases the extent of recurrence was limited to small (<1 cm) islands or tongues. Histological recurrence without visible BE was found in 25 patients: 3 patients had BB in neoupsiious biopsies (4% overall, 0.7% per patient year); 24 patients (33%) showed IM in biopsies just distal to a neoupsiious BE island (76% overall, 0.7% per patient year). A finding of IM in the neo-z-line was found in 50% of patients and BB in none of the patients. Additional treatment was performed in 8 patients: esophagectomy for T1b-cancer, ER of small island with LGD (n = 1), APC for small islands (n = 5), RF-A for LGD in the neo-z-line (n = 1). CE-neo and CE-IM (excluding IM in the neo-z-line) at the last FU endoscopy (after additional treatment) was seen in 100% and 96% respectively.

Conclusion: This study presents the longest published follow-up data on SRR to date. The 6-year outcomes show that after successful SRR of BE ≤5 cm recurrence of HGD/EC is rare (1.4% overall, 0.7% per patient year). Recurrence of IM in endoscopically visible BE was found in 22% of patients and was generally confined to small islands or tongues. Buried glands were rare (0.7% per patient year) and just as IM of the neo-z-line (33% of cases) of insignificant importance.

Disclosure of Interest: B.L.A.M. Weusten: Financial support for research: Coviden/Medtronic; Erbe Medical; C2Therapeutic, Consultancy: Boston Scientific; C2Therapeutic.

J.J. Bergman: Financial support for research: Coviden/Medtronic; Oryx Endoscopy; Cook Medical; Boston scientific; Erbe Medical; C2Therapeutic; Fuji-film; Ninepoint Medical; Consultancy: Boston Scientific; Cook Medical; C2Therapeutic.

All other authors have declared no conflicts of interest.

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4. Ricou M, Liu D, Duan CP, et al. Anti-BMP4 MAb1-24 by generating an RNAseq database of 56 EAC biopsies, and confirmed that patients with high levels of BMP4 expression tend to have a poorer recurrence-free survival than patients with low BMP4 expression, which suggests a more aggressive tumor behavior in BMP4 expressing EAC tumors. Inhibition of BMP4 function in SMAD4 negative EAC cancer cell lines specifically and effectively target leads to an increase in chemosensitivity and a decrease in invasive and migratory capabilities in vitro. Analyses of the signaling pathways showed that inhibition of the BMP4-mediated non-canonical pathways was responsible for these effects. Next, we made use of a patient-derived tumor xenograft (PDXT) mouse model of a SMAD4 negative EAC tumor (4). Preclinical in vivo studies with these mice confirmed that anti-BMP4 antibodies can effectively reduce tumor growth and metastasis formation.

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016
10:30:12:00
ACCURACY IN UPPER GI ENDOSCOPY – ROOM L9

OP222 PREMEDICATION WITH SIMETHICONE AND A PROBIOTIC TO IMPROVE ENDOSCOPY VISIBILITY DURING UPPER ENDOSCOPY – A PROSPECTIVE, DOUBLE-BLINDED RANDOMIZED CONTROLLED TRIAL

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Introduction: Upper endoscopy is the most common method for the diagnosis of upper gastrointestinal tract disease. Our aim was to determine if pre-medication with simethicone or N-Acetylcysteine improves mucosal visualization during upper endoscopy.

Aims & Methods: Randomized double-blinded, placebo controlled trial of 297 patients scheduled for upper endoscopy pre-medicated 15-30 minutes before: A–100 mL of water (placebo); B–water plus 100 mg simethicone; C–water plus simethicone plus 600 mg N-acetylcysteine. Primary outcome was the quality of mucosal visualization (score: 1-excellent; 2-good; 3-inadequate). Trial registered in http://clinicaltrials.gov (NCT02357303). Statistical analysis with X² and one-way ANOVA with Tukey’s correction.

Result: Visualization scores between groups B and C (versus A) were significantly better in the oesophagus 1.09 and 1.15 vs. 1.31 (p = 0.05) and stomach 1.26 and 1.30 vs. 1.67 (p = 0.01) and better without significance in the duodenum 1.07 and 1.09 vs. 1.20 (p = NS). “Excellent” scores versus others provided similar results (B vs. A: oesophagus 91% and 87% vs. 71% (p = 0.001), stomach 76% and 75% vs. 39% (p = 0.001) and duodenum 85% and 82% vs. 73% (p = NS). There was no significant difference in scores between groups B vs. C of different scores between gastric scores if previous subtotal gastrectomy (B and C vs. A): 1.45 and 1.68 vs. 1.86 (p = NS). The rate of reported lesions was higher in group B (without statistical significance).

Conclusion: Pre-medication with simethicone leads to better mucosal visibility, might improve diagnostic yield and should be considered standard practice. Addition of N-acetylcysteine had no benefit over simethicone alone.

Disclosure of Interest: All authors have declared no conflicts of interest.
OP223 DIAGNOSIS OF TUMOR EXTENT OF EARLY GASTRIC CANCER BY VOLUMETRIC LASER ENDOMICROSCOPY: A MULTICENTER PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

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Introduction: Accurate diagnosis of lateral extent of early gastric cancer (EGC) is important in terms of deciding treatment indication and achieving complete resection by endoscopy or surgery. Magnifying narrow band imaging (M-NBI) has been reported to increase yield of endoscopic diagnosis for determining extent of EGC.

Aims & Methods: To compare diagnostic ability of M-NBI for determining lateral extent of EGC with that of chromoendoscopy (CE). This study was conducted as a multicenter prospective randomization controlled trial including one university hospital, one cancer referral center and three general hospitals. Inclusion criteria were patients with EGC sized 1 cm or over who underwent endoscopic or surgical treatment. Exclusion criteria were history of gastric resection and high risk of bleeding for biopsy. After stratification by institution, tumor location, and histological type, patients were randomly assigned to M-NBI or CE groups. In each group, tumor extent was firstly evaluated by white light endoscopy according to difference of mucosal height and color, then oral margin of the tumor was determined by the assigned method. Diagnostic criteria of M-NBI were 1) demarcation line and 2) irregular microvessel/microsurface pattern and that of CE were 1) abrupt change of mucosal structure of the surrounding mucosa and 2) irregular structure patterns. Biopsy specimens were taken from 5-mm outside and inside of the oral boundary of the tumor and sent for histological evaluation. When the outside specimen was non-cancer and the inside specimen was cancer, it was defined as “successful delineation”.

Conclusion: The primary endpoint was defined as proportion of successful delineation between the two groups. A study protocol was approved by institutional review board in each institution and written informed consent for study participation was obtained from all patients.

Result: A total of 382 patients were enrolled and were assigned to the M-NBI group (n = 191) and the CE group (n = 191). Eight patients in the M-NBI group and 12 in the CE group were excluded remaining 183 in the M-NBI and 179 in the CE group for analysis. Successful delineation rates (95% CI) in the M-NBI and CE groups were 86% (81–91%) and 84% (78–89%), respectively (p = 0.498).

Reference

OP224 FEASIBILITY OF A COMPUTER ALGORITHM FOR DETECTION OF EARLY BARRETT’S NEOPLASIA USING VOLUMETRIC LASER ENDOMICROSCOPY

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Introduction: It has been proposed that high-resolution zoom endoscopes (optical zoom up to 115 times) could predict gastric pit pattern for gastric pathology. Recently an image-enhanced endoscopic technology called Optical Enhancement system (OE SystemTM) was introduced, improving visualization of microvessels. In addition to this, new high-definition zoom scopes called Magniview™ are available allowing an optical zoom up to 136 times with a better evaluation of the mucosa and superficial vascular aspects.

Aims & Methods: The aim of this study was to evaluate the utility OE System™ plus Magniview™ in the diagnosis of normal gastric mucosa, Helicobacter pylori associated gastritis, and gastric atrophy. Methods: Prospective, non-randomized and double blind study. All of the participants enrolled had functional dyspepsia according to the Rome III criteria and were tested for Helicobacter Pylori (HP) using stool antigen test. After this phase two groups were selected, dyspeptic HP (+) and dyspeptic HP (-) patients (control group). Finally an upper endoscopy using OE system™ plus Magniview™ scopes was performed and the gastric body evaluated using a previously described classification of four patterns based on the combination of the parameters subepithelial capillary network (SECN), collecting venules and round pits. Type 1 pattern predicts normal

Table 1. (OP224): Overall accuracy of the four patterns predictions

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>Accuracy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>90.00 (55.50–99.75)</td>
<td>79.03 (66.82–88.34)</td>
<td>40.91 (20.70–63.65)</td>
<td>90.00 (89.35–99.95)</td>
<td>80.55</td>
</tr>
<tr>
<td>Type II–III</td>
<td>91.43 (76.94–98.20)</td>
<td>78.38 (61.79–90.17)</td>
<td>80.00 (64.35–90.95)</td>
<td>90.62 (74.98–98.02)</td>
<td>84.72</td>
</tr>
<tr>
<td>Type IV</td>
<td>66.67 (9.43–99.16)</td>
<td>88.41 (78.43–94.86)</td>
<td>20.00 (2.52–55.61)</td>
<td>98.39 (91.34–99.96)</td>
<td>87.50</td>
</tr>
</tbody>
</table>

a) Ability to predict normal mucosa. b) Ability to predict Helicobacter pylori infection. c) Ability to predict mucosa atrophy.
gastric mucosa, types 2 and 3 HP related gastritis and the type 4 gastric atrophy. (I) Intraduodenally recorded biopsies and biopsies taken in order to correlate the images with the histology.

Result: A total of 72 patients were included, 35 in the dyspeptic HP (+) group and 37 in the control dyspeptic HP (-) group. The average age was 46.3 (37–58.5) years old. 69% were women. The images were analyzed and categorized into the four patterns after the agreement of three endoscopists. There were 22 (30.6%) patients with type I, 13 (18.1%) with type II, 27 (37.5%) with type III and 10 (13.9%) with type IV pattern. Almost all patients (90%) with normal mucosa were type I. Most type II and III patients had active chronic gastritis, which correlates with HP infection. In fact, 32/34 (91.1%) of patients with HP (+) were type II-III. The 66% of patients with atrophy had type IV pattern. The Table 1 shows the overall accuracy of the four patterns predictions. Type I patients had normal mucosa, Type II-III HP infection, and Type IV atrophy with a sensitivity of 90%, 91% and 66.7% respectively and an accuracy of 80.5%, 84.7% and 85.7% respectively. Finally the intra and inter-observer agreement was calculated with a kappa value of 0.91 and 0.89 respectively.

Conclusion: Endoscopy plus optical magnification has proved to be useful in the diagnosis of normal gastric mucosa and HP associated gastritis with high accuracy, unlike gastric atrophy evaluation.

Disclosure of Interest: C. Robles-Medranda: Key Opinion Leader for Pentax Medical

All other authors have declared no conflicts of interest.

Reference


OP228 ROAD MAP FLUOROSCOPY FOR SUCCESSFUL GUIDANCE OF ENDOSCOPIC INTERVENTIONS IN THE ESOPHAGUS

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Introduction: Digital subtraction angiography is a method to enhance the contrast information in relation with contrast injection. Structures that are not of interest are deleted from the image by subtraction of image information. A variation of this technique is called Road Map Fluoroscopy (RMF) where an image at peak opacification is used as the mask for subsequent fluorescence images. With this knowledge advanced endoscopists or catheters can be viewed without additional marking or contrast injection. In summary, the opacification is only performed once but the information remains on the image throughout the investigation. In this way anatomic structures such as length or diameter of stenosis can be measured with high accuracy (1–4). Although esophageal stent placement has been reported to be safe also without fluoroscopic guidance most endoscopists prefer to use fluoroscopy during stent deployment (5–7). Mucosal marking using the injection of lipiodol for stent implantation is widely used among endoscopists but may no longer be necessary if RMF is used as guidance of the procedure. The use of RMF has so far not been evaluated for endoscopic procedures.

Aims & Methods: We aimed to evaluate the usefulness of Road Map Fluoroscopy to guide endoscopic interventions in the esophagus. Patients with esophageal strictures were consecutively enrolled in a monocentric observational trial. After identification of the stenosis, a Road Map (Philips Multidimensional EVA, Philips Healthcare, Netherland) was performed using 20 mL of water-soluble contrast media that was applied through the working channel of a gastroscope (Fujifilm EG530NW or Olympus GIF-Q 180). RMF recording requires stable fluoroscopy of the region of interest to generate a mask for consecutive subtraction. Thereafter contrast medium is injected. After RMF application all further fluoroscopy images contain the information of the subtraction as steady overlay. Directly after the RMF was finished, the complete mask was removed from the esophagus to avoid aspiration. Patients were all investigated in recumbent position under sedation or propofol. All further interventions and measurements were performed by using the RM images.

Result: 21 investigations were performed in 18 patients (age:71 ± 13 years male:12, female:6). Indications for interventions were: balloon dilatation of benign strictures: n=9 including 1 pneumatic balloon dilatation for the treatment of achalasia, bougienage of benign stricture: n=3 and diagnostic radiography without intervention: n=1. In addition 8 stents, 5 partially covered and 3 fully covered, were placed using RMF as a guide for exact determination of stent length and positioning. All stents were also placed using RMF guidance. Endoscopic control revealed desired stent position in all cases. The choice of stent was made by measurement of the length of the stenosis as well as diameter of healthy esophagus adjacent to the structure. Available stents that fitted best to the measured dimensions were implanted. In all procedures RMF successfully guided the intervention. The feeling of resistance during bougienage was exactly matching the location for RMF projection of the stenosis. With the help of RM imaging endoscopy the balloons could easily be centered inside the stenosis to avoid slipping of the balloon. Complications did not occur.

Conclusion: RMF provides the possibility of permanent radiographic illustration of stenosis or anatomic changes throughout the intervention by using contrast medium only at the beginning of the intervention. RMF is feasible and safe to guide radiology based interventions in the esophagus. RMF directs the selection of stents better than endoscopy because all relevant dimensions can be measured exactly.

Disclosure of Interest: All authors have declared no conflicts of interest.
Aims & Methods: Aim of the study: To investigate in detail the gastrointestinal problems living in a small town in Finland. Patients: Our study cohort consisted of 105 adult CVID patients followed up between 2007–2015 in Helsinki University Hospitals Adult Immunodeficiency Unit and the respective outpatient clinics of Care and Ekso. CVID patients were diagnosed according to the response to routine diagnostic criteria and lived within the five hospital districts of southern Finland (1.9 million inhabitants). Adult patients of this cohort were diagnosed from the year 1960 to 2015 when recruitment stopped. We investigated retrospectively their medical records, laboratory results, endoscopic and histology reports, and data was collected to an electronic database designed for the study. Of this patient cohort, 12 patients died and 11 were lost to follow up.

Result: Upper endoscopy and ileocolonoscopy were done at least once to 83 (79%) patients, respectively, and Helicobacter pylori was found in 5 patients, was negative in 74 and unknown in 23 patients. Eradication was successful in all Helicobacter-positive patients. Helicobacter-negative chronic gastritis without marked atrophy, but ranging from mild to severe inflammation and atrophy was found in 11 patients (11%). In addition, atrophic gastritis in the stomach was found in 10 patients (10%). Small bowel: All tested patients were seronegative for coeliac disease. Of patients with increased intra-epithelial lymphocytes and villous atrophy of duodenum, 2 had complete histological and clinical response to gluten-free diet and all 4 others were unresponsive but had no enterocyte antibodies. 3 of the patients with refractory duodenal villous atrophy and inflammation had also inflammatory changes in colon as well. 3. Hepatobiliary: Primary sclerosing cholangitis or CVID-associated cholangitis was diagnosed in 5 patients. 3. Large Bowel: Inflammatory changes of mucosa ranged from specific colitis and microscopic colitis (including lymphocytic colitis and collagen colitis) to crypt-destructive and/or graft-versus-host like severe inflammation. Cryptocidal biopsies included IBD-like ulcers which were diagnosed in 5 patients (2 colectomies) and one patient had strictureing ileocolonic Crohn disease. Altogether, inflammation of colon was more common than small bowel enteropathy and it was found in 20 patients (19%). Prior to ileocolonoscopy, bacterial and parasitic infections were ruled out by standard laboratory methods including fecal sample screening. Nodular lymphatic hyperplasia was detected from gastric mucosa to rectum, and ranged from asymptomatic enhanced ileal nodularity to major changes of the gastric and bowel mucosal appearance and function. It was relatively common finding and noted in 36 patients (34%). 4. Mortality and gastrointestinal malignancies: 12 patients died during the follow up and in 3 patients it was directly due to metastatic malignancies of gastrointestinal tract; 2 patients with gastric adenocarcinoma and one patient with gastric dysplasia. Small bowel enteropathy had been found also in other 2 patients that died due to the cardiovascular disease. Meanwhile, one patient with unspecific inflammatory nodularity of colon eventually developed cecal large B-cell lymphoma which was timely diagnosed, and treated successfully.

Conclusion: Gastrointestinal and hepatobiliary manifestations are common among patients with CVID and the risk malignancies are increased.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference
activity were examined by a mutagenesis technique in the promoter assay and 
by Western interference technology. The effects of TPEN on occludin and claudin-3 
expression in mouse colons were also examined in combination with the calpain 
inhibitor.

**Result:** Intracellular zinc depletion by TPEN impaired the TJ barrier of intestinal 
Caco-2 cells. This was decreased due to increased zinc influx. TPEN-induced TJ 
disruption is associated with downregulation of 2 TJ proteins, occludin and 
claudin-3. These changes induced by TPEN were completely restored by 
supplemental zinc. Biostaining of cell surface proteins revealed that the zinc 
deposition induced the proteolysis of occludin, but not claudin-3. Occludin 
proteolysis was sensitive to the inhibition of calpain activity, and increased calpain 
activity was observed in the zinc-depleted cells. Although qPCR analysis and 
proteomic reporter assay have demonstrated that the zinc depletion-induced clau-
din-3 downregulation was not observed at transcriptional levels, a site-directed mutation 
in the egr1 binding site in the claudin-3 promoter sequence induced loss of both 
the basal promoter activity and the TPEN-induced decreases. Reduced egr1 
expression by a specific siRNA also inhibited the claudin-3 expression and bar-
rriod changes in the mouse colon. The zinc-channel inhibitor restored the 
TPEN-induced decrease in occludin, but not claudin-3.

**Conclusion:** This study shows that intracellular zinc has an essential role in the 
maintenance of the intestinal epithelial TJ barrier through regulation of occludin 
protein expression. Loss of intracellular zinc seems to epigenetically suppress 
protein expression by robust calpain activity. Further, zinc finger-containing egr1 
was shown to be critical for the transcriptional regulation of claudin-3.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

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ciency induces membrane barrier damage and increases neutrophil transmi-

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supplements mitigate tight junction impairment in Caco-2 human intestinal 
OP235 THE CENTRAL ROLE OF THE GUT MICROBIOTA IN CHRONIC INTESTINAL PSEUDO-OBSTRUCTION SYNDROME.

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Introduction: Chronic Intestinal Pseudo-Obstruction (CIPO) is a chronic severe disorder of gastrointestinal (GI) motility leading to clinical features of intestinal obstruction without mechanical occlusion. The intestinal microbiota is a key factor in determining gut motility and it is hypothesized that dysbiosis may be found in CIPO and that it contributes to clinical features of the disease.

Aims & Methods: 1) To characterize the gut microbiota of patients with CIPO. 2) To determine whether this microbiota is responsible for clinical features typical of CIPO using a gnotobiotic mouse model. 3) To evaluate whether faecal microbiota transplantation (FMT) improves symptoms of CIPO. The faecal microbiota of 3 patients with CIPO (1 female, median age 38.6±11 years) and 3 healthy volunteers (2 females, 39.5±6.9 years) was analyzed by 16S rRNA based Illumina sequencing. Stool samples from 1 patient with CIPO and 1 healthy control were used to colonize germ-free NIH Swiss mice (n=15 mice per donor, mixed gender) by oral gavage. GI transit was determined at 2 weeks using a validated in vivo videofluoroscopic technique1. Calcium and stomach size, and maximal bowel diameter, were determined using oral contrast-enhanced abdominal CT scan. The faecal microbiota of recipient mice was analyzed 48 hours and 2 weeks after colonization by Illumina and inferred metagenomic analysis was assessed by PICRUSt. The CIPO patient was then treated with FMT by jejunal infusion from a healthy donor at regular intervals for 20 weeks. GI symptoms, overall health and quality of life were assessed using standardized questionnaires.

Results: The microbiota of patients with CIPO exhibited marked dysbiosis with predominance of Proteobacteria species, especially Enterobacteriaceae and Enterococcaceae. In contrast, healthy volunteers showed a predominance of Firmicutes and Bacteroidetes. Bacterial richness and diversity were lower in CIPO patients with CIPO than in controls. LPS and flagellin production scores from patients with CIPO were higher than control microbiota colonized mice. Bacterial genes related to bile acid metabolism and deconjugation were differentially expressed in the faeces of treated mice. Importantly, FMT led to a rapid and sustained improvement in GI symptoms and overall quality of life in our CIPO patient. His microbiota dramatically changed after FMT and resembled that of the donor.

Conclusion: The faecal microbiota composition and its metabolic activity were dramatically changed after FMT and resembled that of the donor. Importantly, FMT led to a rapid and sustained improvement in GI symptoms and overall quality of life in our CIPO patient. His microbiota dramatically changed after FMT and resembled that of the donor.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

OP236 MICROBIOTA DIVERSITY AT TIME OF SURGERY PREDICTS ENDOSCOPIC RECURRENT IN CROHN’S DISEASE: A STUDY FROM THE REMIND GROUP

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Introduction: Operative resection in Crohn’s disease (CD) is not curative. After ileocecal resection, endoscopic recurrence is frequently observed on the anastomosis and/or on the neo-terminal ileum. Aims & Methods: The aim of this study was to analyze the mucosa associated microbiota at time of surgery and to look for predictors of post-operative endoscopic recurrence within the microbiota. This is a prospective study performed in the gnotobiotic model, collecting clinical and biological data at time of...
surgery and of endoscopy (performed at 6 months). Bacterial composition of the ileal mucosa associated microbiota was analyzed at time of surgery using 16S (MiSeq sequencing). The obtained sequences (rarefied to 1000 reads/sample) were analyzed using the QIIME pipeline to assess composition, alpha and beta diversity. Bacterial taxa associated with clinical parameters were identified using Multivariate association with Linear Models (MaAsLin) taking into account host phenotype, clinical parameters and treatments.

Result: 146 patients were included: 73 (50%) were male, median age at surgery was 32 years (IQR 26–42). Median disease duration was 6 years (IQR 2–12). 44 patients (30%) were active smoker at time of surgery. Thirty patients (21%) had a previous resection, and 35 patients (24%) had perianal lesions. Indication for surgery was strictureing disease (n = 95), penetrating disease (n = 53). At time of surgery, 67 patients (46%) had received anti-TNF therapy within the last 3 months. After surgery, 31 patients received thiopurines, and 52 patients received anti-TNF therapy. The microbiota was mainly composed of bacteria from the Firmicutes (Mean 55%, range 0.3–99%), Proteobacteria (Mean 36%, range 0.5–99%), Bacteroidetes (Mean 5%, range 0–52%) and Actinobacteria (Mean 6%, range 0–81%) phyla. As expected, antibiotics treatment within one-month before surgery had a dramatic impact on microbiota composition (Anosim, p < 0.0001) and diversity (mean observed species: 302 ± 17 vs 236 ± 14, p = 0.0005). In multivariate analysis (MaAsLin), antibiotics treatment was notably associated with an increase in Enterococcus (q < 0.0001) and with a decrease in Lachnospiraceae family (q = 0.004). Taking into account only the patients who did not received antibiotics within a month before surgery, we then looked for predictive factors of endoscopic recurrence. Patients with endoscopic recurrence, defined by a RUT (q = 0.001), had a lower bacterial diversity at time of surgery compared to patients in endoscopic remission (n = 65) (mean observed species: 276 ± 14 vs 365 ± 45, p = 0.015).

Conclusion: Ileal mucosa associated microbiota of CD patients at time of surgery is dominated by bacteria belonging to Firmicutes (Mean 55%), Proteobacteria, Bacteroidetes and Actinobacteria phyla. Antibiotics given during the last month prior to surgery induce major perturbations of the microbiota. Reduction in bacterial diversity at time of surgery is predictive of endoscopic recurrence.

All other authors have declared no conflicts of interest.

Reference
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OP237 BILE MICROBIOTA IN PRIMARY SCLEROSING CHOLANGITIS: EFFECTS ON DISEASE STAGE AND RISK FOR BILIARY DYSPLASIA

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic inflammatory liver disease leading to strictures in intra- and extrahepatic bile ducts and finally to cholestasis and secondary biliary cirrhosis (1). The chronic inflammation is associated with increased proliferation of biliary epithelial cells and a markedly increased risk of development of biliary dysplasia and cholangiocarcinoma (2). The cause of the pathogenesis of PSC is unknown, but the frequent association with inflammatory bowel disease, in 62–83% of PSC patients, and increased intestinal permeability in PSC has suggested a role for microbiota or microbial metabolites or derivatives, e.g. pathogen-associated molecular patterns, PAMPs) such as lipopolysaccharide (LPS), lipoteichoic acid, and peptidoglycan in the pathogenesis of the disease (3, 4). It has been proposed that the association between PSC and IBD can be due to increased enterohemorrhagic circulation of PAMPs (“leaking gut”), or abnormal PAMPs (as a result of enteric microbial dysbiosis, disrupted in IBD). Moreover, 16S ribosomal ribonucleic acid (RNA) has been detected in bile and also in cholangiocytes in PSC patients. The microbiota in bile have also been shown to be modified by genetic factors such as FU2T2 (2a1-L-fucosyltransferase 2) polymorphism, a gene involved in protein glycosylation.

Aims & Methods: To study the possible role of bile microbiota in the pathogenesis, disease progression and risk of dysplasia and cholangiocarcinoma (CCA). The clinical part of the study was conducted at Helsinki University, Clinic of Gastroenterology. The patients were recruited from the PSC registry at Helsinki University Hospital. The patients were recruited from the PSC registry at Helsinki University Hospital.

Table (OP237)

<table>
<thead>
<tr>
<th>Specific aim</th>
<th>Study groups</th>
<th>Control groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Role of microbiota in the etiopathogenesis of PSC</td>
<td>Early disease (ERC score ≤5), n = 37</td>
<td>Healthy controls (C), n = 46</td>
</tr>
<tr>
<td>2. Role of microbiota in disease progression</td>
<td>Advanced bile duct disease (ERC score ≥6), n = 36</td>
<td>Early disease, n = 37</td>
</tr>
<tr>
<td>3. Role of microbiota in biliary dysplasia and CCA (DC)</td>
<td>Patients with biliary dysplasia/CCA, n = 11</td>
<td>Early and advanced PSC, n = 73</td>
</tr>
</tbody>
</table>

of the Clinic of Gastroenterology. The indication for ERCP examination was the documentation of diagnosis of PSC due to: 1) constantly elevated or fluctuating alkaline phosphatase (ALP) levels in conjunction with IBD, or 2) magnetic resonance cholangiography findings, or 3) liver biopsy suggestive of PSC, or dysplasia surveillance. During patient’s ERCP and before injecting contrast media a bile sample was aspirated from extrahepatic bile ducts using balloon catheter, whenever possible. Brush cytology was routinely performed during ERC. ERC findings were scored according to the modified Amsterdam score (mAm score) and the number of ERC examination were recorded in each patient group. Isolation, amplification and sequencing of the bacterial 16S rRNA gene were performed. The resulting data was analyzed with negative binomial generalized linear models, PERMANOVA, and non-parametric tests.

Result: 1) A very low abundance OTU (“species”) belonging to the family Neisseriaceae was reduced in abundance in the early disease group. 2) Increase in Streptococcus from early disease to long disease progression. Streptococcus also correlates with increase in ERC severity score and potentially with the number of ERC examinations. More robust are the findings regarding overall community diversity, which decreases in long progression and dysplasia/CCA. 3) A low abundance Prevotella OTU disappears in patients with dysplasia or CCA. Streptococcus seems to again increase.

Conclusion: The data in our exploratory study suggests that the etiology of the disease is not connected with changes in biliary microbiota. Overall, Streptococcus seems to be connected with disease progression and risk of dysplasia and CCA. It may also be related to the number of ERC examinations and therefore a role, at least partially, for nosocomial infection cannot be ruled out at this stage. Overall, microbial diversity decreases in long progression and further more in dysplasia/CCA.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OP238 INCREASED FAECAL LEVELS OF GRANINS IN IRITRABLE BOWEL SYNDROME ARE ASSOCIATED WITH LUMINAL MICROBIOTA COMPOSITION AND SYMPTOM SEVERITY

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Introduction: Chromogranins (Cg) and secretogranins (Sg) are acidic gut hormones, which are secreted from the neuroendocrine system and may regulate immune activation. We have previously shown increased levels of faecal CgA (8.1 (3.3–17.4) pmol/L) and SgA (0.7 (0.4–2.4) pmol/L) in IBS patients (n = 143) and healthy subjects (n = 43). mRNA expression of interleukin (IL)-8, IL-10, tumour necrosis factor (TNF) and corticotropin-releasing hormone receptor was determined with qRT-PCR. Faecal (n = 111 subjects) and mucosal-associated microbiota (n = 50 subjects) were analysed by 16S RNA targeted pyrosequencing. IBS symptom severity and psychological distress were evaluated with the Gastrointestinal Symptom-Score (GSRS-IBS) and the Hospital Anxiety and Depression Scale (HADS), respectively.

Result: IBS patients demonstrated higher levels of faecal CgA (8.1 (3.3–17.4) pmol/L) compared to healthy subjects (4.7 (2.9–9.0), p < 0.02 pmol/L). The levels of SgH (0.8 (0.1–3.6) pmol/L) and SgHI (2.0 (0.8–4.8) pmol/L) in IBS patients were also increased compared to healthy subjects (0.1 (0.0–0.2), p < 0.01) respectively (0.7 (0.4–2.4), p < 0.001, pmol/L). Faecal microbial diversity, as measured with CgA (t = 0.29, p < 0.005), CgB (t = 0.21, p = 0.05)
Table 1. (OP239): Dysbiosis status

<table>
<thead>
<tr>
<th>Dysbiosis status</th>
<th>Patients</th>
<th>Age [med.]</th>
<th>Female</th>
<th>IBD</th>
<th>CD</th>
<th>UC</th>
<th>IBDU</th>
<th>Non-IBD</th>
<th>Healthy control</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>72</td>
<td>28 (19-68)</td>
<td>43</td>
<td>22</td>
<td>18%</td>
<td>7</td>
<td>16%</td>
<td>11</td>
<td>18%</td>
<td>4</td>
</tr>
<tr>
<td>Low</td>
<td>96</td>
<td>33 (19-66)</td>
<td>49</td>
<td>33</td>
<td>28%</td>
<td>14</td>
<td>31%</td>
<td>15</td>
<td>24%</td>
<td>4</td>
</tr>
<tr>
<td>High</td>
<td>126</td>
<td>32 (18-69)</td>
<td>80</td>
<td>65</td>
<td>54%</td>
<td>24</td>
<td>53%</td>
<td>36</td>
<td>58%</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>294</td>
<td>172</td>
<td>120</td>
<td>42</td>
<td>14%</td>
<td>62</td>
<td>22%</td>
<td>56</td>
<td>13%</td>
<td>124</td>
</tr>
</tbody>
</table>

compared to the healthy controls in a PLS analysis, the healthy controls (n = 48) and E1 (n = 22) patients clustered together, while the combined group of E2 (n = 17) and E3 (n = 23) patients made a separate cluster. Among 10 bacteria groups contributing to the clustering we looked into three of the groups in details: Bifidobacterium and Eubacterium were significantly reduced (p < 0.01), and Escherichia/Proteobacteria were significantly increased (p < 0.01) in the E2/ E3 group as compared to E1. healthy controls group. Frequency of high dysbiosis among the healthy individuals was higher than observed in other studies (1).

Conclusion: The present results support that alterations in microbial composition is important in both IBD and symptomatic non-IBD patients. The result demonstrated: 1) Differences in microbiota profiles between IBD and symptomatic non-IBD patients and healthy individuals; 2) Equal levels of dysbiosis frequency in CD and UC, however the bacteria profiles differed; 3) In subgroups of UC, microbiota profiles were dependent upon the localization of the inflammation.

Disclosure of Interest: E. Ciinemiejewa: Employee of Genetic Analysis
M.H. Vatn: Member of Genetic Analysis' Scientific Advisory Board
M. Sekelja: Former employee of Genetic Analysis AS
C. Casen: Employee at Genetic Analysis

All other authors have declared no conflicts of interest.

Reference

OP240 METABOLIC SYNDROME CORRELATES WITH MICROBIOTA ENCROACHMENT IN HUMAN INTESTINE

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Introduction: The intestinal tract is inhabited by a large and diverse community of bacteria collectively referred as gut microbiota. Mucoid structures coating the epithelium, largely devoid of bacteria, are central to maintaining intestinal-microbiota homeostasis. Our recently published work has led to the hypothesis that, in microbial encroachment of the epithelium, as a consequence of an innate immune deficiency or ingestion of substances that alter host-microbiota interactions, promotes low-grade inflammation that can drive metabolic disease (1-2).

Aims & Methods: The aim of the current study was to study microbiota localization in human subjects with metabolic syndromic. Subjects were enrolled at the Veteran’s Administration Hospital (Atlanta, GA, USA). A review of the patient medical record was conducted to determine control and diabetic patients, as shown by their glycosylated hemoglobin and fasted serum glucose levels. During the colonoscopy procedure, two mucosal biopsies were taken in the left colon approximately 40 cm from the anus using a regular forceps. The biopsies were immediately placed in Carnoy fixative and mucus immunostaining was paired with fluorescent in situ hybridization in order to analyze bacteria localization at the surface of the intestinal mucosa.

Result: We found that bacterial encroachment of the epithelium correlates with central features of metabolic syndrome in humans. Specifically, confocal microscopic analysis of biopsies from middle-aged persons revealed an inverse correlation between bacterial-epithelial distance and body mass index, fasting blood glucose, and hemoglobin A1C level. Ethnicity or antibiotic use did not significantly correlate with microbiota-epithelial distance.

Conclusion: These observations support the notion that microbiota promotion of low-grade inflammation may play a causative role in metabolic diseases in humans. These observations will significantly impact our understanding of the epidemic of metabolic syndrome.

Disclosure of Interest: All authors have declared no conflicts of interest.

References
OP241 CLINICAL FEATURES AND FECAL MICROBIOTA PROFILE IN IRRIgable BOWEL SYNDROME PATIENTS WITH SMALL INTESTINAL BACTERIAL OVERGROWTH

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Introduction: Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, but the relationship between diarrhea-predominant IBS (IBS-D) and small intestinal bacterial overgrowth (SIBO) is unclear.

Aims & Methods: We aimed to investigate the clinical features and fecal microbiota profiles of IBS-D patients with SIBO by hydrogen and methane breath test (LBT), and compare them with IBS-D patients without SIBO and healthy controls. IBS-D patients who met Rome II criteria were divided into IBS-D with SIBO (IBS-P) and without SIBO (IBS-N) by hydrogen and methane LBT, while healthy controls with negative LBT (HC) were recruited. All subjects underwent colonoscopy to exclude organic diseases, and barostat for visceral hypersensitivity, intestinal permeability test [lactulose (L), mannitol (M) and L:M in 6-hour urine], systematic inflammation severity (IL-10, IL-12 and IL-10/IL-12). With SIBO (IBS-P) and without SIBO and healthy controls (HC), we observed that patients with pseudomembranous colitis (PMC) needed repeat fecal infusions to be cured; further reports have been clearly proven to be associated with the need for multiple FMT.

Results: 22 HC and 84 IBS-D patients were enrolled. 35 of patients were with SIBO (41.67%) and 49 patients were IBS-D (41.67%). (1) According to Rome II criteria, approximately 41.67% IBS-D patients present SIBO, which can be better screened by hydrogen and methane LBT. (2) SIBO can cause malnutrition and worsen nutritional status. (3) The intestinal permeability, systemic inflammation and visceral hypersensitivity of IBS-P are better than IBS-N. (4) Differences are observed in fecal SCFA between IBS-P and IBS-N. Both IBS-P and IBS-N are different from HC in microbiota abundance and community diversity, in which IBS-P is also different from HC. (5) As a consequence, IBS-P is different from IBS-N in many physiological parameters and fecal microbiota profile, so IBS-P may be just SIBO which should be screened before diagnosis of IBS-D according to Rome II criteria.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP242 FECAL MICROBIOTA TRANSPANTATION FOR RECURRENT C. DIFFICILE INFECTION: ANALYSIS OF FACTORS ASSOCIATED WITH THE NEED FOR MULTIPLE FECAL INFUSIONS

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Introduction: Fecal microbiota transplantation (FMT) from healthy donors is considered a highly effective treatment against recurrent Clostridium difficile infection (rCDI). A single fecal infusion is usually sufficient to resolve symptoms and eradicate rCDI, but a subgroup of these patients need multiple infusions to cure the disease. In our previously published randomized controlled trial of FMT versus vancomycin for rCDI, we observed that patients with pseudomembranous colitis (PMC) needed repeat fecal infusions to be cured, further reports confirmed our findings. To date, however, both PMCs and other factors have been clearly proven to be associated with the need for multiple FMT.
OP243 ESODCOND BALLOON DILATION FOLLOWED BY STEROID INJECTION IN ANASTOMOTIC STRICURES AFTER ESOPHAGECTOMY: A MULTICENTER RANDOMIZED, DOUBLE-BLIND CONTROLLED TRIAL

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Introduction: Esophageal cancer is the fifth most common cause of cancer-related death for men and the eighth for women worldwide. Although the effectiveness of chemotherapy or chemoradiotherapy for the treatment of esophageal cancer has been reported, esophagectomy remains the standard treatment to cure esophageal cancer. Anastomotic stricture, a major complication after esophagectomy, substantially decreases patients' quality of life, and requires treatment with multiple sessions of endoscopic balloon dilation (EBD).

Aims & Methods: We conducted a multicenter randomized controlled trial to evaluate the usefulness of administration of local steroid injections to prevent the recurrence of anastomotic stricture. Patients were randomized to receive either triamcinolone or placebo immediately after EBD. The primary endpoint was the number of dilations required to resolve the stricture. Secondary end-points were restriction-free survival and adverse events. Restriction-free survival is defined as the number of days from randomization to performing EBD for any recurrence of dysphagia from any cause. Patients with a dysphagia symptom score of two or more after esophagectomy with anastomotic stricture confirmed by endoscopy were included. Patients and investigators were blinded to the type of agent injected. The syringe containing triamcinolone or placebo was prepared by nur-

References

Disclosure of Interest: All authors have declared no conflicts of interest.

OP244 THE "TUNNEL + CLIP" METHOD FACILITATES OESOPHAGEAL ESD PROCEDURES: A PROSPECTIVE, CONSECUTIVE BI-CENTRIC STUDY

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Introduction: ESD is the treatment of choice for superficial neoplasms of the oesophagus due to its oncological efficiency and the morbidity associated with the surgical alternative. ESD requires a high level of skill and is technically challenging and time consuming. Therefore, it is often reserved to experts. Combining the tunnel technique and the clip-line counter-traction may enable optimisation of oesophageal ESDs.

Aims & Methods: From January 2014 to April 2016 we performed a prospective bi-centre case series of consecutive tunnel + clip oesophageal ESDs. Four young operators (fewer than 50 ESDs and fewer than 5 oesophageal ESDs) performed consecutively the ESD using the tunnel + clip method: generation of a classic tunnel beneath the lesion followed by constant counter-traction thanks to a clip with line dropped at the oral side of the tunnel.

Results: Thirty-three lesions (14 SCC and 19 ADK/HGD complicating Barrett’s oesophagus) were resected consecutively. En bloc, R0 and curative resection rates were 100% (33/33), 87.8% (29/33) and 75.8% (25/33), respectively. No perfora-

Disclosure of Interest: N. Hanaoka: The Japan Foundation for Research and Promotion of Endoscopy Grant

All other authors have declared no conflicts of interest.
OP246 MANAGEMENT OF DIMINUTIVE, RECTOSIGMOID POLYPS BY USING COMPUTER-SUPPORTED DIAGNOSTIC SYSTEM

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Introduction: The PIVI initiatives propose that a “leave in place” approach is adequate for a diminutive (<5 mm), rectosigmoid hyperplastic polyp when endoscopist’s optical diagnosis provides over 90% negative predictive value (NPV) for adenomas in high confidence predictions [1]; however, expertise is required to achieve a high accuracy and some studies conducted in community-based hospitals have been discouraging [2]. Recently, we have reported the usefulness of computer-aided diagnosis (CAD) in supporting endoscopists’ decision making during colonoscopy [3,4]. The present study was aimed to validate the efficacy of the latest CAD model for endocytoscopy (380-fold ultra-magnifying endoscopy) in management of diminutive, rectosigmoid polyps.

Aims & Methods: The present study was aimed to validate the efficacy of the latest CAD model for endocytoscopy (380-fold ultra magnifying endoscopy) in management of diminutive, rectosigmoid polyps. The CAD for endocytoscopy comprises image acquisition, nuclear segmentation, feature extraction, and classification into three pathological groups (non-neoplastic, adenoma, and invasive cancer). The classification algorithm was programmed based on 296 features of each image (e.g., area, circularity, diameter, and perimeter of nuclei, and over 250 metabolic indices). We used a support vector machine to classify these many features; 6051 endocytoscopic images were used for machine learning in the process of construction of the model. In order to validate this CAD model, the pilot study using a test set was undertaken between August and November 2015. The test set comprised endocytoscopic images of 65 diminutive, rectosigmoid polyps from the database of Showa University Northern Yokohama Hospital. Each image was automatically allocated to the CAD, and the predicted pathology was immediately output by the CAD in 0.2 seconds. The main outcome measure was NPV of the CAD for adenomatous histology for diminutive, rectosigmoid colon polyps when they had been diagnosed with high confidence.

Result: Of the 65 diminutive rectosigmoid polyps (mean size, 3.6 ± 1.0 mm), the CAD diagnosed 55 (19 neoplastic and 36 non-neoplastic) with high confidence. Details of the diagnostic performance by the CAD for these 55 polyps were shown in the Table. The CAD correctly predicted neoplastic histology in 18 of the 36 non-neoplastic polyps (positive predictive value of 90% [95% CI, 68–99]) and non-neoplastic histology in 34 of the 35 non-neoplastic polyps (NPV of 97% [95% CI, 85–100]). This performance of the CAD met the “leave in situ” criteria proposed by the PIVI initiative.

Conclusion: The CAD applying endocytoscopy can be a powerful and quick support tool in management of diminutive, rectosigmoid polyps.

Disclosure of Interest: K. Mori: Cybernet System Corp.
All other authors have declared no conflicts of interest.

References

Table: Details of the diagnostic performance by the CAD

<table>
<thead>
<tr>
<th>Diagnosis of neoplastic by CAD</th>
<th>Diagnosis of non-neoplastic by CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>34</td>
</tr>
</tbody>
</table>

Conclusion: The CAD applying endocytoscopy can be a powerful and quick support tool in management of diminutive, rectosigmoid polyps.

Disclosure of Interest: K. Mori: Cybernet System Corp.
All other authors have declared no conflicts of interest.

References

TUESDAY, OCTOBER 18, 2016 14:00–15:30
BIOMARKERS IN IBD – ROOM K

OP247 IBDOC – FIRST SMARTPHONE BASED CALPROTECTIN HOME TEST – 18 MONTHS EXPERIENCE

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Introduction: Inflammatory Bowel Disease (IBD) is a chronic inflammation of the gut presenting with phases of active inflammation, remission and relapses. IBD treatment goals are mucosal healing and persistent remission. Calprotectin measurement of patients’ stool samples is a well-established biomarker to measure the inflammatory activity in the gut. Periodical assessment of calprotectin levels is important to measure effectiveness of the treatment as well as predicting relapses. Until now this meant that patients send in their stool sample for laboratory analysis, leading to long delays between sample collection, final test result and potential adaptations of therapies.

Aims & Methods: We have developed a smartphone-based calprotectin home test, called IBDoc®, that allows real-time information about the inflammatory activities in the gut for both, the patient and the health care provider. The IBDoc® consists of a stool collection and extraction device (CALEX® Valve) and an immunochromatographic calprotectin rapid test, which is measured using a smartphone, which controls the phone’s camera. Once the test is
measured the result is instantly sent to a webserver (IBDoc Portal) allowing the treatment provider to access the result. IBDoc® has achieved CE-IVD mark for self-testing in March 2015 and has since then been in routine use by patients throughout Europe and overseas. We have gathered data concerning technical performance of the device in the hands of both professional and lay users as well as usability aspects for patients.

Result: In a direct method comparison with an existing point-of-care test (Quantum Blue®) and a laboratory based ELISA method (BUHLMANN fCAL® ELISA) IBDoc® correlated very well with both methods with a mean bias of 0% in regard to repeatability and precision the smartphones as measuring devices alone showed a coefficient of variability of below 10%, while the entire method including pre-analytical steps showed a coefficient of variability between 15% and 24%. IBDoc® displays results as Normal/green (below 100 μg/g mean bias at cut-off, –7.0 to 5.4%). Moderate/amber (100–300 μg/g) and as High/red (above 300 μg/g, mean bias at cut-off, 1.1–6.5%). No false positive or false negative results (Normal/green instead of High/red and vice versa) were observed when lay-users performing the test were compared to professional lab testing. 97% of the agreement observed. The test was judged the entire IBDoc® system as extremely user friendly with a mean of 93 points (out of 100) on a standardized System Usability Scale (SUS) score1,2,3.

Conclusion: IBDoc® is the first Calprotectin Home Test available for patients with IBD. IBDoc® is well accepted by patients and caregivers and provided excellent correlation to existing calprotectin point-of-care and laboratory based methods and has proven to be a supportive tool in daily clinical routine.

Disclosure of interest: Reinhard: Christian Reinhard is an employee of BUHLMANN Laboratories AG. A. Ritz: Aliea Ritz is an employee of BUHLMANN Laboratories AG M. Uberschlag: Marie-Eve Uberschlag is an employee of BUHLMANN Laboratories AG J. Weber: Jakob Weber is an employee of BUHLMANN Laboratories AG All authors have declared no conflicts of interest.

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OP249 ACCURACY OF NON-INVASIVE TESTS IN THE INITIAL DIAGNOSTIC WORK-UP OF PEDIATRIC INFLAMMATORY BOWEL DISEASES

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Introduction: Upper and lower endoscopy with histology together with imaging of the small bowel is the gold standard for the diagnosis of inflammatory bowel disease (IBD) in children. Due to high costs and invasive nature of these techniques, accurate selection of patients is mandatory.

Aims & Methods: We aimed to assess the accuracy of non-invasive tests including fecal calprotectin (FC), blood inflammatory markers (BIM) and bowel ultrasound (US) alone or in combination as first level investigations in children with suspected IBD. Consecutive patients referred to our Unit for a clinical history compatible with IBD were enrolled during a 3-year period. All underwent FC (Calprotectin®, Eurospital), C-reactive protein [CRP], erythrocyte sedimentation rate [ESR] and bowel US as first investigations. Endoscopy with biopsies was the gold standard for diagnosis. At US pathological findings were: BWT > 3mm, BW vascularity, loss of stratification, enlarged mesenteric nodes. Multiple logistic analysis with stepwise method considering IBD diagnosis as dependent variable was conducted. Sensitivity (SE), specificity (SP), positive and negative predictive values (PPV and NPV) of laboratory and US parameters alone or in combination were analyzed according to the final diagnosis.

Result: 100 patients (58 males, median age 12) were enrolled. The final diagnosis was IBD in 69 (57 CD, 12 UC) other than IBD in 31. The mean values of ESR, FC and BWT were higher in IBD vs non-IBD patients (p < 0.001). Multiple logistic analysis showed that independent variables predictive of IBD were: FC (OR 44.8; p < 0.001), BWT (OR 20.4, p < 0.001) and ESR (OR 9; p < 0.001). The combination of 3 or 2 parameters was more frequent in IBD patients (p < 0.01). Table 2 shows SE, SP, PPV, NPV of these parameters alone or in combination.

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Introduction: Telemedicine programmes are of interest for inflammatory bowel disease patients but should include adequate monitoring of mucosal inflammation to prevent long-term complications. Different clinical activity questionnaires are available, however, none are patient-reported, clear and easy to fill out and validated against endoscopy. For this reason we previously developed the MIAH questionnaire (MIAH) (1). The score does not include laboratory tests or physical examination. The objective of this study was to investigate whether a combination of the MIAH questionnaire and a calprotectin home test yields higher diagnostic accuracy.

Aims & Methods: Between September 2015 and April 2016 all consecutive IBD patients with a scheduled endoscopy in the Maastricht University Medical Centre+ were eligible for inclusion. Patients with an ileostomy, colostomy, ileoanal pouch anastomosis or ileorectal anastomosis were excluded. Patients were invited to fill out our two-item MIAH questionnaire for UC, regarding blood loss, number of stools, urgency, abdominal pain and general well-being, or the 6-item MIAH-CD questionnaire for CD, including questions on blood loss, mucus, number of stools, urgency, fatigue and general well-being. In addition, patients were asked to collect a stool sample prior to bowel cleansing. Fecal calprotectin was determined with a calprotectin home test. Mucosal inflammation was assessed with the simple endoscopic activity score (SES-CD) for Crohn’s disease (CD) and the Mayo endoscopic subscore (MES) for ulcerative colitis (UC). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the MIAH-UC and MIAH-CD in combination with the calprotectin home test were calculated.

Result: Thirty-two CD patients (50.0% male, mean age 51.4 ± 15.2 years, 43.8% active disease) and 58 patients (80.0% male, mean age 57.3 ± 10.4 years, 39.3% active disease) were included. The combination of the MIAH-CD and the calprotectin home test showed a sensitivity of 100.0%, a specificity of 61.1%, a NPV of 100.0% and a PPV of 67.0%. The combination of the MIAH-UC and the calprotectin home test yielded a sensitivity of 91.7%, a specificity of 68.3%, a NPV of 91.7% and a PPV of 68.8%.

Conclusion: The MIAH is the first patient-reported questionnaire developed to predict endoscopic inflammation in IBD patients. The MIAH-CD and a calprotectin home test shows a high sensitivity and thus can be used in clinical practice as a diagnostic questionnaire to screen for patients who need further assessment of disease activity with biochemical markers, imaging or endoscopy.

Disclosure of Interest: M.J. de Jong: Non financial support Immunodiagnostik All other authors have declared no conflicts of interest.

Reference


OP250 THE SEROLOGIC MARKERS ASCA AND PANCA SHOW BETTER PREdictability THAN CRP, ESR AND CALPROTECTIN FOR ANTI-TNF TREATMENT AMONG PEDIATRIC IBD PATIENTS

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Introduction: Serologic nuclear and anti microbial antibodies have been recognized as predictive markers of disease course and complications in ulcerative colitis (UC) and Crohn’s disease (CD). The significance of serological markers from onset of the disease, their ability to predict disease outcome and their stability over time is not fully explored in IBD patients.

Aims & Methods: To study the prevalence of serological markers in treatment-naive pediatric patients with newly diagnosed inflammatory bowel disease and prospectively evaluate the antibody and titer-variations related to disease sub-
serological markers with the biochemical markers C-reactive protein (CRP), elevated sedimentation rate (ESR) and fecal calprotectin. Patients aged 18 years, (n = 59) diagnosed with IBD were included between 2005-2007 as part of a prospective population based study in South-Eastern Norway (IBSEN- II). Fecal samples were analyzed for calprotectin (Bühlmann, Basel, Switzerland) and blood specimens were analyzed for antibodies (Prometheus labs, San Diego, CRP and ESR at diagnosis and after 1-2 years of treatment. Treatment was decided at the courtesy of the treating pediatrician. Tumor necrosis factor (TNF) blocker treatment was regarded as aggressive treatment compared to conventional treatment.

Result: Among the UC patients, 13% (72%) were perianal anti-neutrophil cytoplasmic antibody (pANCA) positive, versus 13% (35%) of the CD patients. None of the UC patients harbored anti-Saccharomyces cerevisiae (ASCA) antibodies, whereas 11% (33%) of CD patients were ASCA IgA or IgG positive (p < 0.0001). 18 (49%) were positive for ASCA IgA, 14 (38%) for ASCA IgG, and 12 (33%) for both. There were statistically significant differences between CD and UC patients in the prevalence of antibodies against *Pseudomonas fluorescens* associated with ASCA positivity (3%, 33%), the outer membrane protein of *Escherichia coli* (OmpC) (8% vs. 6%) or flagellin expressed by Clostridial phylum (C2l) (22% vs. 0%, respectively). The 18 (49%) CD patients who received aggressive therapy with TNF blockers had higher presence of antibodies against ASCA IgA (p = 0.005) and ASCA IgG (p = 0.045) as well as higher titers of ASCA IgG (p = 0.046) compared to the 19 (51%) CD patients who received conventional treatment. If ASCA antibodies were present at baseline the probability of receiving inflammasome treatment in CD patients was 70%, with OR 8.2 (2.077), p = 0.004. The presence of pANCA antibodies was less frequent at diagnosis in TNF blocker treated CD patients compared to conventionally treated CD patients. The OR of receiving aggressive therapy being pANCA negative was 5.1 (95% CI 1.13–22). CD patients with positive ASCA or TNF inhibition had significantly higher levels of fecal calprotectin. CRP and ESR at diagnosis compared to conventionally treated CD patients with median values of fecal calprotectin (mg/kg) 1306 vs. 501 (p = 0.01), CRP (mg/l) 28 vs. 7.5 (p = 0.02) and ESR (mm/h) of 32 vs. 18 (p = 0.01) respectively. Being pANCA negative and/ or ASCA IgA or ASCA IgG positive was associated with the need for TNF blocker therapy, even after adjustment for CRP, ESR and fecal calprotectin levels. After treatment there was no difference in antibody prevalence for ASCA IgA, ASCA IgG, 12, Crohn’s disease and UC patients. In case of treatment failure, follow-up of detectable CRP and ESR indicated resolution of disease activity. Fewer UC patients, 9 (64%), tested positive for pANCA after treatment, compared to at baseline, 13 (72%), p = 0.013. Only one of the 18 UC patients received TNF blocker treatment.

Conclusion: ASCA and pANCA status was associated with the need for early aggressive therapy with TNF blockers in our CD patients. We found that being pANCA negative and/ or ASCA IgA or ASCA IgG positive were more predictive of needing aggressive treatment than CRP, ESP or fecal calprotectin levels. A negative pANCA and CRP is a reliable, regardless of treatment modality, and might be a prognostic tool at any time in the disease course.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OP252 ANALYTICAL PERFORMANCE OF A NEW IPHONE-BASED PATIENT MONITORING SYSTEM COMPARABLE TO ELISA FOR MEASURING FECAL CALPROTECTIN IN IBD PATIENTS

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Introduction: Fecal calprotectin (FC) is a chronic intestinal inflammatory disorder presenting with phases of active inflammation, remission and relapse. Fecal calprotectin (fcalpro) measurement has become established for the monitoring of inflammatory activity. Periodical assessment of fcalpro levels has been demonstrated to be an important parameter to determine efficacy and predict the relapse. However, until now, fcalpro determination required patients to send stool samples in for laboratory analysis, resulting in a long delay between sample collection and final test results. We developed a smartphone-based calprotectin test system called QuantOnCal in FC to allow patients to regularly monitor their own inflammatory status by testing fcalpro levels in the comfort of their own home.

Aims & Methods: QuantOnCal consists of a stool extraction device (IDK® Extract) and an immunochromatographic rapid test performed by an iPhone App via the phone camera. Results are automatically sent to a webserver (QuantOnCal website), where they are displayed for monitoring by the consulting physician or IBD nurse. The objective of this study was to validate the QuantOnCal test system by comparing its quantitative performance with a standard ELISA-based method. Stool samples from 157 IBD and non-IBD patients containing various levels of calprotectin (95 IBD: CU/CAP/active/emission, 42/ 4340±47, 35 SBS: 23 Cm: 6): were either loaded onto immunochromatographic test cassettes (TCCs) or analysed with a commercial ELISA test (Immundiagnostik, Bensheim, Germany). The QuantOnCal app was installed on 4 different iPhone models (iPhone 4, 4s, 5c, 6). Agreement between QuantOnCal testing versus ELISA was assessed by Analyse-it for Microsoft Excel.

Result: The QuantOnCal system produces a quantitative test result between 25–2000 mg/g fcalpro/g of stool, covering the clinically relevant range of this biomarker. The total agreement (TA) was 95% with 0% false positive and 0% false negative rates. The TA for fcalpro between the 4 different iPhone models was 91.3%.

Conclusion: QuantOnCal is a new, complete and validated test system which can be easily followed by IBD patients to monitor their inflammation level by measuring the IBD biomarker, faecal calprotectin, using his/her own smartphone. The performance of the QuantOnCal test system was shown to be comparable to the professional, ELISA-based method.

Disclosure of Interest: K.F. Wintgens: Karl Florian Wintgens is an employee of Immunodiagnostik AG, Bensheim, Germany.

J. Stein: Jürgen Stein has received payment for lectures and consultancy from Immunodiagnostik AG, Bensheim, Germany.
Guided control of abdomino-thoracic muscular activity.

Conclusion: Abdominal distension can be effectively corrected by biofeedback. Biofeedback treatment resulted in a 56% reduction in intercostal activity (by 45% vs 5% ± 2% on placebo; p < 0.001) and 20% on placebo; p = 0.001 vs 4 ± 2% on intervention. Biofeedback treatment resulted in a 56% reduction of abdomino-thoracic muscle activity by EMG during basal conditions (no distension) and during an episode of distension to prove the abdomino-phrenic origin of their distension. Each patient underwent three treatment sessions over a 10-day period. Between-session abdomino-thoracic muscular activity was recorded by EMG-guided control.

Aims & Methods: Our aim was to demonstrate the superiority of biofeedback versus placebo for the treatment of abdominal distension. We performed a randomized, placebo-controlled in a referral center (Clinical Trials Gov Registration Number 01205100). Forty-three patients complaining of episodes of visible abdominal distension who fulfilled the Rome III criteria for functional intestinal disorders (47 women, 1 men; 21–74 yrs age range) were recruited and randomized to either biofeedback and placebo treatment. Abdomino-thoracic muscle activity was recorded by EMG during basal conditions (no distension) and during an episode of distension to prove the abdomino-phrenic origin of their distension. Each patient underwent three treatment sessions over a 10-day period. Between-session abdomino-thoracic muscular activity was recorded by EMG-guided control of abdomino-thoracic muscular activity.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:
2. Results: Patients on biofeedback, but not on placebo, effectively reduced intercostal activity (by 45.3% vs 5.2% ± 2% on placebo; p < 0.001) and total abdomino-thoracic muscle activity (by 101 ± 10% vs −4 ± 2%). Biofeedback treatment resulted in a 56% ± 1% reduction of abdominal distension (from 6.1 ± 2.0 to 0.2 ± 0.0 score after intervention) vs 13 ± 8% on placebo; p = 0.001 (from 4.7 ± 0.1 to 4.1 ± 0.4 score after intervention).

Conclusion: Abdomino-thoracic muscle activity can be controlled by biofeedback-guided control of abdomino-thoracic muscular activity.
Result: Abdominal pain and bloating were the most common symptoms before initiation of treatment, occurring in 62 (82.7%) patients. The frequency of the symptoms was decreased significantly after treatment in doxepin and norotryptiline line groups compared with pre-treatment. The responder rate was 80%, 52%, and 36% for doxepin, norotryptiline, and placebo groups, respectively (p = 0.007). The responder rate for doxepin group was superior to norotryptiline and placebo groups (p = 0.037 and p = 0.002, respectively) but there was no significant difference in responder rates of norotryptiline and placebo groups (p = 0.254). There were no significant differences in improvement rates in individual symptoms between doxepin and norotryptiline groups (all p > 0.05).

Conclusion: Treatment of diarrhea-predominant IBS with low dose of doxepin or norotryptiline could be effective. Improvement rates of the symptoms are similar in doxepin and norotryptiline groups but doxepin has a better response rate than norotryptiline.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

Table (OP258): Composite response rates over longer treatment intervals in ELX-treated patients who were composite or adequate relief responders over Month 1

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Placebo (n = 809)</th>
<th>ELX 75 mg BID (n = 808)</th>
<th>ELX 100 mg BID (n = 806)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint: Weeks 1–4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-responder</td>
<td>101 (12.5)</td>
<td>708 (87.5)</td>
<td>184 (22.8)</td>
</tr>
<tr>
<td>Responder</td>
<td>708 (87.5)</td>
<td>184 (22.8)</td>
<td>624 (77.2)</td>
</tr>
<tr>
<td>Composite endpoint: Weeks 1–12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-responder</td>
<td>78 (77.2)</td>
<td>23 (22.8)</td>
<td>150 (81.5)</td>
</tr>
<tr>
<td>Responder</td>
<td>23 (22.8)</td>
<td>150 (81.5)</td>
<td>34 (8.5)</td>
</tr>
<tr>
<td>Composite endpoint: Weeks 1–26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-responder</td>
<td>67 (66.3)</td>
<td>34 (33.7)</td>
<td>136 (73.9)</td>
</tr>
<tr>
<td>Responder</td>
<td>34 (33.7)</td>
<td>136 (73.9)</td>
<td>48 (26.1)</td>
</tr>
<tr>
<td>Adequate relief: Weeks 1–4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-responder</td>
<td>399 (49.3)</td>
<td>410 (50.7)</td>
<td>484 (59.9)</td>
</tr>
<tr>
<td>Responder</td>
<td>410 (50.7)</td>
<td>484 (59.9)</td>
<td>324 (40.1)</td>
</tr>
<tr>
<td>Adequate relief: Weeks 1–12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-responder</td>
<td>329 (82.5)</td>
<td>70 (17.5)</td>
<td>405 (83.7)</td>
</tr>
<tr>
<td>Responder</td>
<td>70 (17.5)</td>
<td>405 (83.7)</td>
<td>79 (16.3)</td>
</tr>
<tr>
<td>Adequate relief: Weeks 1–26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-responder</td>
<td>278 (69.7)</td>
<td>121 (30.3)</td>
<td>341 (70.5)</td>
</tr>
<tr>
<td>Responder</td>
<td>121 (30.3)</td>
<td>341 (70.5)</td>
<td>143 (29.5)</td>
</tr>
</tbody>
</table>

BID, twice daily; ELX, eluxadoline

aPercentage calculated based on number of patients who were composite responders over Weeks 1–4

bPercentage calculated based on number of patients who were adequate relief responders over Weeks 1–4

Disclosure of Interest: All authors have declared no conflicts of interest.

OP258 1-MONTH TREATMENT WITH ELUXADOLINE FOR IBS-D PREDICTS SUSTAINED RESPONSE: CONTINUATION ANALYSES OF RESPONSE IN TWO PHASE 3 STUDIES

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Introduction: Eluxadoline (ELX), a mixed μ-opioid receptor (OR) and δ-OR antagonist that is locally active in the gastrointestinal tract, is approved for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults. In two Phase 3 studies, ELX significantly improved symptoms of IBS-D based on a composite endpoint, defined by simultaneous improvement in stool consistency and reduction in abdominal pain scores, and the historical ‘adequate relief’ endpoint. Given the potential long-term use of eluxadoline treatment, it is important to understand the time course of clinical benefits as experienced by patients and clinicians, including time to onset and the sustainability over time, to establish reasonable expectations about the effectiveness of treatment.

Aims & Methods: The efficacy of ELX over longer treatment intervals was evaluated in patients who were responders or non-responders for the composite endpoint or adequate relief endpoint over the first month of treatment in the Phase 3 studies. Two double-blind, placebo-controlled, Phase 3 clinical trials (IBS-3001 and IBS-3002) randomised patients meeting Rome III criteria for IBS-D to twice-daily treatment with ELX (75 or 100 mg) or placebo. Patients rated IBS symptoms daily, including worst abdominal pain (WAP) (10 scale) and stool consistency (Bristol Stool Scale [BSS]). The primary efficacy endpoint was composite response, based on simultaneous daily improvement of ≥30% in WAP score vs. baseline and BSS score <5, with ≥50% of days demonstrating a response, evaluated over 12 and 26 weeks. Composite endpoint response rates over Weeks 1–12 and 1–26 were calculated for patients who were responders and non-responders over Month 1 (Weeks 1–4) using a pooled analysis of the intent-to-treat (ITT) population. Comparable analyses for adequate relief were conducted, for which a responder was defined as reporting a “yes” response to the question “Over the past week have you had adequate relief of your IBS symptoms?” for ≥50% of weeks in the treatment interval.

Result: The pooled ITT analysis set included 2423 patients with IBS-D. Over Month 1, 49.3% (399/809), 59.9% (484/808), and 61.8% (498/806) of patients were adequate relief responders in the placebo, ELX 75 mg, and ELX 100 mg groups, respectively. Over Month 1, 49.3% (399/809), 59.9% (484/808), and 61.8% (498/806) of patients were adequate relief responders in the placebo, ELX 75 mg, and ELX 100 mg groups, respectively. For both ELX doses, the majority of patients who were composite or adequate relief responders over Month 1 showed sustained response over Weeks 1–12 and 1–26 (Table). Of the patients who were not composite or adequate relief responders in Month 1, approximately 13–18% subsequently achieved response over months of treatment.

Conclusion: Approximately two-thirds of patients who achieved either the composite or adequate relief endpoint over the first month of ELX treatment demonstrated sustained response over 6 months.


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OP259 HUMAN PLURIPOTENT STEM CELL-DERIVED EXOCRINE/ DUCTAL ORGANOIDS GENERATE HUMAN PANCREAS UPON ORTHOTOPIC TRANSPLANTATION AND ALLOW DISEASE MODELLING

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Introduction: Exocrine/ductal pancreatic differentiation from human pluripotent stem cells is a poorly understood process albeit various diseases arise from this compartment.

Aims & Methods: We designed a straightforward approach to direct human pluripotent stem cells (PSCs) toward pancreatic exocrine and ductal progeny.

Result: Extensive phenotyping of the organoids not only shows the appropriate marker profile but also ultrastructural and functional hallmarks of human pancreas in the dish. Upon orthotopic transplantation into immunodeficient mice, these organoids form normal pancreatic ducts and acinar tissue resembling fetal human pancreas without any evidence of tumour formation or transformation. Finally, we implemented this unique phenotyping tool as a model for pancreatic facets of cystic fibrosis (CF) but also other inherited pancreatic disorders. We provided evidence that pancreatic commitment occurs generally unhindered in CF. Importantly, CFTR-activation in mutated pancreatic organoids mirrors the CF-phenotype in a series of functional assays. We also conducted a scalable proof-of-concept screen in CF-pancreatic organoids using a set of CFTR-correc tors and activators. Finally, we did orthotopic transplantation of CF-organoids to generate diseased human pancreata in mice and established a mRNA-mediated gene repair approach in CF-organoids. Similar assays were applied to another inherited pancreatic disorder.

Conclusion: Thus, our platform provides novel opportunities to model pancreatic disease and development but also to screen for disease rescuing agents.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP260 CANCER ASSOCIATED FIBROBLASTS (CAFs) SEQUESTER GEMCITABINE TO INCREASE INTRATUMORAL DRUG DELIVERY IN CANCER OF THE PANCREAS

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Introduction: The pronounced tumour stroma in pancreatic cancer has recently been appreciated as physical barrier impeding delivery of therapeutic agents. Herein, we aim to investigate the delivery of gemcitabine metabolites in primary pancreatic tumour and matched liver metastases and dissect stromal and neoplastic compartments.

Aims & Methods: The cellular and acellular tumour stroma was assessed in human and mouse primary tumours and matched liver metastases. Gemcitabine metabolites were analysed in LSL-KrasG12D+/LSL-Top5flox/flox1; Pdx-1-Cre (KPC) tumours and matched liver metastases, primary tumour cell lines, cancer associated fibroblasts (CAFs), and pancreatic stellate cells (PSCs) by liquid chromatography- mass spectrometry/mass spectrometry (LC-MS/MS). Exposure analysis of gemcitabine metabolism pathways was performed in vitro and in vivo. Viability of CAFs was assessed in vivo following a preclinical trial in the KPC model.

Result: Fibroblast density and collagen deposition were significantly reduced in human and murine liver metastases as compared to matched primary tumours. Gemcitabine (dFdC) and its active metabolite dFdCTP were significantly higher in stroma rich tumours compared to stroma poor liver metastases and normal liver. Mean vessel density did not correlate with gemcitabine delivery at pharmacodynamically relevant endpoints. In cell culture, significantly increased concentrations of activated dFdCTP and greatly reduced levels of the inactive gemcitabine metabolite dFU were detected in PSCs and CAFs. Importantly, key metabolite enzymes for gemcitabine inactivation such as deoxyxycytidylate deaminase (DCTD), cytidine deaminase (CDA) and hydrolytic cytosolic 5’ nucleotidases (Nt5c1A, Nt5c3) were differentially expressed in PSCs and CAFs. Moreover, treatment of KPC mice revealed intrinsic resistance of CAFs to gemcitabine.

Conclusion: Our findings suggest that CAFs sequester gemcitabine and thus may contribute to the clinical failure of this drug in desmoplastic pancreatic cancer. Therefore, metabolic engineering of CAFs may constitute a promising new avenue to enhance the cytotoxic effects of gemcitabine in patients.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OP261 CIRCULATING CELL-FREE DNA IS A RELIABLE TOOL TO DETECT HOT SPOT MUTATIONS IN INTRADUCTAL PAPILLARY MUCINUS NEOPLASMS

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is the most common cancer type of the pancreas. The three PDAC precursor lesions are: (i) pancreatic intraepithelial neoplasia (PanIN), (ii) mucinous cystic neoplasm (MCN), and (iii) IPMN. In contrast, serous cystadenomas are strictly benign cystic neoplastic lesions and rarely require surgery.

Aims & Methods: Frequently, differential diagnosis of neoplastic cysts remains cumbersome. Thus, non-invasive diagnostic stratification would be welcome. Such a test should allow both discrimination of (i) IPMN from strictly benign pancreatic cysts but also (ii) low- from high-grade IPMN.

Result: Little is known about the molecular alterations of IPMN, but GNAs mutations have been described to promote IPMN formation. A tumor-derived fraction of cell-free DNA (cfDNA) circulating in the bloodstream represents the mutational makeup of tumors and could be a tool for non-invasive monitoring. We demonstrate that cfDNA levels discriminate controls from a cohort of Fukuoka-negative branch-duct IPMN but also from pancreatic cancer. Furthermore, GNAs mutations were detected in IPMN patients but were absent in serous cystadenomas (SA) and in controls. Moreover, we observed a relevant concordance between tissue and liquid biopsies-based GNAs mutations in an independent cohort of resected IPMN patients.

Conclusion: These findings establish cfDNA and targeted genotyping as a diagnostic tool for IPMN, which may aid differential diagnosis and risk stratification of cystic pancreatic lesions.

Disclosure of Interest: All authors have declared no conflicts of interest.
INTESTINAL FAILURE: FROM PATHWAYS TO TREATMENT — ROOM 17

OP262 NOVEL GENE MUTATIONS IN NEUROGENIC CHRONIC INTESTINAL OBSTRUCTION E. Bonora1, C. Graziano1, F. Bianco1, A. Stanzausi1, R. Rinaldi1, R. D’Angelo1, E. Bescotti1, J. D. Smith1, G. Assadi2, M. Bamshad3, D. Nickerson2, G. Lindberg7, M. D’Amato8, V. Stanghellini1, M. Seri1, R. De Giorgio1

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Aims & Methods: This study aimed to identify other mutated genes in a selected set of probands whose cases were associated with peripheral nerve hyperplasia (SFN), a condition affecting peripheral nerves including those of the autonomic system. Whole exome sequencing (WES) was performed on DNA of n = 6 probands (3 patients and 3 sporadic cases) with clinical, radiological and manometry features consistent with SFN. A neurological work-up established SFN in each of them. Libraries were enriched with the NimbleGen SeqCap EZ v3.0 and sequenced via paired-end 50 bp reads on HiSeq2500 Sequencer. Variants were annotated with the SeattleSeq157 Annotation Server. Additional 77 patients were collected for replication study. Target resequencing on selected genes was performed using the TruSeq amplicon panel designed with Design Studio software. Data analysis and variant calling was performed with the TruSeq Amplicon application in BaseSpace.

Conclusion: WES analysis performed considering pathogenic variants present as autosomal recessive (compound heterozygotes), X-linked or de-novo in the affected probands, since all the parents were healthy. We identified novel/rare missense mutations in FAT1 and in CROCC genes, inherited in an autosomal recessive pattern (homozygous or compound heterozygous) in two patients, and a de-novo variant in B3GAT2 in the affected individual of the other trio analyzed, in combination with two rare/novel variants in Lipoprotein Related Receptor 2 (LRP2), that binds APOE which we have previously related to CIPO. Analysis of these genes in 77 additional CIPO patients is currently ongoing. All the identified pathogenic variants were absent in our in-house database of 1,000 Italian chromosomes.

Disclosure of Interest: All authors have declared no conflicts of interest.


OP263 PROTEASE SIGNALING IN HUMAN SENSORY NEURONS C. Desoumeaux1, T. Batastoz2, C. Rolland3, N. Vergnolle4, N. Cenac5

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Introduction: CIPO (chronic intestinal pseudo-obstruction) is a severe gut motility disorder involving an intestinal sub-occlusion without demonstrable mechanical causes. Several genes have been identified in familial cases, suggesting a genetic heterogeneity. We identified a novel mutation in the RAD21 gene in a recessive form of familial CIPO. RAD21 is a transcription factor essential for a number of functions including sister chromatid division during cell replication.

Materials & Methods: This study aimed to identify other mutated genes in a selected set of probands whose cases were associated with peripheral nerve hyperplasia (SFN), a condition affecting peripheral nerves including those of the autonomic system. Whole exome sequencing (WES) was performed on DNA of n = 6 probands (3 patients and 3 sporadic cases) with clinical, radiological and manometry features consistent with SFN. A neurological work-up established SFN in each of them. Libraries were enriched with the NimbleGen SeqCap EZ v3.0 and sequenced via paired-end 50 bp reads on HiSeq2500 Sequencer. Variants were annotated with the SeattleSeq157 Annotation Server. Additional 77 patients were collected for replication study. Target resequencing on selected genes was performed using the TruSeq amplicon panel designed with Design Studio software. Data analysis and variant calling was performed with the TruSeq Amplicon application in BaseSpace.

Conclusion: WES analysis performed considering pathogenic variants present as autosomal recessive (compound heterozygotes), X-linked or de-novo in the affected probands, since all the parents were healthy. We identified novel/rare missense mutations in FAT1 and in CROCC genes, inherited in an autosomal recessive pattern (homozygous or compound heterozygous) in two patients, and a de-novo variant in B3GAT2 in the affected individual of the other trio analyzed, in combination with two rare/novel variants in Lipoprotein Related Receptor 2 (LRP2), that binds APOE which we have previously related to CIPO. Analysis of these genes in 77 additional CIPO patients is currently ongoing. All the identified pathogenic variants were absent in our in-house database of 1,000 Italian chromosomes.

Disclosure of Interest: All authors have declared no conflicts of interest.

MULTIVISCERAL TRANSPLANT PATIENTS

OP265 NUTRITIONAL OUTCOME IN SMALL BOWEL AND MULTIVISCERAL TRANSPANT PATIENTS


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Introduction: There has been an increase in the numbers of small bowel and multivisceral transplants performed in the UK over the past 10 years. Despite successful transplants, these patients require close monitoring long-term and currently there is limited data on their nutritional outcome.

Aims & Methods: Our primary end points are to examine 1) the percentage of patients who achieved nutritional autonomy (without oral nutritional supplement ONS, enteral nutrition EN, intravenous IV fluid or parenteral nutrition PN) post-transplant and 2) the change in their weight and body mass index (BMI) in the immediate and long-term. Secondary end points include 1) the duration on nutritional support post-transplant; 2) change in anthropometry and 3) difference in nutritional outcome in patients who have colon-containing graft or received continuity surgery. Data was collected prospectively on all patients who underwent small bowel or multivisceral transplants at Addenbrookes's Hospital, Cambridge. UK. There were 54 procedures; the last being performed from January 2006 to April 2015. Patients with survival less than 6 months post-transplant (n=9) and with incomplete data (n=1) were excluded. This resulted in 44 eligible patients whose weights, BMI and growth (in non-dominant hand) were analysed. Growth were performed by one of two dedicated dietitians.

Result: Patient characteristics: Transplants included 12 isolated small bowel (SBT), 5 liver and small bowel (LSBT), 12 modified multivisceral (small bowel, stomach, pancreas-MMVT) and 22 multivisceral (small bowel, stomach, pancreas, liver-MMVT). 7 patients were re-transplanted. Recently, donor colon has been included in the graft to help with fluid balance. Mean age at transplant was 43.9 years. Patients were followed up for a median of 30 months, to April 2016 or death (n=9). Primary outcomes: Out of the 30 long-term survivors, 73.3% (22) of them are maintained on oral diet alone at the end of follow up. The other 5 patients require ONS, 2 require IV fluids and 1 patient continues on PN. Most patients (95.5%; 21/22) who achieved nutritional autonomy were previously dependent on nutritional support (2 ONS: 1 EN: 18 PN) except for one patient who was listed super-urgently. Of the patients who died, 3 out of 14 were requiring PN. The mean BMI pre-transplant was 21.7 (SD = 3.5). Post-operatively, the majority of patients (86.7%) lost weight (mean 14.3%; range 1–30%) with their nadir weight occurring at a mean of 10.7 months. 11 lost ≥20% of their pre-transplant weight. However more than half (26/44) of the patients weights improved over time. Compared to the time of assessment, their BMI improved by 1.4 kg/m² (SD = 4.3) in the first year (median = 11 months) and increased further by 1.4 kg/m² (SD = 4.3) at the end of the follow up. The most recent mean BMI in 30 survivors were 23.3 kg/m² (SD = 5.2). Further analysis revealed 20 patients have healthy weight (BMI 18.5–25), 4 underweight (BMI <18.5), 3 overweight (BMI >25) and 2 obese (BMI >30). Surgery outcomes: Among the 13 patients who received primary transplant, PN was given for a median of 22 days (range 2–241) and 39.5 days (range 11–262) of EN. At the end of the follow up, those who have nutritional autonomy required a considerably shorter duration of nutritional support post-transplant compared to those who are nutrition dependent (mean of 65.3 vs 120.7 days). This suggests that the duration on nutritional support post-transplant may predict nutritional autonomy. Of the patients who have colon (graft or continuity), 64% have nutritional autonomy. However those without functioning colon are less likely to (47.4%) (P = 0.36). Handgrip strength was measured in 31 patients pre and post-transplant. At median of 9 months (range from 2–32), there was a slight reduction by 6% of expected value which correlates with their weight loss. 18 patients had further handgrip strength test and they increased with a mean of 7% at last follow up (median 16 months).

Conclusion: The majority of patients achieved nutritional autonomy post-transplant and a colon-containing graft may be beneficial. It is common for patients to lose a moderate amount of weight, up to 30% post-operatively. Therefore timely referral is crucial to allow optimisation of perioperative nutritional status.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP266 SUBANALYSIS OF TEDUGLUTIDE EFFICACY AND SAFETY DATA FROM PATIENTS WITH CROHN’S DISEASE AND ULCERATIVE COLITIS IN THE STEPS STUDY


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Introduction: Inflammatory bowel disease (IBD; Crohn’s disease [CD] and ulcerative colitis [UC]) is a major underlying condition for massive intestinal resection leading to intestinal failure associated with short bowel syndrome (SBS-IF).

Aims & Methods: This post hoc subgroup analysis compared response to teduglutide (TED) in patients with SBS-IF due to IBD (SBS-IF vs) those with noninflammatory causes of SBS-IF (SBS-IF-n). STEPS (NCT00798967, EndraCT2008-006193-15) was a 24-week, phase III, placebo-controlled study of 0.05 mg/kg/day TED in patients with SBS-IF. Patients were screen-eligible at baseline according to intestinal failure associated with short bowel syndrome (SBS-IF). TED was given weekly at baseline. Response was a ≥20% reduction from baseline in weekly parenteral support (PS) volume at Week 20 that was maintained at Week 24. Descriptive summary statistics are presented with 95% confidence intervals (CIs); this post hoc analysis was not powered for statistical significance.

Result: The Table details patient characteristics (SBS-IF; n = 19; SBS-IF-n, n = 67). Patients with SBS-IF had lower colon-in-continuity, higher stoma presence, and higher baseline PS volume than those with SBS-IF-n. After 24 weeks, 73% (95% CI 39–94%) of patients with SBS-IBD and 59% (95% CI 41–76%) with SBS-IF-n were responders to TED. In the patients, mean PS volume was reduced by 45% (95% CI, 31–59%) in patients with Clostridium difficile and 29% (95% CI 22–35%) in those with non-IBD. Two of 9 (22%) patients with SBS-IF and 6/30 (20%) patients with SBS-IF-n achieved a PS reduction of ≥2 days per week. Overall safety profile was similar in both groups (SBS-IF; n = 19, SBS-IF-n, n = 66). Among patients receiving treatment-emergent adverse events (TEAEs) were reported by 100% of patients with SBS-IBD and 77% of those with SBS-IF-n. Serious adverse events among those receiving TED occurred in 27% of patients with SBS-IF and 39% of those with SBS-IF-n. No TEAEs of CD were reported in either
Disclosure of Interest: U. Pape: Has received grant/research support and served as an advisory board member or speaker's bureau for NPS Pharmaceuticals, Shire plc, and Fresenius Kabi GmbH; served as a study investigator for NPS Pharmaceuticals Inc.

P.B. Jeppesen: Has received grant/research support and served as a consultant, advisory board member, and study investigator for NPS Pharmaceuticals Inc., A. Grimm: Employee of Shire plc.

A.A. Grimm: Employee of Shire plc.

S.J. O'Keefe: Has received research funding support from NPS Pharmaceuticals, Inc.

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AIMS AND OUTCOMES OF INTESTINAL AND MULTIVISCERAL TRANSPLANT

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Introduction: Despite a reduction in numbers worldwide, we have seen an increase in adult Intestinal and Multivisceral transplants in the UK in the past 3 years. Some recent transplants have been performed 'superurgently' for acute widespread splanchic ischaemia. Longstanding indications include complications of intestinal failure in patients with type 3 Intestinal failure (IF-associated liver disease (IFALD), recurrent cathereter infections and loss of vascular access), cirrhosis with extensive portomesenteric venous thrombosis precluding an isolated liver transplant and the need for extensive evisceration due to benign tumour. Re-transplantation is indicated for loss of previous graft due to rejection, ischaemia or primary non-function.

Aims & Methods: We describe the indications and outcomes for Intestinal and Multivisceral transplant at Addenbrooke's Hospital, Cambridge, UK Data was collected prospectively on an internal database of all patients transplanted from January 2006 to April 2016. All patients considered for an intestine-containing transplant were included. Some recent transplants have been performed 'superurgently' for acute widespread splanchic ischaemia. Longstanding indications include complications of intestinal failure in patients with type 3 Intestinal failure (IF-associated liver disease (IFALD), recurrent cathereter infections and loss of vascular access), cirrhosis with extensive portomesenteric venous thrombosis precluding an isolated liver transplant and the need for extensive evisceration due to benign tumour. Re-transplantation is indicated for loss of previous graft due to rejection, ischaemia or primary non-function.

Aims & Methods: In this study, we analyzed correlations of DDR2 expression with clinicopathological factors in colorectal cancer, especially peritoneal dissemination. We selected 63 cases with colorectal cancer who had an operation in our hospital between 2009 and 2014. Among them, 13 cases had synchronous or metachronous peritoneal metastasis. We performed immunohistochemical examinations for 63 primary colorectal cancers and 12 peritoneal dissemination lesions in 11 cases with DDR2 expression. We found that DDR2 expression was especially high in synchronous and metachronous peritoneal dissemination. We performed immunohistochemical examinations for 63 primary colorectal cancers and 12 peritoneal dissemination lesions in 11 cases with anti-DDR2 antibody. We detected histological localization of DDR2 expressing cells, and divided the DDR2 expressing cells into two groups by the degree of DDR2 expression, and compared various clinicopathological factors and overall survival between these two groups.

Result: In primary lesions, DDR2 expression was more preferentially in cancer cells at invasive front of tumors. The group with high DDR2 expression had significantly more proportion of T4, lymph node metastasis, and peritoneal dissemination than the former group. The prognosis of the former was significantly poorer than that of the latter group (p = 0.0025, 0.012, 0.012, respectively), and the prognosis of the former was significantly poorer than that of the latter group (p = 0.0164). In peritoneal dissemination lesions, 12 out of 12 exhibited intense DDR2 expressions.

Conclusion: High DDR2 expression correlates with peritoneal expression and poor prognosis in colorectal cancer as well as in gastric cancer. DDR2 might be one of promising driver genes of peritoneal dissemination universally in gastro-intestinal peritoneal dissemination.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

OP269 GENETIC SUSCEPTIBILITY AND FAMILY HISTORY OF COLORECTAL CANCER RELEVANCE OF SINGLE NUCLEOTIDE POLYMORPHISMS IN THE DEVELOPMENT OF COLORECTAL PNEUMOPLASMS

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Introduction: The role of common variants associated with colorectal cancer (CRC) development is not well characterized yet. The present work aims to explore the association of some genetic variants with CRC in different populations.

Methods: We carried out a meta-analysis to evaluate the association of 22 common single nucleotide polymorphisms (SNPs) with CRC risk. The primary analysis was performed using the SNPassoc package in R. To address the issue of adjustment for multiple testing, the false discovery rate method and Bonferroni’s correction were applied.

Results: Average age of participants was 54.5±9.4 years with a slight predominance of women (51.7%). In 57% of patients, no ploidyaneic lesions were found. By contrast, 288 patients (144 cases and 144 controls) showed non-advanced adenomas (NAA), and 354 patients (177 cases and 177 controls) had advanced adenomas (AA). Concerning gene analysis, 2 SNPs (rs10505477 A > G and rs6838267 G > T) located in the CASC8 gene were associated with the development of adenomas. Thus, the rs10505477G and the rs6838267T alleles were associated with a reduced risk of adenomas in patients with a positive family history of CRC (controls). Logistic–additive models, OR: 0.67, 95% CI: 0.54–0.84, respectively. However, such a protective effect was not observed in FDR of patients with CRC (cases). In the stratified analysis, the rs10505477G and the rs6838267T variants were significantly associated with a reduced risk of both, NAA and AA in controls, although this effect was stronger on the risk of developing NAA (recessive models, OR: 0.38, 95% CI: 0.21–0.70 for rs10505477, and OR: 0.32, 95% CI: 0.17–0.61 for rs6838267), suggesting their possible implication in early stages of CRC development. Finally, 2 SNPs (rs10795660G > A and rs11255841T > A) located in the lncRNA gene LINC00709 were significantly associated with a reduced risk of CRC (dominant models, OR: 0.30, 95% CI: 0.13–0.67 for rs10795660, and OR: 0.52, 95% CI: 0.28–0.97 for rs11255841), suggesting their possible implication in early stages of CRC development.

Conclusion: Family history of CRC and some specific variants associated with CRC risk (rs10505477 and rs6838267 in CASC8 gene and rs10795660 and rs11255841 in LIN00709 gene) are involved in the development of colorectal pnuemoplaes according to the family history of CRC.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP271 PREDICTION OF COMPLETE RESECTIONS AFTER CYTOREDUCTIVE SURGERY BASED ON THE EXTENT OF COLORECTAL PERITONEAL CARCINOMATOSIS


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Introduction: The curative effect of PCID2 mediated through degrading its interaction partner promyelocytic leukemia (PML) by ubiquitination. PML played a tumor suppressive role in CRC. PCID2 induced Wnt signal pathway and inhibited p53/p21 pathway activity. PCID2 expression level was evaluated in CRC patients. Recurrence curves showed that PCID2 overexpression was a prediction marker for recurrence of patients with CRC (p = 0.004 for cohort I, p = 0.03 for cohort II).

Conclusion: PCID2 plays a pivotal oncogenic role in colorectal carcinogenesis by degrading its downstream effectors and signaling pathway and inhibited p53/p21 pathway activity.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP272 PREVALENCE OF LYMPH NODE METASTASIS AND LONG TERM SURVIVAL OF TI RECTAL CARCINOID TUMORS: AN ANALYSIS OF SURVEY, EPIDEMIOLOGY, AND END RESULTS (SEER) DATABASE


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Introduction: Rectal carcinoids are the most common neuroendocrine tumors of the gastrointestinal tract and their incidence is increasing due to colorectal cancer screening. Several previous studies have suggested that local excision (endoscopic or transanal excision) is effective for lesions ≤10 mm but data on long-term pathways were elucidated by promoter lucerase assay and co-immunoprecipitation. The molecular impact of PCID2 was assessed in three cohorts of 114 CRC patients from Beijing (cohort I), 46 CRC patients from Hong Kong (cohort II) and 376 CRC cases from TCGA dataset (cohort III).

Result: Amplification of PCID2 was detected in 32.5% (37/114) of CRC patients from Beijing and 62.0% (29/46) of CRC patients from cohort III by Copy Number Assay. The copy number gain was positively correlated with its mRNA overexpression both in cohort I (r sq = 0.327, p < 0.0001) and in cohort III (r sq = 0.619, p < 0.0001). Biological functional investigation of PCID2 revealed that mRNA expression of PCID2 in colon cancer cell lines (DLD1 and HT29) significantly increased cell proliferation (p < 0.01 in DLD1 and p < 0.001 in HT29), GI1 cell cycle transition (p < 0.01 and p < 0.05, respectively), invasion (p < 0.01 and p < 0.01, respectively) and migration (p < 0.01 and p < 0.05, respectively). Increased cell viability, and suppression of cell apoptosis (p < 0.01 and p < 0.05, respectively). In addition, PCID2 significantly promoted xenograft tumor growth as well as lung metastasis in nude mice. On the other hand, knockdown PCID2 in colon cancer cell lines (HT116 and SW480) showed opposite effects.

Conclusion: PCID2 overexpression is an independent recurrence prediction marker for CRC patients.

Disclosure of Interest: All authors have declared no conflicts of interest.
OP273 LONG-TERM FOLLOW-UP FEATURES ON RECTAL MRI DURING ‘WATCH-AND-WAIT’ IN CLINICAL COMPLETE RESPONDERS AFTER CHEMORADIOThERAPY: AN UPDATE OF 68 PATIENTS

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Introduction: Treatment with stringent follow-up (‘watch-and-wait’) is emerging as an alternative to surgical resection in rectal cancer patients who show a clinical complete response after chemoradiotherapy. An important question is how (how frequently and with what modalities) to monitor patients once surgery is deferred. In addition to clinical examination and endoscopy imaging – mainly MRI – plays an important role. Given the novelty of the ‘watch-and-wait’ approach, limited data exists yet on what we can expect to see on MRI during long-term follow-up after chemoradiotherapy. A pilot study described various patterns of a complete response during watch-and-wait in a small group of patients.

Aims & Methods: Aim of this study was to follow-up on this previous research in a larger patient cohort. Objectives are to describe the morphology of the rectal wall in patients with complete response after chemoradiotherapy and to evaluate the evolution in rectal wall morphology during long-term follow-up in these patients.

68 patients with a sustained complete response (i.e. no evidence of recurrence on sequential clinical examination and endoscopy (biopsy examinations) were analysed during long term follow-up within the scope of a watch-and-wait protocol. Patients underwent MRI (as well as corresponding clinical examination and endoscopy) 3-monthly in the first year and 6 monthly during the second to fifth year. Two repeat biopsies of the rectal wall (post-chemoradiotherapy MRI scan and studied the evolution in morphology on the various sequential follow-up MRIs. MRIs were performed at 1.5T. Routine T2-weighted sequences in sagittal, transverse and coronal plane were analysed.

Results: Mean follow-up time was 30 months (range 6–96). A total of 512 MRIs was analysed (median 7, range 3–15 patient). In 7% of patients the rectal wall completely normalised post-CRT. The other 93% showed a fibriotic remnant (60% minimal fibrosis limited to the bowel wall; 21% thick/mass-like fibrosis and 12% irregular/sparse fibrosis). In 94% the rectal wall morphology remained unchanged during long-term follow-up, in 2% initial fibrosis later developed into a normalised wall, in 3% the fibrosis slightly thinned (without evidence of recurrence).

Conclusion: In the majority of patients with a complete response residual fibrosis is present post-chemoradiotherapy which remains unchanged during long-term follow-up in almost all patients. A completely normalised wall is observed in approximately 1 in 10 patients. The findings of this study may serve as a reference and provide teaching for radiologists involved in the clinical follow-up once surgery is omitted. In addition to clinical examination and endoscopy.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

TUESDAY, OCTOBER 18, 2016
14:00-15:30
GENERAL HEPATOLOGY – ROOM 1.86

OP274 ACCURACY OF A POINT SHEAR WAVE ELASTOGRAPHY TECHNIQUE (ELASTPQ) IN THE NON-INVASIVE ASSESSMENT OF LIVER FIBROSIS IN A LARGE COHORT OF LIVER PATIENTS

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Introduction: ElastPQ is a novel point shear wave elastography (PSE) technique that assesses liver stiffness by measuring liver softness (kPa) with few studies published so far. The aim of this study was to determine the accuracy and feasibility of the assessment of liver stiffness in a large cohort of patients undergoing liver biopsy (LB) for various etiologies.

Aims & Methods: Consecutive patients scheduled for LB were studied by using the iU22 Philips ultrasound system with ElastPQ technique. The correlations between laboratory findings, liver stiffness and the Metavir score will be evaluated.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference
elastographic reference method: Transient Elastography (TE): FibroScan, Elastoscan. Reliable liver stiffness values in patients with liver cirrhosis were 9.93 (6.20–15.64 kPa) for 2D-SWE:GE and 11.09 (6.57–20.51 kPa) for 2D-SWE:SSI. The median value of 3 measurements acquired in a homogeneous area and an interquartile range (IQR) <30% (1), for 2D-SW: the median value of 3 measurements acquired in an homogeneous area and an interquartile range of measurements with a success rate of >60% and an interquartile range <30%. (3). Spearman’s rank correlation coefficient (r) was used to assess the correlation of LS measurements by means of 2D-SWE, 2D-SWE:SSI and TE.

**Conclusion:** Both 2D-SWE techniques have a very good feasibility for the non-invasive assessment and liver cirrhosis. For 2D-SWE:SSI the best liver stiffness cut-off value to differentiate between liver cirrhosis and other stages of liver fibrosis (p = 0.095). Taking TE as the reference method, both 2D-SWE:SSI and 2D-SWE:GE had a good value to differentiate between stages of liver fibrosis and liver cirrhosis. For 2D-SWE:GE the best liver stiffness cut-off value to differentiate between liver cirrhosis and other stages of fibrosis was >13.7 kPa with 88.37% sensitivity, 75.68 Sp, 87.3 positive predictive value (PPV) and 77.8 negative predictive value (NPV) (AUROC = 0.831, p < 0.0001). For a liver stiffness cut-off value >10.7 kPa, 2D-SWE:GE had 91.43 Se, 78.38 Sp, 88.9 PPV, 82.9 NPV (AUROC = 0.904, p < 0.0001) for differentiating liver cirrhosis. The AUROCs of 2D-SWE:SSI and 2D-SWE:GE for predicting the presence of liver cirrhosis were similar (p = 0.09).

**Conclusion:** Both 2D-SWE techniques have a very good feasibility for the non-invasive liver fibrosis assessment and both have a strong correlation with TE. Liver stiffness values obtained by 2D-SWE:GE are significantly lower than those obtained by 2D-SWE:SSI.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

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**OP276: UTILIZATION OF REAL-TIME SHEAR WAVE ELASTOGRAPHY FOR ASSESSING LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS C**

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**Introduction:** The human Toll Like receptors (TLRs) family consists of ten receptors that respond to diverse microbial molecules and enable the innate immune system to discriminate among groups of pathogens and to induce an appropriate cascade of effector responses. HCV has different effects upon TLR pathway stimulation in various cellular compartments and in this way is able to both stimulate proinflammatory cytokine production leading to liver damage and evade immune responses to establish viral persistence.

**Aims and Methods:** The aim of this work is to investigate the association of TLR SNPs with the outcome of the HCV infection. Four SNPs of TLR2 and TLR4 were genotyped by real time PCR using TaqMan® allelic discrimination kit (Applied Biosystems) according to the manufacturer’s protocol. A total 392 families (1176 individuals) were recruited in this study from upper & lower Egypt (east and west delta), we compared the risk of allele carriage of selected markers in different HCV genotypes and different TLR genotypes. These groups included spontaneous virus clearance (SVC) (108 subject), chronic HCV patients (549), and negative control (519) individuals. The rs4986791 (C/T) and rs62522600 (G/A) were genotyped for TLR2 while rs4987911, rs5473708 (G/A) and rs25222619 (G/A) were genotyped for TLR4.

**Result:** As regard TLR2, The allele of rs121917864 (C/T) is significantly higher in HCV group compared to that control group and spontaneous (SVC) group (OR = 2.21 (95% CI 1.95 to 2.54 P = 0.0001) and 2.635 (95% CI 2.14 to 4.15 P = 0.0001)) respectively. While in the case of the rs5473708 the (G/A) was highly significantly associated with HCV group compared to that control group and spontaneous (SVC) group (OR = 2.207 (95% CI 1.206 to 4.040 P = 0.007) and 2.132 1.957 (95% CI 1.525 to 2.927 P = 0.0001)) respectively. The allelic mutation of rs4987911 was significantly higher in negative and spontaneous (SVC) group compared to that of chronic HCV group (OR= 0.4834 0.388 to 0.646 and 0.4449 and 95% CI: 0.2917-0.6787) significantly indicating that the C allele act as protective allele against HCV infection and development of chronic HCV. Linkage Disequilibrium of rs4987971 and rs6252260 SNPs indicating that the carriage of TA haplotype was significantly higher in chronic HCV compared to that of the chronic HCV group (OR= 2.199 (95% CI 1.95 to 4.35 P = 0.0001) and 2.16 (95% CI 1.95 to 4.35 P = 0.0001)). No one of spontaneous (SVC) group was carriage for TA haplotype, this revealing the role of TA haplotype as a risk indicator for HCV infection.

**Conclusion:** Current study demonstrated that spontaneous clearance of HCV was associated with the carriage of C allele of rs4987911 of TLR4 and chronicity of HCV infection is associated with the risk haplotype (TA) of TLR4 & T allele of rs121917864 & A allele of rs5473708 of TLR2.

All authors have declared no conflicts of interest.

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new-onset diabetes mellitus after kidney transplantation. From previous studies we can reasonably infer that adiponectin would be 1 and 6 into are involved in TLR2-mediated macrophage activation by hepatitis C virus core and NS3 proteins, Journal of Leukocyte Biology, Vol. 82, no. 3, pp. 479–487, 2007.

References


OP278 USEFULNESS OF MULTIPOLAR BIPOLAR RADIOFREQUENCY SYSTEM AND VALUE OF 3D SIM-NAVIGATOR

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Introduction: Fusion imaging technology is reportedly useful for radiofrequency ablation (RFA), and various types of ultrasound equipment with integral fusion imaging technology have been developed. Several RFA devices have also become available in Japan. CelonPOWER (Olympus Surgical Technology), a multipolar and bipolar RFA device, was approved for use in Japan in 2012. A single procedure using several applicators simultaneously can ablate an extensive area and reduce treatment time. A sufficiently wide area of ablation requires the optimal placement of multiple applicators. The accurate positioning of two applicators can be quite easily visualized by ultrasonography, whereas precise three-dimensional (3D) positioning of three applicators cannot. The 3D-Sim-Navigator (Hitachi Medical System) is a new fusion system that can be used during ultrasonograph (RVS) by simulating the 3D positions of multiple applicators, which can facilitate their ideal 3D positioning. We evaluated local hepatocellular carcinoma (HCC) recurrence rates after treatment using a multipolar RF system and determined the applicability of the 3D-Sim-Navigator to the system.

Aims & Methods: We compared the local recurrence rates of 209 HCC treated using multipolar or monopolar RF systems between January 2013 and October 2015 using propensity-score matching analysis. We evaluated 77 nodules from 63 patients treated using a bipolar RFA system with multiple applicators and compared complete necrosis rates (CNR) generated with or without the 3D-Sim-Navigator.

Results: Propensity-score matching analysis showed that the mean tumor diameter of 24.7±5.4 mm and the cumulative annual local recurrence rates were 0% and 14.9% for the multipolar and monopolar RF systems, respectively (p = 0.228). Thirty-two and 45 nodules with mean diameters of 28.1±11.5 and 22.2±5.7 mm (p = 0.011) were treated with and without the 3D-Sim-Navigator, respectively, with CNR of 68.8% and 66.6%, respectively, indicating that the two groups did not significantly differ (p = 0.847).

Conclusion: Case matching analysis of local recurrence rates of HCC after RFA showed that the multipolar RF system is more effective than the monopolar RF system with a diameter >25 mm. Although tumor diameter was significantly larger in the group with, than without the 3D-Sim-Navigator, CNR did not significantly differ between the two groups, because multiple applicators could be placed in ideal 3D positions using the 3D-Sim-Navigator. Therefore, HCC with a tumor diameter >25 mm should be ablated using a multipolar RF system with ideal 3D positioning facilitated by the 3D-Sim-Navigator.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference


OP279 ASSOCIATION BETWEEN ADIPOQ GENE POLYMORPHISMS AND THE RISK OF NEW-ONSET DIABETES MELLITUS AFTER LIVER TRANSPLANTATION

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Introduction: New-onset diabetes mellitus (NODAT) is a common complication after liver transplantation (LT). The prevalence of NODAT stays high and has been reported as 17–36%. NODAT contributes to a increased risk of infections, cardiovascular disease, chronic rejection and renal failure, which subsequently lead to a reduced life quality and high mortality. Recent findings suggest a tight link between ADIPOQ gene polymorphism and glucose metabolism and diabetes mellitus. Several studies have found that serum adiponectin levels are lower in diabetic patients than healthy people. In addition, reduced pretransplantation serum adiponectin would be 1 and 2 in non-diabetic liver transplantation patients. Since therapeutic options for patients with inflammatory bowel disease (IBD) who lose response to anti-TNF therapy are limited, optimal use of these agents is crucial. Loss of response can be caused by anti-drug antibody (ADA) formation and subsequent neutralization of the effect of the drug. Addition of an immunomodulator (IM) to anti-TNF therapy has been proposed as an approach to reduce antibody formation, increase serum concentrations and to regain clinical response.

Aims & Methods: We investigated whether addition of an IM to anti-TNF monoclonal antibody (MAB) can lead to a decrease of ADA levels and regained clinical response. Therefore, we retrospectively collected measurements of infliximab (IFX) and adalimumab (ADL) serum concentrations together with ADA levels from 602 patients at our IBD centre (September 2005-September 2015). ADA levels were determined with a drug sensitive assay by Sanquin Biologicals Laboratory. As a next step, we identified all ADA positive patients with secondary loss of response to IFX or ADL who received an IM in an attempt to eliminate ADA and to

Reference

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Introduction: New-onset diabetes mellitus (NODAT) is a common complication after liver transplantation (LT). The prevalence of NODAT stays high and has been reported as 17–36%. NODAT contributes to a increased risk of infections, cardiovascular disease, chronic rejection and renal failure, which subsequently lead to a reduced life quality and high mortality. Recent findings suggest a tight link between ADIPOQ gene polymorphism and glucose metabolism and diabetes mellitus. Several studies have found that serum adiponectin levels are lower in diabetic patients than healthy people. In addition, reduced pretransplantation serum adiponectin would be 1 and 6 into are involved in TLR2-mediated macrophage activation by hepatitis C virus core and NS3 proteins, Journal of Leukocyte Biology, Vol. 82, no. 3, pp. 479–487, 2007.

References

regain clinical response. Detailed documentation of disease activity was recorded.

**Result:** In 98/376 patients ADA directed against IFX and in 61/226 patients ADA against ADL were detectable. From all 159 ADA positive patients, 17 patients had received an IM, either a thiomune or MTX, because of secondary loss of response. Seven patients received MTX, ten a thiomune (4 azathioprine, 2 mercaptopurine and 2 6-TG). In 7 out of 8 patients treated with IFX, addition of an IM resulted in an increase of serum drug concentrations accompanied with a decrease of ADA till they were undetectable. The median time for ADA to IFX to become undetectable was also 11 months (IQR 6–28). For patients treated with ADL, an increase of the serum drug concentrations, together with a decrease of ADA levels, was reached in 6 out of 7 patients after addition of an IM. The median time for the ADA levels to be undetectable was also 11 months (IQR 2–37). All patients receiving MTX responded clinically which resulted in continuation of the ongoing anti-TNF treatment.

**Discussion:** The results of the current study indicate that a combination of IFX or ADL and a thiomune or MTX may be effective in the management of patients with IBD complications when female gender and delay between diagnosis and surgery were associated with late POC. These results reinforce the need for specialized and dedicated management of these at-risk elderly patients.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References**


**TUESDAY, OCTOBER 18, 2016**

**1545-1715**

**FROM GUIDELINES TO CLINICAL PRACTICE: H. PYLORI – ROOM D**

**OP281 PAN-EUROPEAN REGISTRY ON H. PYLORI MANAGEMENT – AFL-EUREG INTERIM ANALYSIS OF THE SINGLE-CAPSULE BISMUTH QUADRUPLE TREATMENT (PYLERA®)**


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12Hospital Universitario de La Fe, Valenc/Spain
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**Introduction:** The most novel treatment used in H. pylori management in Europe is the single-capsule bismuth quadruple treatment (Pylera®), but there is still very little evidence of its efficacy and safety on routine clinical practice. Pylera® is still not commercially available in most countries in Europe and, in most of those available, it has just recently reached pharmacies.

**Aims & Methods:** We aimed to evaluate the use and outcomes of Pylera® in the European Registry on H. pylori Management (Hp-Eureg). Methods: A systematic prospective registry of the clinical practice of European gastroenterologists regarding H. pylori infection and treatment (31 countries and 280 recruiting investigators). A local coordinator was selected from each country. Each coordinator selected a representative group of recruiting investigators from its country. An electronic clinical research database (e-CRF) was created on AEG-REDCED. All investigators systematically register all adult patients infected with H. pylori. Variables included: Patient's demographics, previous eradication attempts, prescribed eradication treatments, adverse events, and outcomes (cure rates, compliance, follow up, etc.). Patients with both eradication confirmatory test and with less than one year follow-up have been considered ongoing and were excluded from the analysis.

**Results:** Up to now, 15,660 patients have been included, and 12,921 have followed up (59% females, 88% Caucasian). Mean age was 55 years. Pylera® was used in 175 patients (1.2% of all treatments registered: 44% in first-line, 27% in second, 22% in third, and 8% in following rescues). Omeprazole was used in 69% of cases and esomeprazole in 24%. Overall efficacy was 76% (95%CI: 66–86%) by ITT and 78% (69–87%) by PP. In first line, efficacy was 93% (84–100%) both by ITT and PP. Second line efficacy was 68% (51–85%) by ITT and 74% (58–90%) by PP. Compliance with treatment was 98%. Adverse events were reported in 14% of cases and did not cause treatment discontinuation in any patient.

**Conclusion:** Experience with single-capsule bismuth quadruple therapy (Pylera®) is still limited. Wide confidence intervals do not allow drawing conclusions for rescue regimens; however, our preliminary data suggests that given its safety profile, compliance rates and efficacy, it may be an acceptable option as first-line treatment in Europe.

**Disclosure of Interest:** A.G. McNicholl: Speaker for Allergan, A. Perez Aisa: Speaker for Allergan, J.P. Gisbert: Has acted as speaker and advisor for Almirall, Allergan, AstraZeneca, Casen Recordati, Nycomed. All other authors have declared no conflicts of interest.
Aims & Methods: To prospectively study the efficacy and safety of peroral AstraZeneca, Casen Recordati, Nycomed. A. Perez Aisa: Speaker for Allergan

Disclosure of Interest:

Result: Thirty patients (12 f. 18 m; mean age [range]: 62 [20–92] years with positive findings of video capsule endoscopy or other small bowel imaging modality (angiectasias n = 18, jejunal/ileal polyps n = 3, thickening of wall/stricture n = 3, other n = 1) have so far been included in the trial. 27 of 30 patients had IDA. NMSE could be performed in 29 of the 30 patients with advancement of the endoscope beyond the ligament of Treitz. In one case further insertion was not performed because of a bradycardia which caused discontinuation of the procedure. Mean insertion time to the jejunum was 6.4 [2–19] min. and to the deepest point of insertion distal from ligament of Treitz 22.6 [7–52] min. The mean insertion depth from ligament of Treitz was 393 [0–600] cm. Panenteroscopy to secum could be achieved in one patient from the oral route. The diagnostic yield of NMSE was 83.4% corresponding to no findings in 5 cases, at least one angiectasia in 18 cases, one or more benign polyps in 6 and no other findings in 12 patients. Thirty-two interventions were performed in 22 patients (biopsies n = 8, APC n = 17, tattooing n = 3, clipping n = 3, EMR n = 2). Without interventions was 14 [7–54] min. Mild mucosal trauma in the esophagus or duodenum was registered in 6 cases. There were no serious adverse events.

Conclusion: First clinical data of an ongoing large prospective trial demonstrate that NMSE can be effectively and safely performed for diagnostic and therapeutic enteroscopy. The procedure offers advantages over traditional methods in terms of procedural duration and ease of use.

Disclosure of Interest: All authors have declared no conflicts of interest.

**OP28 CROSS-SECTIONAL EVALUATION OF TRANSMURAL HEALING IN PATIENTS WITH CROHN’S DISEASE ON MAINTENANCE TREATMENT WITH BIOLOGICS**

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Introduction: Transmural healing (TH) of Crohn’s disease (CD) is a new under-explored and interesting outcome in the concept of deep remission. Aims & Methods: The aim of this study was to assess the rate of TH evaluated by bowel sonography (BS) and magnetic resonance enterography (MRE) in CD patients. The study was conducted with biologic responders after tapering the two cross-sectional procedures. We performed a 2-year observational longitudinal prospective study evaluating steroid-free clinical remission (CR), mucosal healing (MH), and TH in all patients with CD who would complete a 2-year period of maintenance treatment with biologics. All patients underwent endoscopy, BS and MRE before starting biologics and 2 years later. Furthermore, the Crohn’s Disease Activity Index (CDAI) score was calculated before treatment and 2 years later. Result: The study included 40 CD patients biologic (38% infliximab and 62% adalimumab). TH was evidenced in 35 (87.5%) patients (25% at BS (k = 0.84; P < 0.01). No significant differences were noted about TH in relation to the type of biologic used (P = NS). MH was obtained in 14 subjects (35%). A good agreement was observed between MH and TH at BS (k = 0.63; P = NS). A poor agreement between MH and TH at MRE (k = 0.64; P = 0.001). CR was achieved in 24 patients (60%). A poor agreement was found between CR and TH, both at BS and MRE (k = 0.27 and 0.29, respectively; P < 0.01). Conclusion: TH can be reached in about 25% of CD patients treated with biologics. TH is a high agreement between MH and MRE on defining this outcome. After considering the advantages of BS (high diagnostic accuracy, low costs, high patient compliance, high availability) and the limitations or MRE (high costs, patient compliance, high availability) and the limitations or MRE (high costs, low availability), we suggest the use of BS as first cross-sectional procedure in defining TH in patients with CD.

Disclosure of Interest: All authors have declared no conflicts of interest.
TABLE 1 (OP288): Association between pathophysiological alterations and Patient Reported Outcomes (data shown as mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>No abnormality (n = 76)</th>
<th>1 abnormality (n = 128)</th>
<th>2 abnormalities (n = 121)</th>
<th>≥3 abnormalities (n = 82)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS symptom severity (z score)</td>
<td>−0.55 ± 0.94</td>
<td>−0.22 ± 1.06</td>
<td>0.11 ± 0.96</td>
<td>0.37 ± 0.86</td>
<td>F = 14.0, p &lt; 0.0001</td>
</tr>
<tr>
<td>Somatic symptom severity (z score)</td>
<td>−0.47 ± 0.80</td>
<td>−0.30 ± 0.93</td>
<td>0.17 ± 0.91</td>
<td>0.68 ± 0.98</td>
<td>F = 26.7, p &lt; 0.0001</td>
</tr>
<tr>
<td>IBSQOL Emotional</td>
<td>60 ± 19</td>
<td>55 ± 24</td>
<td>44 ± 17</td>
<td>51 ± 20</td>
<td>F = 35.4, p &lt; 0.0001</td>
</tr>
<tr>
<td>IBSQOL Mental Health</td>
<td>82 ± 16</td>
<td>76 ± 22</td>
<td>65 ± 20</td>
<td>51 ± 20</td>
<td>F = 35.4, p &lt; 0.0001</td>
</tr>
<tr>
<td>IBSQOL Sleep</td>
<td>82 ± 16</td>
<td>76 ± 22</td>
<td>69 ± 24</td>
<td>58 ± 24</td>
<td>F = 15.3, p &lt; 0.0001</td>
</tr>
<tr>
<td>IBSQOL Energy</td>
<td>69 ± 24</td>
<td>58 ± 27</td>
<td>48 ± 24</td>
<td>35 ± 23</td>
<td>F = 25.0, p &lt; 0.0001</td>
</tr>
<tr>
<td>IBSQOL Physical Functioning</td>
<td>75 ± 20</td>
<td>74 ± 21</td>
<td>68 ± 20</td>
<td>57 ± 26</td>
<td>F = 11.8, p &lt; 0.0001</td>
</tr>
<tr>
<td>IBSQOL Food</td>
<td>67 ± 20</td>
<td>64 ± 21</td>
<td>59 ± 18</td>
<td>55 ± 20</td>
<td>F = 6.3, p &lt; 0.0001</td>
</tr>
<tr>
<td>IBSQOL Social Role</td>
<td>71 ± 20</td>
<td>65 ± 23</td>
<td>62 ± 20</td>
<td>51 ± 24</td>
<td>F = 13.5, p &lt; 0.0001</td>
</tr>
<tr>
<td>IBSQOL Physical Role</td>
<td>64 ± 28</td>
<td>56 ± 31</td>
<td>47 ± 29</td>
<td>40 ± 28</td>
<td>F = 10.3, p &lt; 0.0001</td>
</tr>
<tr>
<td>IBSQOL Sexual</td>
<td>71 ± 23</td>
<td>70 ± 25</td>
<td>63 ± 25</td>
<td>50 ± 25</td>
<td>F = 8.2, p &lt; 0.0001</td>
</tr>
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</table>

TUESDAY, OCTOBER 18, 2016 15:45-17:15
COELIAC DISEASE FOR THE CLINICIAN – ROOM F2

OP286 THE ENZYME ACTIVITY OF SMALL INTESTINAL MUCOSA IN ADULT PATIENTS WITH CELIAC DISEASE

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Introduction: Some patients with celiac disease (CD), who have followed gluten-free diet (GFD) and have a normal histological structure of small intestine mucosa, may still have symptoms of bloating, rumbling and diarrhea. These symptoms may be associated with changes of the activity of the small intestine enzymes. Objective: To determine the activity of enzymes (glucoamylase, maltase, and sucrase). Method: In 37.5% reduction of maltase activity - in 62.5%, the activity of all enzymes and maltase, and in 81.8% of cases we observed a decreased activity of sucrase. The atrophy (Marsh IIIc) was associated with a reduced recovery of the intestine mucosa showed improvement of activity of all enzymes. Conclusion: Patients with coeliac disease and IBS-symptoms had significant improvement in abdominal symptoms and physical health from a low FODMAP diet for 6 weeks. A gluten-free diet with reduced FODMAP content was more effective than a more strict gluten-free diet, and should be offered to coeliac patients with refractory IBS-symptoms on a gluten-free diet.

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 15:45-17:15
PHYSIOPATHOLOGY OF IBS – ROOM N2

OP289 ADDITIVE EFFECT OF PATHOPHYSIOLOGICAL FACTORS ON PATIENT REPORTED OUTCOMES IN IBS

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Introduction: Both central and peripheral pathophysiologic factors are thought to contribute to the symptoms of IBS. Psychological symptoms reflect CNS dysfunction, while abnormal GI sensorimotor function reflects mainly peripheral dysfunction; both have been associated with symptoms in IBS. These factors may have additive effects on patient reported outcome (PRO) measures in IBS.

Aims & Methods: Our aim was to study whether these pathophysiological alterations have additive effect on PROs in patients with IBS. To achieve this, we included 407 patients fulfilling the Rome II or Rome III IBS criteria (74% females; mean age 43 ± 12 years). The following pathophysiological factors were measured in all subjects: colonic transit time (radiopaque markers); compliance, allodynia (low pain thresholds) and hyperalgesia (increased pain intensity) (rectal barostat); and anxiety and depression (HAD scale). Abnormal findings on the physiology assessments were defined based on the 5th and 95th percentiles in healthy controls, and on the HAD scale by score > 7. The patients also completed questionnaires to assess IBS symptom severity (IBSSS or GSSRS-IBS total score) and somatic symptom severity (SCS-30 somatization subscale or PHQ-15), and quality of life (IBSQOL).

Result: Allodynia was seen in 40% of patients, hyperalgesia in 17%, accelerated colonic transit in 18%, delayed transit in 7%, anxiety in 52% and depression in 24% - these factors were associated with severity of ≥ one IBS-related symptom. As PRO measures we used z-scores of IBS symptom severity (IBSSS or GSSRS-IBS), and somatic symptom severity (SCS-30) and PHQ-15, and quality of life (IBSQOL).

Conclusion: In patients with IBS, the coexistence of multiple pathophysiologic factors is associated with more severe IBS symptoms. At least 3 pathophysiological abnormalities relevant for symptoms were present in 20% of patients, 2 in 30%, 1 in 31%, and 18% of patients had none. The number of pathophysiological abnormalities was not associated with age (p = 0.15), gender (p = 0.12) or IBS subgroup (p = 0.21). With increasing number of pathophysiological abnormalities, there was a gradual increase in the severity of IBS symptoms (p < 0.0001) and somatic

Scale) were randomized and instructed by dieticians: Group A excluded all wheat starch and “traces of gluten” from their diet, Group B excluded FODMAPs as well as gluten. Symptoms on IBS-SSS were recorded at baseline, 3 and 6 weeks, as well as quality of life (SF-36). Four days prospective dietary intake records at baseline and 6 weeks, compliance and satisfaction after 6 weeks, and 1 month later. Dietist Net Free was used for FODMAP calculations. Statistics: paired T-tests and Wilcoxon’s. Result: 20 patients were included in each group: A (18F/2M, age 39 ± 15B (15F/5M, age 43 ± 12). 42.5% had constipation, 27.5% diarrhea and 30% both. The mean total IBS-SSS score was significantly reduced: Group A from 260 to 204 (p = 0.0022), group B from 263 to 145 (p < 0.0001), p = 0.0247, group B vs. A. In group A 10% reached remission, in Group B 25% (p = 0.048). All subscalers improved significantly in group A, only IBS-SSS in Group B (p = 0.0081), but in group A. Patients in group B were significantly more satisfied with pain relief (p = 0.0132), but it was also more challenging to follow their diet (p = 0.0088).

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016 15:45-17:15
PHYSIOPATHOLOGY OF IBS – ROOM N2

OP287 FODMAP RESTRICTION OF A GLUTEN-FREE DIET IN PATIENTS WITH COELIAC DISEASE: A RANDOMIZED, CONTROLLED CLINICAL STUDY

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Introduction: In 30% of coeliac patients on gluten free diet still have irritable bowel syndrome (IBS) symptoms. A low FODMAP (fermentable oligo-, di-, monosaccharides and polyols) diet is effective to reduce symptoms in IBS patients.

Aims & Methods: We wanted to investigate the benefit from restricting the FODMAP content of the diet in patients with coeliac disease, who are still symptomatic on a gluten-free diet. 40 patients with coeliac disease and IBS symptoms confirmed by the Rome III-criteria and SF-36, SF-12, IBSQOL, NNTS, were randomized into two groups: patients with SF-36 physical health score improved in group B (p = 0.0081), but not in group A. Patients in group B were significantly more satisfied with pain relief (p = 0.0132), but it was also more challenging to follow their diet (p = 0.0088).

Disclosure of Interest: All authors have declared no conflicts of interest.
OP289 INCREASED INHIBITORY NEUROTRANSMISSION WITHIN ANTERIOR CINGULATE CORTEX IS RELATED TO COMORBID ANXIETY IN IRITABLE BOWEL SYNDROME

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Introduction: Inspired by the concept of Irritable Bowel Syndrome (IBS) as a disorder of brain-gut-communication, alterations in central mechanisms are increasingly acknowledged in IBS pathophysiology. Given high comorbidity with affective disorders, emotional factors likely play a role in disturbed central processes in IBS. Dysfunctions particularly in brain regions involved in emotion processing, including the rostral anterior cingulate cortex (rACC) as a unique hub of both, affect regulation and anti-nociception, may constitute a central link between abdominal pain and psychiatric comorbidities. While a growing number of neuroimaging studies support a crucial role of rACC in altered pain processing and emotional disturbances in IBS, the biochemical basis of these alterations remains unknown.

Aims & Methods: We compared IBS patients and healthy controls (HC) regarding concentrations of glutamate (Glu) and γ-Aminobutyric acid (GABA+) in rACC using quantitative magnetic resonance spectroscopy (qMRS). We further addressed associations with anxiety and depression as the most common psychiatric conditions in IBS patients. A combined MTR and MRS study, GABA+ concentrations in 38 female IBS and 19 age-matched female HC were measured using a Philips Ingenia 3T scanner and a MEGA-PRESS sequence with a 3x3x3cm³ voxel placed in the rACC, localized based on individual T1-weighted images. Symptoms of anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS) and correlated with metabolite concentrations in IBS, the biochemical basis of these alterations remains unknown.

Results: Compared to HC, IBS as a group exhibited significantly increased GABA+ concentrations within rACC (p < 0.05), while no differences were observed in concentrations of Glu. Both anxiety (r = 0.407; p < 0.01) and depression (r = 0.276; p < 0.05) correlated with GABA+ concentrations. Inclusion of HADS scores as covariates diminished group differences in GABA+ concentrations in ANCOVA with anxiety, but not with depression. Analyses on IBS subgroups revealed a group effect (p < 0.05) with higher GABA+ levels in IBS+ compared to HC (p < 0.01) and compared to IBS (p = 0.056), whereas differences between IBS+ and HC did not yield significance.

Conclusion: Our findings provide first evidence of dysregulated rACC neurotransmission in IBS. This imbalance appears to be driven by increased GABA+ concentrations in rACC as a crucial structure for anti-nociception and affect regulation. Abnormal GABA+ levels were most pronounced in patients with comorbid anxiety, supporting a key role of psychiatric comorbidities in altered brain processes in IBS. Altered inhibitory GABAergic neurotransmission may be fundamental for dysregulations of affective and nociceptive processing, contributing to functional as well as long-lasting neuropsychological changes in IBS.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP290 BACTERIAL PASSAGE IS INCREASED IN THE COLON OF WOMEN WITH IRITABLE BOWEL SYNDROME INDEPENDENTLY OF STOOL CONSISTENCY SUBGROUP

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Introduction: Irritable bowel syndrome (IBS) is a chronic functional intestinal disorder with a strong female predominance. The pathophysiology is incompletely understood, but an increasing body of evidence demonstrates a role of the bacteria-microbiota axis. Altered compositions in microbiota have been associated with onset as well as changes in symptoms of IBS. Prior data suggest that intestinal barrier function is disturbed in IBS, but to our knowledge the passage of living bacteria through the colon mucosa has never been investigated.

Aims & Methods: Aims: To study the paracellular permeability and the passage of living bacteria, both commensal and pathogenic, through the colon mucosa of women with IBS and female healthy controls (HCs). The second aim was to investigate whether IBS stool consistency subgroups differ in terms of intestinal barrier function.

Methods: Colonic biopsies from 32 women with IBS (mean age 32.6y; 17 with mixed stool pattern IBS-M, 7 with diarrhea IBS-D and 8 with constipation predominance IBS-C, according to Rome III criteria) and 15 HCs (mean age 29.7y) were mounted in Ussing chambers®. Macosqal passage of living Esherichia coli (E.coli) HS and Salmonella typhimurium was investigated. The paracellular passage was measured by using 51Cr-EDTA.

Result: Table: Macosqal passage of bacteria (bacteria/chamberx10⁶) and 51Cr-EDTA (cm²/sx10⁻⁴) are shown in median (25%-75% percentile)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>IBS</th>
<th>HC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.coli (3x3x3cm³)</td>
<td>627 (563–688)</td>
<td>333 (291–387)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Salmonella (8x8x10μm²)</td>
<td>880 (689–1104)</td>
<td>315 (194–457)</td>
<td>0.0001</td>
</tr>
<tr>
<td>51Cr-EDTA (1.7x10⁻⁴)</td>
<td>1.1 (0.7–1.5)</td>
<td>0.9 (0.5–1.1)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

The colonic mucosa of IBS patients had a significantly greater passage both for living Salmonella typhimurium and E. coli HS compared with HCs (p < 0.0001 and p < 0.0001 respectively). The 51Cr-EDTA passage was also significantly increased in IBS (p < 0.05). IBS-M, IBS-D and IBS-C did not differ significantly in terms of mucosal barrier function measures, neither for bacterial nor for paracellular passage.

Conclusion: The present study demonstrated that passage through the colonic mucosa of both pathogenic and commensal living bacteria is altered in female IBS patients. These findings elucidate new aspects of peripheral abnormalities and support the importance of microbiota as a major factor in the pathophysiology of IBS.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:

OP291 LUBIPROSTONE IMPROVES THE INTESTINAL PERMEABILITY, A NEW APPROACH FOR “LEAKY GUT”: A PROSPECTIVE RANDOMIZED PILOT CLINICAL STUDY IN HEALTHY VOLUNTEERS

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Introduction: Several disease and disorders are associated with “leaky gut” (or increased intestinal permeability), such as inflammatory bowel diseases, celiac disease, food allergy, irritable bowel syndrome, and obesity-metabolic disorders. Therefore, this topic is an area of growing interest, and a well-established therapy for preventing or reverting increased intestinal permeability would be valuable. Since there are no effective medications for “leaky gut” to date, it would be important to establish a new therapy which aiming at improvement of intestinal permeability. Previous studies have reported that non-steroidal anti-inflammation drugs (NSAIDs) induce small intestinal damage and increased permeability [1]. Other basic studies have reported that lubiprostone, a chloride channel activator used for chronic constipation, repairs intestinal mucosal barrier function and also prevents NSAID-induced small intestinal damage in rodent models [2]. Aims & Methods: Our aim was to verify the effect of lubiprostone on intestinal permeability in healthy volunteers administered with dicolfenac. We conducted a prospective, randomized parallel-group trial. Healthy male volunteers, with documented absence from certain drugs (NSAIDs, proton-pump inhibitors, antibiotics, and probiotics) for at least 3 months prior to the study were enrolled. The subjects were randomly assigned to either the lubiprostone or control groups. All participants performed sugar permeability tests on baseline, after lubiprostone and after 28 days of treatment (day28). The
subjects ingested 400 ml of water containing 10 g lactulose and 5 g mannitol, after an overnight fast. Total urine for the following 4 hours was collected and rapidly frozen for analysis. Both groups started with oral intake of 75 mg diclofenac daily for 7 days. Thereafter, the lubiprostone group was treated by oral intake of 24 mg lubiprostone daily for 28 days, while the control group did not receive any medicine after diclofenac. Permeability was expressed as lactulose:mannitol ratio (LMR), calculated from urinary excretion of the initially administered dose of each sugar.

Result: Fourteen subjects for each with a median age of 23.5 (range, 21–32) completed the study. The background characteristics including baseline LMR between the two groups showed no significant difference. Treatment after 28 days of lubiprostone showed significant improvement of LMR (p = 0.0497), while 14 days treatment did not reach statistical significance compared to control group (p = 0.403).

LMR results (analyzed by analysis of covariance: ANCOVA)

<table>
<thead>
<tr>
<th>LMR</th>
<th>control group (n = 14)</th>
<th>lubiprostone group (n = 14)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>0.019 (0.016–0.022)</td>
<td>0.021 (0.017–0.025)</td>
<td>0.403</td>
</tr>
<tr>
<td>day14</td>
<td>0.055 (0.023–0.047)</td>
<td>0.024 (0.019–0.029)</td>
<td>0.099</td>
</tr>
<tr>
<td>day28</td>
<td>0.028 (0.023–0.033)</td>
<td>0.017 (0.015–0.019)</td>
<td>0.0497</td>
</tr>
</tbody>
</table>

Conclusion: In our study, 28 days treatment with lubiprostone demonstrated an improvement of increased intestinal permeability after 1-week administration of diclofenac in healthy volunteers. This is the first study to demonstrate a significant effect of a medication for treatment of increased intestinal permeability, and suggests a new approach towards several diseases associated to “leaky gut”.

References

OP292 VISCERAL HYPERSENSITIVITY IS ASSOCIATED WITH GI SYMPTOM SEVERITY IN FUNCTIONAL GI DISORDERS: CONSISTENT FINDINGS FROM FIVE DIFFERENT PATIENT COHORTS

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Introduction: Divergent results have been reported regarding the association between visceral hypersensitivity and GI symptom severity in patients with functional GI disorders (FGIDs). Moreover, it has been proposed that the association between hypersensitivity and GI symptoms is secondary to psychological factors and tendency to report symptoms.

Aims & Methods: Our aim was to evaluate the association between visceral hypersensitivity and GI symptom severity in large cohorts of FGID patients. To do this, we included 5 cohorts of patients with FGIDs, who had undergone GI balloon distensions and completed questionnaires to assess GI symptom severity. Moreover, it has been proposed that the association between visceral hypersensitivity and GI symptoms is secondary to psychological factors and tendency to report symptoms.

Aims & Methods: To do this, we included 5 cohorts of patients with FGIDs, who had undergone GI balloon distensions and completed questionnaires to assess GI symptom severity. Furthermore, it has been proposed that the association between visceral hypersensitivity and GI symptoms is secondary to psychological factors and tendency to report symptoms.

Conclusion: A gradual increase in GI symptom severity with increasing GI sensitivity, with significant differences in GI symptom severity between the sensitivity tertiles, and small, but significant correlations between pain/discomfort thresholds and GI symptom severity, across all five patient groups (r = −0.20 to −0.29). The differences between sensitivity tertiles remained significant in all cohorts after correction for anxiety and depression, and after correction for somatization (without GI symptoms) in all of the cohorts (p < 0.05).

References

OP293 CHRONIC ORAL ADMINISTRATION OF THE GUANYLATE CYCLASE-C AGONIST LINACLOTIDE ATTENUATES COLITIS-INDUCED LONG-TERM BLADDER AFFERENT HYPERACTIVITY

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Introduction: There is significant comorbidity between the symptoms of IBS and the urological symptoms of urgency and frequency experienced in overactive bladder and interstitial cystitis. The sigmoid colon is a rich source of colonic afferent sensory nerve fibers (nerve fibers with a diameter of 1–2 μm). Colon and rectal afferent fibers supply the bladder via the pelvic splanchnic nerves and the inferior hypogastric plexus. Increased afferent activity from the sigmoid colon is associated with altered bladder cystometry and bladder afferent hyperactivity.

Aims & Methods: Our aim was to evaluate the association between visceral hypersensitivity and GI symptom severity in large cohorts of FGID patients. To do this, we included 5 cohorts of patients with FGIDs, who had undergone GI balloon distensions and completed questionnaires to assess GI symptom severity, somatization, anxiety and depression. Furthermore, it has been proposed that the association between visceral hypersensitivity and GI symptoms is secondary to psychological factors and tendency to report symptoms.

Table 1 (OP292): Association between visceral hypersensitivity and GI symptom severity in five FGID cohorts

<table>
<thead>
<tr>
<th></th>
<th>Belgian FD cohort</th>
<th>US IBS cohort (colon; n = 243)</th>
<th>US IBS cohort (rectum; n = 159)</th>
<th>Swedish IBS cohort 1 (n = 353)</th>
<th>Swedish IBS cohort 2 (n = 147)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 242)</td>
<td>(n = 243)</td>
<td>(n = 159)</td>
<td>(n = 353)</td>
<td>(n = 147)</td>
</tr>
<tr>
<td>z score GI sx severity (mean ± SD)</td>
<td>DSS</td>
<td>IBS-SSS</td>
<td>IBS-SSS</td>
<td>IBS-SSS</td>
<td>IBS-SSS</td>
</tr>
<tr>
<td>Low sensitivity tertile</td>
<td>−0.48 ± 0.99</td>
<td>−0.29 ± 0.99</td>
<td>−0.34 ± 0.90</td>
<td>−0.40 ± 0.98</td>
<td>−0.46 ± 0.89</td>
</tr>
<tr>
<td>Mid sensitivity tertile</td>
<td>−0.07 ± 0.88</td>
<td>−0.04 ± 1.00</td>
<td>−0.00 ± 1.04</td>
<td>0.11 ± 0.99</td>
<td>0.31 ± 0.83</td>
</tr>
<tr>
<td>High sensitivity tertile</td>
<td>0.32 ± 0.99</td>
<td>0.25 ± 0.95</td>
<td>0.28 ± 0.97</td>
<td>0.25 ± 0.95</td>
<td>0.06 ± 1.14</td>
</tr>
<tr>
<td>ANOVA (adjust for somatization)</td>
<td>F = 13.2; p &lt; 0.0001</td>
<td>F = 5.9; p = 0.003</td>
<td>F = 5.1; p = 0.007</td>
<td>F = 14.0; p &lt; 0.0001</td>
<td>F = 8.5; p &lt; 0.0001</td>
</tr>
<tr>
<td>ANOVA (adjust for anx &amp; dep)</td>
<td>F = 9.2; p &lt; 0.0001</td>
<td>F = 4.9; p = 0.004</td>
<td>F = 4.1; p = 0.018</td>
<td>F = 10.8; p &lt; 0.0001</td>
<td>F = 3.2; p &lt; 0.0001</td>
</tr>
<tr>
<td>Correlation sensitivity - GI sx</td>
<td>r = −0.27; p &lt; 0.0001</td>
<td>r = −0.20; p &lt; 0.0001</td>
<td>r = −0.27; p = 0.001</td>
<td>r = −0.29; p &lt; 0.0001</td>
<td>r = −0.20; p &lt; 0.02</td>
</tr>
</tbody>
</table>

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administration, consisting of a once daily oral gavage for 2 weeks prior to experi-
ment. Groups were four per treatment, with four whole cell patch clamp recordings from retro-
grade tracer thoracolumbar and lumbar sacral bladder dorsal root ganglion (DRG) neurons determined neuronal excitability, whilst ex vivo electrophysiologi-
cal recordings determined bladderafferent andcontractile sensitivity to ramp dis-

References
S.M. Brierley: Research support: Ironwood Pharmaceuticals Inc, Takeda

References

TOP294 DIAGNOSING RARE INHERITED DISORDERS USING
TARGETED NEXT GENERATION SEQUENCING IN PATIENTS
WITH EARLY-ONSET INFLAMMATORY BOWEL DISEASE: A
POPULATION-BASED STUDY
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Introduction: Several recent referral center studies showed that a significant propor-
tion (3-10%) of children with an early-onset (EO, defined by an age at diagnosis less than 12 years) inflammatory bowel disease (IBD) present with an underly-
ing monogenic disorder. Currently, more than sixty disorders of this type have been identified and their pathophysiological mechanisms are very heteroge-
neous. Most of them affecting the intestinal epithelial barrier, are asso-
ciated with defects in phagocytosis or immune deficiency, or are hyper- and auto-

Aims & Methods: Using a next-generation sequencing (NGS) of the 63 genes whose abnormalities are responsible for these disorders, and a targeted CGH analysis of other chromosomal loci, 91 patients with an initial diagnosis of EO-IBD between 1988 and 2004 (54% of the whole EO-IBD cohort) issued from EPI-

Conclusion: OP295 HYPOXIA INHIBITS INTESTINAL INFLAMMATION THROUGH THE INHIBITION OF NLRP3 INFLAMMASOME AND THE ACTIVATION OF AUTOPHAGY
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Disclosure of Interest: All authors have declared no conflicts of interest.

Aim: To study the effects of hypoxia in IBD, healthy volunteers (n = 10), patients with Crohn’s disease (CD, n = 11) and patients with ulcerative colitis (UC, n = 9) were subjected to hypoxic conditions resembling an altitude of 4,000 m above sea level for 3 h using a hypobaric chamber. Distal colonic biopsies were collected the day before hypoxia, immediately after hypoxia, and one week after collection of the first biopsy. To further study the effects of hypoxia in colitis and the role of the NLRP3 inflammasome, wild-type (WT), interleukin (IL)-10−/−, Nlrp3−/− and IL-10−/− Nlrp3−/− double knockout mice were subjected to hypoxia (8% O2) for 18 h prior to colonic biopsy collection. Mice under normoxic

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Disclosure of Interest: All authors have declared no conflicts of interest.

References
4. Nakaikira K, et al. Hypoxia induces autophagy through the direct induction of autophagy gene expression and signaling. Hypoxia-induced autophagy was enhanced in the absence of NLRP3 further supporting a role for NLRP3 in the regulation of autophagy. Our results confirm a reciprocal regulation between hypoxia, inflammation, and autophagy, and suggest that hypoxia ameliorates inflammation through the induction of autophagy via the regulation of NLRP3.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

Conclusion: Our results suggest a protective effect of hypoxia in CD patients and the IL-10−/− mouse model of colitis. IL-10−/− , but not IL-10−/− Nlrp3−/− mice under prolonged hypoxia exhibited inhibition of autophagy indicating that NLRP3 is involved in the blockage of autophagy. Interestingly, hypoxia restored autophagy in IL-10−/− mice, as well as in THP1 and HT-29 cells concomitantly with a reduction of inflammatory gene expression and signaling. Hypoxia-induced autophagy was enhanced in the absence of NLRP3 further supporting a role for NLRP3 in the regulation of autophagy.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

Disclosure of Interest: All authors have declared no conflicts of interest.

References
OP296 EPIGENETIC ALTERATIONS IN INFLAMMATORY BOWEL DISEASE - THE INFLUENCE OF GERMLINE VARIATION (MEQTLS) ON GENOME-WIDE METHYLATION ALTERATIONS

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Introduction: Exploring DNA methylation in Inflammatory Bowel Disease (IBD) may provide an insight into complex gene-environment interactions, identify novel targets involved in pathogenesis, and allow development of powerful new biomarkers. Our study aims to characterize disease-associated methylation changes in newly diagnosed IBD and to define the contribution of genetic variation, by discovery of associated quantitative trait loci (meQTL).

Aims & Methods: Genome-wide methylation was measured in 641 DNA samples from peripheral blood mononuclear cells (PBMC controls, 150 Crohn’s disease, with our previous cohort of IBD patients in six European centres as part of the European Commission funded IBD-Characater project.

Result: 195 probes exhibited Bonferroni significant IBD-associated methylation differences, including VMP1/MIR21 (p = 3.7 × 10−8), RPS6K2A (1.1 × 10−8), SBN02 (2.7 × 10−8), and TNSF10 (1.1 × 10−8); data which provide important replication and confirmation of methylation differences previously reported in paediatric CD and adult IBD. Novel findings include PHOSPHO1 (1.3 × 10−3), MUC4 (5.5 × 10−3), and CDH24 (1.7 × 10−4), 1709 differentially methylated regions of consecutive FDR significant probes were defined in genes including VMP1/MIR21, ITGB2, TGF, and at multiple sites throughout the HLA region. Results were highly similar in CD and UC, with only one probe showing a significant methylation difference between diagnoses (NAV2, 6.82 × 10−7).

Paired genetic and methylation data showed 2327 FDR significant MeQTLs

OP297 AN AUTOPHAGY-RELATED PERIPHERAL BLOOD MICRORNA SIGNATURE DIFFERENTIATES COLONIC CROHN’S DISEASE FROM ULCERATIVE COLITIS

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Introduction: Phenotypic expression of colonic inflammation in inflammatory bowel disease (IBD) in patients with colonic Crohn’s disease (CCD) and ulcerative colitis (UC) can sometimes have a similar appearance and be difficult to differentiate. MicroRNAs (miRNAs) may offer a method of distinction as differential expression of peripheral blood miRNAs has been shown in small studies of CCD patients and healthy controls. Aims & Methods: This study aimed to assess peripheral blood mononuclear cell (PBMC)-derived miRNA signatures in a well-phenotyped cohort of colonic IBD and to identify differentially expressed miRNAs in patients with CCD and UC. An IBD cohort with UC and CCD was prospectively accrued. Colonicoscopy was performed and patients with CCD (Montreal Classification L2/L3) or left-sided UC (Montreal Classification E2/E3) were enrolled. Colonicoscopy and endoscopic scores for presence/absence, severity and extent of inflammation. Pathology reports were reviewed for presence/absence and severity of inflammation. On the day of endoscopy, C-reactive protein (CRP) was measured and blood was collected in PAXgene tubes (Qiagen). Total RNA was extracted from blood using the PAXgene Blood miRNA kit (Qiagen) and miRNA counts from 798 probes were measured using the Human v3 miRNA nCounter Platform (NanoString Technologies). Raw counts were normalized, log2 transformed and batch corrected. Non-parametric Kruskal-Wallis tests assessed differential miRNA expression across phenotypes.

Conclusion: This study aimed to assess peripheral blood mononuclear cell (PBMC)-derived miRNA signatures in a well-phenotyped cohort of colonic IBD and to identify differentially expressed miRNAs in patients with CCD and UC. An IBD cohort with UC and CCD was prospectively accrued. Colonicoscopy was performed and patients with CCD (Montreal Classification L2/L3) or left-sided UC (Montreal Classification E2/E3) were enrolled. Colonicoscopy and endoscopic scores for presence/absence, severity and extent of inflammation. Pathology reports were reviewed for presence/absence and severity of inflammation. On the day of endoscopy, C-reactive protein (CRP) was measured and blood was collected in PAXgene tubes (Qiagen). Total RNA was extracted from blood using the PAXgene Blood miRNA kit (Qiagen) and miRNA counts from 798 probes were measured using the Human v3 miRNA nCounter Platform (NanoString Technologies). Raw counts were normalized, log2 transformed and batch corrected. Non-parametric Kruskal-Wallis tests assessed differential miRNA expression across phenotypes.

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several appear to be associated with the autophagy pathway. These findings may aid individualization of patient care through identification of novel diagnostic and therapeutic targets.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP298 ASSESSMENT OF INFLAMMATORY BURDEN IDENTIFIES CROHN'S DISEASE AND ULCERATIVE COLITIS PATIENT GROUPS WITH DIFFERENT DISEASE PROGRESSION PATHWAYS AND THERAPEUTIC RESPONSE TO ANTI-TNF TREATMENT  
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Introduction: Crohn's disease (CD) and ulcerative colitis (UC) are considered to be driven by both common and distinct underlying mechanisms of pathobiology. In both diseases there is heterogeneity underscored by the variable clinical responses obtained to therapeutic interventions. We aimed to identify disease-driving pathways as well as classify individuals into subpopulations that differ in their disease pathobiology and response to a specific treatment.

Aims & Methods: Hierarchical clustering on enrichment scores (ES) from gene set variation analysis (GSVA) was used probing a normal healthy volunteer (NHV), CD and UC disease clusters of signature sets (GSE16879) with testing of gene set signatures representative of various immunological and inflammatory processes as well as specific activated cell types. Patient stratification at baseline (BL) or after anti-TNF treatment (PT) in either clinical responders (R) or non-responders (NR) was assessed.

Result: Gene set signatures whose ES differed significantly (ES change \( p < 0.05 \)) between comparisons were identified from general linear model analyses. Comparisons were made at BL in all participants irrespective of clinical response.2 Gene set signatures were compared to NHV. 59% of the tested signatures were commonly enriched in both CD and UC at BL underlining the commonality of both diseases. These signatures included e.g. activated T cells, monocytes, macrophages or neutrophil signatures as well as polyIC and bemicon signatures, representing acute inflammation and a complex mix of potential disease-driving biology. Comparing R and NR separately at BL to NHV, 43% and 70% of signatures were enriched, respectively, indicative of a higher inflammatory burden in NR. Indeed, specific macrophage, innate lymphoid cell and neutrophil signatures were particularly enriched in NR. Hierarchical clustering of the ES that significantly differed in the comparisons clearly separated disease BL from NHV samples. It also clustered R PT samples with the NHV while the NR PT samples clustered with the BL died samples, with a between separation observed in CD when compared to UC. Also, clear UC and CD patient clusters could be observed with increasing ES at BL correlated with NR to anti-TNF treatment recapitulating the observation of a higher inflammatory burden in NR.

Conclusion: Our analysis has identified common disease-driving pathways for CD and UC supporting the notion of a disease continuum rather than two distinct diseases. However, within that disease continuum, distinct patient groups could be defined by their overall inflammatory burden correlating with their response to an anti-TNF therapy. This methodological approach could facilitate better targeted design of clinical studies to test therapeutics under development, concentrating on subsets of patients sharing similar underlying molecular pathology and therefore increasing the likelihood of clinical response.

Disclosure of Interest: S. Pavlidis: Employee of Janssen Research & Development Ltd, High Wycombe, UK  
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OP300 THE IMPLANTABLE MEDICATED MICRORESERVOIRS IN THE TREATMENT OF COLORECTAL CANCER: THE GOOD EFFECTS OF A SIMPLE PROCEDURE. EARLY RESULTS  
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Introduction: Colorectal cancer (CRC) is the third most common in the world of men, and the second - in women. In Europe remains steady increase in incidence and mortality according to Globocan 2012 and source Eurocancer. The main problem after surgery is local recurrences that often develop even after resection of CRC. Local recurrences in a developed survival is less than 30%. The main reason is a development of metastatic远处 metastasis. We have studied the influence of microreservoirs with 5-fluorouracil (5FU) supported on polyvinylpyrrolidone (PVP). In fact, it was a mixture of 30% PVP solution 5 ml and 5 ml 5FU intramuscularly in naive genetically susceptible mice (10 g/mouse), and AIEC colonization in the gut and AIEC-induced intestinal inflammation were analyzed.

Conclusion: Our study shows that infection with CD-associated AIEC induces secretion of exosomes carrying several CD-associated circulating miRNAs by human THP-1 macrophages. These exosomal miRNAs, when being transferred into recipient naïve THP-1 macrophages, may be involved in the regulation of cell-mediated and autophagic responses, contributing to host innate defense to AIEC infection.

Disclosure of Interest: All authors have declared no conflicts of interest.

TUESDAY, OCTOBER 18, 2016
15:45-17:15
NOVEL TECHNIQUES IN LOWER GI MALIGNANCIES – ROOM L8

OP299 CROHN'S DISEASE-ASSOCIATED CIRCULATING MICRONAS ARE SECRETED IN EXOSOMES FROM AIEC-INFECTED HUMAN MACROPHAGES AND INVOLVED IN REGULATION OF HOST INNATE IMMUNE RESPONSES IN RECIPIENT CELLS

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Introduction: A high prevalence of invasive Escherichia coli strains, named AIEC (adherent-invasive E. coli), has been reported in the intestinal mucosa of Crohn’s disease (CD) patients. A deregulated microRNA (miRNA) expression profile has been reported in CD patients’ peripheral blood. Exosomes are small endosomal-derived vesicles involved in cell-to-cell communication. Exosomes have been shown to carry miRNAs that can be efficiently transferred and modulate the immune system.

We recently showed that AIEC-infected human macrophages released exosomes that increase CD-related inflammatory response and an increased bacterial intracellular replication in recipient cells.

Aims & Methods: Here, we investigated whether exosomal miRNAs are involved in such processes. Exosomes were purified using ExoQuick Exosome Precipitation kit. miRNA expression profiles were analyzed by qRT-PCR. In vivo infection with AIEC bacteria was performed using ideal loop assays and exosomes were purified. Purified exosomes were then intravenously injected in naïve mice (10 µg/mouse).

Result: We analyzed the levels of the CD-associated circulating miRNAs reported in literature in exosomes released from AIEC LF82-infected (Exo-AIEC) THP-1 macrophages. A significant upregulation of several miRNAs in Exo-AIEC compared with exosomes released from uninfected (Exo-U) cells or cells infected with a non-pathogenic commensal E. coli HT strain was observed (Exo-HS). To analyze their transfer to recipient cells, naïve THP-1 macrophages were stimulated with the exosomes, and the levels of miRNAs in recipient cells were analyzed. The levels of several exosomal miRNAs were increased in THP-1 cells compared with Exo-AIEC compared with cells stimulated with Exo-HS, suggesting an efficient transfer. In silico analysis showed that the upregulated and transferred miRNAs are involved in inflammatory responses and autophagy, which is necessary to control AIEC intracellular replication, among other biological processes. These miRNAs in THP-1 cells inhibited the Exo-AIEC-triggered increases in pro-inflammatory response and AIEC intracellular replication in recipient cells, suggesting that these exosomal miRNAs are functional and are involved in the effects of Exo-AIEC in recipient cells.

To confirm the in vitro data, we developed an in vivo model to analyze the impact of Exo-AIEC on gut colonization by AIEC and AIEC-induced inflammation. In this model, exosomes were isolated from ileal loops of CD mice infected with AIEC. Purified exosomes were then intravenously injected in naïve genetically susceptible mice (10 µg/mouse), and AIEC colonization in the gut and AIEC-induced intestinal inflammation were analyzed.

Conclusion: Our study shows that infection with CD-associated AIEC induces secretion of exosomes carrying several CD-associated circulating miRNAs by human THP-1 macrophages. These exosomal miRNAs, when being transferred into recipient naïve THP-1 macrophages, may be involved in the regulation of cell-mediated and autophagic responses, contributing to host innate defense to AIEC infection.
OP301 ENDOSCOPIC SUBMUCOUS DISSECTION IN LATERALLY SPREADING TUMORS: EXPERIENCE OF 282 CASES FROM A TERTIARY REFERENCE CENTER IN TURKEY

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Introduction: Endoscopic submucosal dissection (ESD) is a minimally invasive technique, providing en-bloc resection of premalignant and malignant lesions in early stage gastrointestinal (GI) cancers. Lateral Spreading Tumors (LSTs), which are endoscopically seen as granular (LST-G) or non granular (LST-NG) types, are technically difficult to remove as en-bloc with ESD method because of anatomical features of the colon. In the present study, we present our results of colorectal ESD procedures in LSTs.

Aims & Methods: Between April 2012- April 2016, a total of 655 colorectal lesions were referred to our unit for the purpose of removal with advanced endoscopic techniques (EMR or ESD). Colorectal ESD was performed to 290 lesions. Data was recorded prospectively before and after the procedure. 8 ESD cases were excluded because the lack of control endoscopy. The results of 282 ESD procedures performed in colon and rectum with diagnosed LST were analyzed retrospectively.

Result:

Table: Demographic data and colorectal endoscopic submucosal dissection results [Case (n)=273 Lesion (N)=282]

| N=282 |
|---|---|
| Lesion size, mm, mean (SD) (median; range) | 40.44 (26.2) (33; 14–176) |
| Tissue size, mm, mean (SD) (median; range) | 49.81 (28.9) (42; 20–198) |
| Duration of procedure, min, mean (SD) (median; range) | 79.5 (71.1) (61.5; 6–540) |
| Dissection speed, mm²/min, mean (SD) (median; range) | 24.46 (15.41) (21; 1.74–79.55) |
| En-Bloc resection rate, N (%) | 257 (91.1) |
| Complete Resection, N (%) | 255 (90.4) |
| Paris Classification, N (%) Is 1s 1s+ 2a 2a | 4 (1.4) 142 (50.4) 101 (35.8) 35 |
| 2a+ 2c | (12.4) |
| Adverse Events, N Delayed bleeding | 2 |
| Perforation | 9 |
| Localization, N Rectum Sigmoid colon | 133 42 16 6 15 25 14 6 |
| Descending colon Splenic flexura | Transverse colon Hepatic flexura |
| Ascending colon Cecum Ileocecal valve | Pathology, N (%) Carcinoma | 124 (44.9) (35.2) 4 (1.4) 21 (7.4) |
| Intramucosal Sm1 invasion Sm2 | Invasion Tubular Adenoma | 28 (9.9) 102 (36.2) 17 (6.0) |
| Tubulovillous Adenoma Villous Adenoma Serrated Adenoma | LST LST-G LST-NG | 11(3.9) |
| 236 46 |

The 282 colorectal ESD procedures were performed in 273 patients, the demographic data and results of which are shown in the table. The overall en-bloc and complete resection rates were 91.1% and 90.4%, respectively. The lesion type of endoscopic procedure: ESMR-L group (n=117), CSI-EMR group (n=282), CSI-ESD group (n=282), and 95.2% (20 of

Disclosure of Interest: All authors have declared no conflicts of interest.

OP302 EVALUATION OF RECTAL CANCER ANGIogenesis USING IMMUNOHistoCHEMICAL AND COMPUTER-ASSISTED ENDOscopIC GRAPHIC METHODS

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Introduction: The conventional way for evaluation of rectal cancer angiogenesis requires a biopsy or a tissue specimen applying specific immunohistochemical or molecular biological tests. The evaluation of microvessel density is a gold standard in the assessment of tumour angiogenesis. Doppler ultrasound is an attractive tool for imaging angiogenesis in vivo which can be repeated without exposing the patient to any risk.

Aims & Methods: The aim of the current study is to evaluate the preoperative rectal cancer angiogenic status with Endorectal Power Doppler Ultrasound by using a novel software for Vascularity Index calculation. 110 cases of colorectal cancer were included in this study. For preoperative evaluation, PDVI was calculated using Calis software. In this study, we compared results with microvessel density in surgical specimens A total of 110 patients (59 males; 51 females, mean age 61.5 years) with rectal cancer were enrolled in this study. The patients were operated and staged as follows: in stage I – 20pts (18%), stage II – 19 (20%) stage III – 47 pts (43%); stage IV – 14 pts (13%). Microvessel density was evaluated by using immunohistochemical staining of surgical specimens with anti-CD-31 antibody. The PDVI of each tumor was determined using endorectal power Doppler ultrasound with computer assisted quantification of colour pixels. The PDVI was defined as the ratio of the number of the colored pixels within a tumor section to the number of total pixels in that specific tumor section, and was calculated using a software.

Result: The mean microvessel density (MVD) was 163 ±69 microvessels/mm². Median MVD was used as the cutoff point divided two groups of tumours with high (≥160 vessels/mm²) and low angiogenic activity (<160 vessels/mm²). Mean PDVI was 8.9 ±6.0% (range: from 0 to 27.3). Median PDVI (8%) was used as the cutoff divided two groups of tumours with high (>8%) and low PDVI (<8%). The MVD and PDVI showed a good positive linear correlation (r=0.438, p=0.002).

Conclusion: Endorectal Power Doppler ultrasonography is a useful noninvasive method of evaluating the extent of angiogenesis. Tumor angiogenesis assessed by power Doppler US are easier, faster, and portable than conventional angiography methods. The presented endosonographic Power Doppler examination is a reliable and reproducible mean for in vivo preoperative quantitative assessment of the tumour vascularityisation.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP303 COMPARISON OF CLINICAL OUTCOMES AMONG DIFFERENT ENDOscopic MODALITIES FOR RECTAL NEUROendocrine TUMOR

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Introduction: Rectal neuroendocrine tumor (NET) less than 10 mm in diameter can be removed by various endoscopic techniques, such as endoscopic mucosal resection (EMR), modified EMR, and endoscopic submucosal dissection (ESD). This study aimed to compared efficacy and safety of endorectal submucosal resec-

Result: There was no different in tumor diameter between different endoscopic procedures (ESMR-L, 4.5 ± 1.6 mm; CSI-EMR, 5.6 ± 2.0 mm; ESD, 5.0 ± 2.2 mm, p = 0.236). En bloc resection was achieved in all patients. There was no lateral margin involvement in all patients. Basal margin involvement occurred in one patients in the ESD group and two in the CSI-EMR group. The rates of pathological complete resection were 100% (17 of 17) in the ESMR-L group, 100% (18) in the CSI-EMR group, and 95.2% (20 of
Introduction: The human papilloma virus (HPV) is the leading cause of anal squamous cell carcinoma. The cytological screening can reduce morbidity and mortality associated with this cancer, although current recommendations are based on expert opinion.

Aims & Methods: The authors intend to estimate agreement between anal cytology examination, histopathology, and analoscopic visual impression. This is a prospective study of patients receiving anal dysplasia screening between 2010 and 2015, in a proctology consultation of a tertiary referral center. Descriptive statistics was performed using IBM SPSS Statistics 22 with p < 0.05 deemed to be statistically significant. Agreement between measures was estimated by weighted kappa-statistics.

Results: During the period of the study, 141 patients (91% men, mean age 37 ± 14 years, 87% with HIV infection) underwent 175 anal cytology tests: 33% negative (ASCUS), 33% low-grade squamous intraepithelial lesion (LSIL) and 33% high-grade squamous intraepithelial lesion (HSIL). Concerning analoscopic visual impression, 40% patients had uncertain significance (ASCUS), 33% low-grade squamous intraepithelial lesion (LSIL) and 27% high-grade squamous intraepithelial lesion (HSIL).

Conclusion: Anal endoscopic resection method, including ESMR-L, CSI-EMR, and ESD were effective and safe for the treatment of rectal NET. Compared with CSI-EMR or ESD, ESMR-L procedure has the advantages of easier and shorter procedure time. ESMR-L may be considered the treatment of choice for rectal NET in patients > 65 years in diameter. Complete endoscopic excision in a single session was achieved in 28/31 patients (93%); in one patient a second TASER session was required for completion procedure. Numerous endoscopic and trans-anal surgical approaches (CRPs, ESMR-L, ESD, ESMR-P, ESD, P-EMR, EMA and TAE) could be undertaken. Mean procedure time was 185 min, range 65-480 min. Thirty two TASER sessions were employed using ESD in 12/32, ESD + P-EMR in 6/32, ESD + P-EMR + EMA in 4/32, ESD + TAE in 3/32, ESD + P-EMR + EMA + TAE in 4/32. Intra-procedural bleeding was controlled with haemostatic endoscopic devices (coagrasper/ clips); surgical clipping and suturing on 2 occasions. Prophylactic endoscopic clipping was also applied in 8 cases and suturing on 4 occasions. In 6/10 TASER - TAE cases there was a need for a full-thickness rectal dissection due to submucosal fibrosis: 4/6 cases were closed with surgical sutures plus endoscopic clips and in the remaining 2/6 cases only endoscopic clips were deployed. Two episodes of delayed bleeding were reported among the TASER-ESD/P-EMR and CSI-EMR sub-cohorts. In 6/10 sub-cohorts, complications or rectal excisions were reported. All patients were discharged the day after the TASER PROCEDURE apart from one patient who developed bacteremia post TASER-ESD requiring intravenous antibiotics and a 4-night hospital stay and the patient who required a second anal endoscopic resection on day 4 post procedure. First diagnosis was performed at 4–6 months interval in 25/31 patients showed: 21/25 with no recurrence (84%) and 4/25 (16%) with a minimal (<15 mm) polyph recurrence, amenable to endoscopic therapy. No rectal stricturing was identified and only one recurrence was reported.

Disclosure of Interest: TASER appears to be a safe and efficient endo-surgical approach providing an optimal platform for the minimally-invasive management of high-risk, complex rectal polyps.

Reference

TUESDAY, OCTOBER 18, 2016
15:45-17:15
THE INTESTINAL EPITHELIUM - STEM CELLS, INFLAMMATION AND CANCER – ROOM 1.86

OP306 THE PROREGENERATIVE ROLE OF INTERLEUKIN-22 IN THE INTESTINAL EPITHELIUM DEPENDS ON AUTOAPHOPSY AND ER STRESS
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Introduction: Endoplasmic reticulum (ER) function and autophagy are necessary to maintain cellular homeostasis. Genetic variants of inflammatory bowel disease (IBD) risk genes ATG16L1 or XBP1 are associated with epithelial endoplasmic reticulum (ER) stress which promotes cell death. While XBP1 plays a beneficial role in resolving ER stress, ATG16L1 represents an essential component of the autophagy machinery, a conserved mechanism for protein degradation. Both processes are strongly connected since impaired autophagy subsequently results in deregulation of ER function. Interleukin-22 (IL-22) is known to be a protective cytoprotecte in mucosal regeneration by promoting epithelial proliferation via STAT3 activation. Therefore, conjugates of IL-22 are in trials as potential drugs in IBD treatment.

Aims & Methods: Here, we investigate the impact of the IBD risk genes ATG16L1 and XBP1 on regenerative function of IL-22 in intestinal epithelium in mice and human-derived human colon carcinoma HT-29 and Caco2 cells were treated with recombinant IL-22 and ER stress inducers like Tunicamycin or autophagy inducers like Rapamycin before they were subjected to wound healing assays, gene expression analysis and immunoblot analyses. Intestinal organoids derived from XBP1 +/− mice were treated with recombinant IL-22 and gene expression analysis using qRT-PCR. RNA sequencing and transcriptome analysis were performed. A120 United European Gastroenterology Journal 4(5S)
References

3. Pickert G et al. STAT3 links IL-22 signaling in intestinal epithelium and spontaneous cell death in intestinal crypts which exacerbates after IL-22 treatment. Finally, IL-22-induced autophagy in premalignant intestinal inflammation led to Atg16l1 ΔIEC mice. On the flipside, same treatment of wild type control mice does not affect cell death and inflammation, underlining a genotype dependency of beneficial and adverse effects of IL-22 application.

Conclusion: These data suggest an unexpected role of the IBD risk genes ATG16L1 and XBP1 in coordinating regenerative IL-22 function in intestinal epithelium and may contribute to the development of genotype-based personalisation of medicine. However, further studies are necessary to decipher the molecular link between IL-22 signaling and the ER stress/autophagy axis.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

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Conclusion: These data suggest an unexpected role of the IBD risk genes ATG16L1 and XBP1 in coordinating regenerative IL-22 function in intestinal epithelium and may contribute to the development of genotype-based personalisation of medicine. However, further studies are necessary to decipher the molecular link between IL-22 signaling and the ER stress/autophagy axis.

Disclosure of Interest: All authors have declared no conflicts of interest.

References
western blot analysis. The gene expression of transformed organoids was assessed by microarray analysis and quantitative RT-PCR.

**Result:** The treatment with the inflammatory reagents in mouse colonic organoids showed the time-dependent induction of NF-κB target genes. Particularly, the expression of DUOX2 gene was gradually increased by the continuous stimulation with inflammatory reagents for 40 weeks. 3D immunostaining analysis showed NF-κB p65 was accumulated in nuclei by longer time of the stimulation, indicating that long-term stimulation might lead to a stronger activation of NF-κB signaling. Interestingly, accumulated NF-κB signaling by long-term stimulation remained active after the removal of all inflammatory reagents, whereas NF-κB signaling induced by short-term stimulation was completely shut down by the removal of all inflammatory reagents, suggesting that NF-κB might be irreversibly activated by long-term stimulation. Moreover, the organoids required neither R-spondin nor Wnt3a after the treatment with GSK3 inhibitor for 8 weeks, indicating that the organs might be transformed like colitis-associated cancer. Microarray analysis and Gene Set Enrichment Analysis of transformed organoids showed irreversible Akt signal activation and reduced expression of Tgfβ2, indicating that this transformation might involve the inflammation-related carcinogenesis.

**Conclusion:** Long-term inflammation and nuclear accumulation of β-catenin leads to irreversibly activated cell transformation, which is not dependent on survival capacity of colonic organoids. In this vitro model mimics the natural history of epithelial cell transformation during inflammation-related carcinogenesis in UC.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**Reference**

attenuated as compared with their wild type controls. Importantly, pretreatment with Roneparstat significantly reduced, in a dose-related manner, the HSP expression, the tissue inflammatory response, autophagy and serum amylase and lipase levels.

Conclusion: HSPE appears to play an important role in the pathogenesis of AP. The HSPE inhibitor (Roneparstat) significantly reduced the severity of the AP in an animal model. This new concept may provide a basis for prophylaxis and treatment of AP.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP313 CIGARETTE SMOKE EXTRACT INHIBITS FLUID AND HCO3- SECRETION AND CFTR ACTIVITY IN GUINEA PIG PANCREATIC DUCTAL CELLS

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Introduction: Ghrelin (GHRL), a 28-amino acid polypeptide, that was originally isolated from the stomach, was shown to protect the pancreas from caerulein-induced acute pancreatitis in rats. J Physiol Pharmacol 2003; 54(4): 561–573.

Aims & Methods: In this study, we would like to understand whether smoking has any effects on pancreatic ductal fluid and HCO3- secretion. Guinea pigs were exposed to cigarette smoke four times a day for 30 min for 6 weeks. The expression of GHS-R1a and TNF-alpha in the pancreatic acini were determined by RT-PCR and the gene expressions were isolated from control, GHRL rats and then hyperstimulated by caerulein (20 μg/kg i.p.)

Conclusion: Cigarette smoke and CSE inhibits pancreatic ductal fluid and HCO3- secretion via inhibition of CFTR activity and activity of the CFTR which may play a role in the smoke-induced pancreatic damage. This study was supported by OTKA, MTA and TAMOP.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP315 IDENTIFICATION AND CHARACTERISATION OF A NOVEL EARLY ONSET DIABETES GENE USING HUMAN PLURIPOTENT STEM CELLS

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Disclosure of Interest: All authors have declared no conflicts of interest.

Introduction: Diabetes represents one of the major burdens in the 21st century with an estimated 350 million people affected worldwide. Monogenic diabetes such as juvenile onset insulin-dependent diabetes (JOD) or maturity onset diabetes of the young (MODY) accounts for approximately 1–2% of diabetes cases and results from mutations that primarily reduce β-cell function. The identification of the genes that are mutated in these diseases focuses has translated into novel avenues of personalization medicine in the diabetes field, but only few of these genes have been identified to date.

Aims & Methods: Based on published data, we hypothesize that a proportion of these mutations contribute to type 1 diabetes (T1D) and type 2 diabetes (T2D) may be caused by rare monogenic variants/mutations missed by the current GWAS strategies targeting common variants. The current project reports on such a novel gene relevant as regulator of human pancreatic islet formation but also as a novel early onset diabetes genes.

Result: Using stage-specific genome-wide profiling complemented with Chip-Seq data in differentiating human embryonic stem cells, we show that our gene binds and activates Nkx2.2, Nkx6.1 and Pdx1, all belonging to the core suite of islet transcription factors. Hence, this gene co-occupies the enhancer and promoter regions of the latter genes together with Foxa2, Pdx1 and GatA. Finally, we engineered human embryonic stem cells with previously identified mutations in JOD patients. Directed differentiation studies of these cells shows a perturbed binding pattern of Krox22, Nkx2.2, Nkx6.1 and Pdx1 finally leading to reduced amounts of monohormonal β-cells. This reduced target gene binding results from a limited zinc affinity, due to the mutation, that would be necessary as co-factor for gene binding.

Conclusion: This platform not only allows personalised drug-testing but also sheds light on the mechanism how our JOD gene regulates pancreatic development and leads to diabetes in case of certain mutations in humans. Disclosure of Interest: All authors have declared no conflicts of interest.

OP334 GHRELIN INHIBITS TNF-ALPHA PRODUCTION IN ACUTE PANCREATITIS

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Disclosure of Interest: All authors have declared no conflicts of interest.

Introduction: Ghrelin (GHRL), a 28-amino acid polypeptide, that was originally isolated from the stomach, was shown to protect the pancreas from caerulein-induced pancreatitis (AP) [1–3].

Aims & Methods: To determine the effects of GHRL on tumor necrosis factor-alpha (TNF-alpha) production in in vitro and on the signals for growth hormone secretagogues receptor type 1a (GHS-R1a) and TNF-alpha in the pancreatic acini. AP was induced by caerulein infusion (25 μg/kg s.c.). GHRL (12.5; 25; 50 μg/kg i.p.) was given to the control rats and prior to the start of inflammation in vivo. Plasma TNF-alpha concentration was measured by ELISA. Pancreatic acini were isolated from control, GHRL rats and then hyperstimulated by caerulein (105 M) in vitro. The gene expressions were determined by RT-PCR and the protein contents by Western-blot.

Result: Administration of GHRL to the control rats failed to affect TNF-alpha concentration in plasma. AP significantly increased its, but application of GHRL prior to the inflammation significantly dose-dependently reduced this pro-inflammatory cytokine. Protein expressions and mRNA signals for GHS-R1a and TNF-alpha have been detected in the pancreatic acini under basal conditions and GHRL resulted in a statistically increase of GHS-R1a without changing TNF-alpha.

Conclusion: Caerulein upregulated molecular signals for TNF-alpha and downregulated that for GHS-R1a in the pancreatic acini. This effect could be prevented by pretreatment of the AP rats with GHRL. Above mechanism could be implicated in the protective action of AP.

Disclosure of Interest: All authors have declared no conflicts of interest.

References


OP336 LACK OF CFTR RESULTS IN THE IMPAIRED FUNCTION OF THE PLASMA MEMBRANE CA2+-PUMP THAT CAUSES INTRACELLULAR CA2+-OVERLOAD AND MITOCHONDRIAL DAMAGE IN THE PANCREATIC DUCTAL EPITHELIAL CELLS OF CFTR KNOCK OUT MICE

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Disclosure of Interest: All authors have declared no conflicts of interest.

Introduction: The cystic fibrosis transmembrane conductance regulator (CFTR) has a significant role in pancreatic ductal epithelial secretion and it’s genetic defects damage the pancreas. The exact mechanism of this pancreatic damage is only partially known. The toxic cellular Ca2+ overload is hallmark of acute pancreatitis and in CFTR-deficient airway epithelial cells the intracellular Ca2+ homeostasis was disturbed. However the Ca2+ homeostasis of CFTR-deficient pancreatic ductal epithelial cells (PDEC) has never been investigated.

Aims & Methods: Our aim was to characterize the Ca2+ homeostasis of CFTR-deficient PDEC. Pancreatic ducts and acinar cells were isolated from wild type (WT) and CFTR knockout (KO) mice. Intracellular Ca2+ concentration ([Ca2+]i) and changes of the mitochondrial membrane potential was measured.

Result: Maximal [Ca2+]i release upon carbacol stimulation showed no difference in WT and CFTR KO PDEC. Notably, the plateau phase of the Ca2+ signal was significantly higher in CFTR-deficient PDEC, but completely normal in pancreatic acinar cells. Interestingly, the functional inhibition of CFTR with 10μM CFTR(inh)-172 had no effect on the Ca2+ signals. Next we investigated the mitochondrial membrane potential and found that the Ca2+ extrusion was significantly lower
in CFTR KO PDEC compared to WT due to the impaired function of the plasma membrane Ca²⁺ pump (PMCA). In addition, the sustained elevation of [Ca²⁺]ᵢ lead to a drop in mitochondrial membrane potential in CFTR KO PDEC.

Conclusion: Dysfunction of PMCA leads to disturbed Ca²⁺ homeostasis in CFTR-deficient PDEC and the consequent cellular Ca²⁺ overload impairs mitoc

Disclosure of Interest: All authors have declared no conflicts of interest.

OPI318 CARDIOVASCULAR RISK IN PATIENTS WITH CHRONIC CFTR-deficient PDEC and the consequent cellular Ca²⁺ homeostasis. These changes might contribute to the pancreatic damage seen in cystic fibrosis.

Disclosure of Interest: All authors have declared no conflicts of interest.

OPI319 USE OF THE URINARY TRYPsinogen-2 DIPSTICK TEST IN EARLY DIAGNOSIS OF PANCREATITIS AFTER ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAphY

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Introduction: One of the most common complications of (ERP) is acute pancreatitis. The reported incidence varies from 1.3% to 24.4% [1]. Measurement of serum amylase and lipase levels after the procedure may have a possible role for early recognition of post-ERP pancreatitis [3]. Asymptomatic elevation in serum amylase and lipase activities after ERP is common, occurring in approximately 25% to 75% of all patients. A rapid test strip has been developed for the detection of trypsinogen-2 in urine (The urinary trypsinogen-2 dipstick test—UT2DSTactim pancreatitis) which is based on the immunochromatogra phy principle and shows a good sensitivity and specificity in diagnosing acute pancreatitis [6]. The aim of this study was to evaluate the diagnostic value of the urinary trypsinogen-2 dipstick test for early diagnosis of post-ERP pancreatitis.

Aims & Methods: After an informed consent by the patients the selected patients were divided to: Full clinical assessment (history taking, physical examination), laboratory investigations including (complete blood count (CBC), Bilirubin (total and direct), ALT, AST, alkaline phosphatase (ALP), Prothrombin time and concentration (PT & PC), urea, creatinine, serum amylase, serum lipase, urinary trypsinogen-2 dipstick test (UT2DST).

Result: Post ERP UT2DST was negative in 30 patients of the non pancreatitis group (96.8%) and positive in one of them (3.2%). The test was positive in all patients of ERP Pancreatitis (100%). The positive predictive value of UT2DST was 100%. The Specificity was 97% with PPV 86%, NPV 100% and the P value was <0.01. Comparison between serum lipase and amylase levels post ERP in relation to UT2DST test shows that positive UT2DST test was significantly associated with higher amylase and lipase serum levels after ERP (post amylase and post lipase) (P < 0.01).

Conclusion: The urinary trypsinogen-2 dipstick test can be used as an easy and rapid test for early diagnosis of post-ERP pancreatitis with high sensitivity and specificity and can help clinicians to provide intensive care and possible medical treatment as early as possible.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:
Disclosure of Interest: than standard hydration for prevention of post-ERCP pancreatitis.

Result: visual analogue scale) persisting for /C21

Aims & Methods: reduce the incidence of post-ERCP pancreatitis. The present larger multi-
center study aimed to determine what kind of intravenous hydration could

Contact E-mail Address: PROSPECTIVE RANDOMIZED MULTICENTER CLINICAL TRIAL

Contact E-mail Address: PROGRESS

Contact E-mail Address: DISCLOSURE: D. Domagk: Dirk Domagk has received research support

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Disclosure of Interest: All authors have declared no conflicts of interest.

References
1. Babbaum J, Yan A, Yeh K, et al. Aggressive hydration with lactated ringer’s solution may reduce the development of post-endoscopic retro-
grade cholangiopancreatography (ERCP) pancreatitis. The present larger multi-
center study aimed to determine what kind of intravenous hydration could reduce the incidence of post-ERCP pancreatitis.

Aims & Methods: In a prospective randomized multicenter clinical trial, patients who underwent first-time ERCP were randomly assigned to 3 groups (1:1:1) that received aggressive hydration with lactated ringer’s solution (3 mL/kg.h during the procedure, and 1 mL/kg bolus after the procedure, and 3 mL/kg for 8 hours after the procedure), standard hydration with the same solution (1.5 mL/kg.h during and for 8 hours after the procedure), or aggressive hydration with physiologic saline (3 mL/kg.h during the procedure, a 20 mL/kg bolus after the procedure, and 1 mL/kg for 8 hours after the procedure). The primary end point, post-ERCP pancreatitis, was defined as hyperamylasemia (level of amylase marker of pancreatic necrosis in acute pancreatitis.


WEDNESDAY, OCTOBER 19, 2016

OP321 GASTROINTESTINAL SAFETY OF LEVODOPA-CARBIDOPA INTESTINAL GEL IN ADVANCED PARKINSON’S DISEASE

PATIENTS: FINAL RESULTS FROM THE GLORIA LONG-TERM REGISTRY

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OP324 INCREASED MUCOSAL EXPRESSION OF TOLL-LIKE RECEPTORS IN ADULT PATIENTS WITH EOSINOPHILIC ESOPHAGITIS

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Introduction: An adaptive Th2-type immune response to food antigens is involved in eosinophilic esophagitis (EoE). Evidences of a potential role for the innate immunity in EoE has also been paralleled to the recognition of changes in the esophageal microbiome in adult and pediatric EoE patients compared to non-EoE controls. The likely role that microbial pattern recognition receptors (PRRs) might play in EoE arises as a potential source of research in understanding the relationship of diet, the esophageal microbiome, and the immune system activation in EoE, that has not been assessed yet.

Aims & Methods: To gather data about the potential implication of Toll-like receptors (TLRs), the most investigated group of transmembrane PRR in EoE, we characterized TLR mRNA expression and protein staining in esophageal mucosal biopsy samples from adults before and after dietary treatment, and compared with control patients. Esophageal mucosal samples were fixed in formalin, embedded in paraffin, and routinely processed for hematoxylin and eosin staining. Specific antigen retrieval and permeabilization processes were performed before samples were incubated with the primary antibodies anti-TLR1, TLR2, TLR3, TLR4, TLR6, or TLR9. Incubation with the secondary antibodies Alexa Fluor 594 goat anti-rabbit IgG or Alexa Fluor 488 goat anti-mouse IgG were counterstained with DAPI. Gene expression for the different TLRs assessed in all samples after RNA was isolated with MirVanaTM Kit. Simultaneous real-time PCRs were performed with TaqMan Low-Density Arrays. Thermal cycling conditions were 2 min at 50 °C, 10 min at 95 °C, followed by 40 cycles of denaturation at 95 °C for 15 s, and annealing and extension at 60 °C for 1 min in an ABI PRISM 7900 HT Sequence Detection System. Relative changes in mRNA expression were calculated with the cycle threshold (Ct) method.

Result: A total of 10 EoE patients (8 men) and 10 gender-matched control subjects were included in the analysis. The groups had a mean age of 33.1 (10.1) and 53 (19.9) years, respectively. In the EoE group, peak intraepithelial eosinophil density was 56.8 (29.9) cells/hpf, which decreased to 3 (4.2) cells/hpf after SFB-fed-based treatment (p < 0.001). Eosinophilic eosinophils were detected in any of the esophageal samples from controls. No differences in eosinophil counts were detected for atopic and non-atopic EoE patients, being 55 (30.4) vs. 61 (34.8) cells/hpf, respectively. Active EoE characterized by significant upregulation of TLR1 (2.7-fold increase), TLR2 (3.7-fold increase) TLR4 (4.6-fold increase) and TLR9 (3.4-fold increase) in comparison with the controls (p < 0.05 for all comparisons). Dietary treatment significantly decreased all the four TLRs to control group values (p < 0.05). Immunofluorescence staining demonstrated epithelial-predominant staining in TLR2 and TLR4, and scattered cell staining for TLR1 and TLR9. TLR expression patterns showed differences in lamina propria and epithelial layers.

Conclusion: EoE is associated with changes in expression levels of several TLRs, that reverse after effective dietary therapy. Our results points towards an interplay of diet, microbiome and innate immune responses in the pathophysiology of EoE.

Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016
08:30-10:00
Eosinophilic Oesophagitis and GORD – Room M

OP323 STEP-UP EMPIRIC ELIMINATION DIET FOR PEDIATRIC AND ADULT EOSINOPHILIC ESOPHAGITIS: THE 2-4-6 STUDY


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Introduction: A six-food elimination diet (SFB) for eosinophilic esophagitis (EoE) requires almost a year on a high level of dietary restriction and multiple elimination steps. A four-food elimination diet (FFED), eliminating the four most common culprit foods in EoE (animal milk, gluten-containing cereals, egg, legumes) has been a first step to simplify empiric elimination strategies. The most common food triggers were animal milk (60%), gluten-containing cereals, egg, and legumes in both children and adults. All patients included fulfilled clinic and histologic criteria for EoE and lack of response to PPI therapy. Remission rates increased to 52% and 65% with a FFED and a step-up strategy (2-4-6) allows reducing endoscopic procedures and the diagnostic process time by 35%.

Conclusion: A two-food elimination diet (animal milk, gluten-containing cereals) achieves 40% remission in a group of patients unresponsive to PPI therapy. This diet allows prompt identification of two thirds of responders to empiric elimination diets, with few food triggers (one food trigger in 85% of responders) and consequently, good candidates for dietary maintenance therapy. A step-up empiric diet strategy (2-4-6) might be a cost-effective dietary strategy for pediatric and adult EoE.

Disclosure of Interest: All authors have declared no conflicts of interest.
OP325 A RANDOMIZED, DOBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF A NOVEL RECOMBINANT, HUMANIZED, ANTI-INTERLEUKIN-13 MONOCLONAL ANTIBODY (RPC4046) IN PATIENTS WITH ACTIVE EOSINOPHILIC OESOPHAGITIS: RESULTS OF THE HEROES STUDY

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Introduction: Interleukin-13 (IL-13) has been implicated in the pathogenesis of eosinophilic oesophagitis (EOE). RPC4046 prevents the binding of IL-13 to both the IL-13Rα1 and IL-13Rα2 receptors. This study evaluated the efficacy and safety of 2 dose levels of RPC4046 compared to placebo (PBO).

Aims & Methods: Two parallel randomized studies were randomized 1:1:1 to receive either RPC4046 180 mg [LD (n = 31)], RPC4046 360 mg [HD (n = 34)], or PBO (n = 34). An IV day on 1 was followed by weekly subcutaneous doses. Oesophageal biopsies, read by a central blinded pathologist, were obtained at baseline (BL) and Wk12 to assess eosinophilic epidermis, the primary endpoint. Secondary endpoints included symptom improvement measured by a Daily Symptom Diary (DSD), improvement in endoscopic features as measured by the EOE Endoscopic Reference Score (EREF), and Subject’s Global Assessment of Disease Severity. Safety was also assessed.

Result: 90 subjects completed the 16Wk double-blind period. Demographic/disease characteristics were generally comparable between treatment arms. At BL, mean eosinophilic esophagitis counts (cells/hpf) were 92.4 (PBO), 116.6 (LD), and 127.6 (HD), and mean count was significantly reduced from BL for both RPC4046 dose levels compared to PBO (mean change: PBO –4.4, LD –94.8, and HD –122.6 (HD). At Wk16, the mean count was significantly reduced from BL for both RPC4046 dose levels compared to PBO (mean change: PBO –0.9, LD –4.2, and HD –4.8 [both p < 0.001 vs PBO]). There was a greater improvement in dysphagia symptoms as measured by the DSD with HD compared to PBO, but this did not achieve statistical significance (PBO –6.4, LD –5.3 [p = 0.096 vs PBO], and HD –13.3 [p = 0.073 vs PBO]). There were significant improvements in endoscopic features as determined by the reduction in the mean total EREF score with both RPC4046 dose levels (mean change: PBO –0.9, LD –4.2, and HD –4.8 [both p < 0.0001 vs PBO]). There was a significant improvement in Subject’s Global Assessment of Disease Severity at the HD (PBO –1.5, LD –2.0, HD –2.8 [HD p = 0.0017 vs PBO]). The rates of overall adverse events (AEs) were 64.7% (PBO), 64.5% (LD), and 85.3% (HD). The most frequent AE was headache (PBO 14.7%, LD 20.6%, HD 20.6%), upper respiratory infection (PBO 8.8%, LD 16.1%, HD 14.7%), and arthralgia (PBO 0%, LD 12.9%, HD 5.9%).

Conclusion: RPC4046 demonstrated significant reductions in oesophageal eosinophilic inflammation and improvements in endoscopic features at both dose levels compared to placebo. HD had greater symptom improvement than LD. This did not achieve statistical significance. At Wk16 these phase 2 data support the further study of RPC4046 as a novel treatment for EOE.

M. Collins: I have received research funds (through contracts) from Receptos (now Celgene), Meritage (now Celgene), Meritage Pharma, Abbott Laboratories, Nestle S.A., QOL, Receptos, Inc., and Meritage Pharma, Inc.
S. Gupta: Sandeep K. Gupta received consulting fees and/or speaker fees from Abbott Laboratories, Nestle S.A., QOL, Receptos, Inc., and Meritage Pharma, Inc.
A. Schoepfer: I received consultant fees from: Receptos, Regeneron and grant support from: Receptos, Regeneron, Falk.
A. Straumann: Dr. Straumann is a consultant to Dr Falk Pharma GmbH and has received consulting fees and/or speaker fees and/or research grants from Actelion, AG; AstraZeneca AG, AG; Apsalis Pharma; GSK; AG; Nestle S.A.; Novartis, AG; Pfizer, AG, and Regeneron.
M. Grimm: I am an employee of Celgene.
H. Smith: I am an employee of Celgene.
C. Tompkins: At is a former employee of Celgene.
A. Woo: I am an employee of Celgene.
R. Peach: I am a former employee of Celgene.
P. Frohna: I am an employee of Celgene.
S. Gujratli: I am a former employee of Celgene.
R. Aranda: I am an employee of Celgene.
E. Dellon: I have received research funding from Receptos/Celgene; and am a Consultant for Receptos/Celgene.

All other authors have declared no conflicts of interest.
investigating PPI-refractory patients studied off-therapy, further improving the meaningfulness of the clinical procedure. Aims & Methods: We aimed to investigate whether the impairment of chemical clearance, expressed by PSPW index, and of mucosal integrity, expressed by MNBI, are helpful in segregating NERD from FH studied with impedance-pH monitoring on-PPI therapy. Further, we assessed the value of these novel parameters as predictors of PPI-refractory GERD confirmed by 3-year positive surgical outcome. On-therapy impedance-pH tracings from consecutive patients referred for PPI-refractory heartburn with/without regurgitation (i.e. <50% of symptoms are relieved after 30 min high-dose PPI therapy) were blindly reviewed. All tracings were manually analyzed to detect: acid exposure time (AET; abnormal if ≥3.2% over 24 hours), characteristics of reflux episodes (acid/weakly acidic and symptom-reflux association using both symptom association probability (SAP; positive if ≥95%) and symptom index (SI; positive if ≥50%)). MNBI values were calculated at 3 cm above the LES, during the overnight rest, for at least 30 minutes after excluding swallows and reflux induced changes. The PSPW index was calculated by dividing the number of refluxes followed by ≥5 mmHg nadir by swallow-induced peristaltic waves with the number of total refluxes. Patients were subdivided into refluxatory esophageal sphincter (R ES), healed reflux esophagitis (HRE), non-reflux esophageal disease (NERD); defined by abnormal acid exposure time or normal AET but positive symptom-reflux correlation) and functional heartburn (defined by negative symptom-reflux correlation) according to endoscopy and conventional impairment-pH variables.

Result: Median PSPW index and MNBI were significantly lower in 39 RRE (16%; 1145 Ohms) than in 41 HRE (25%; 1741 Ohms) and in 68 NERD (29%; 2374 Ohms) patients, and in all three GERD subgroups compared to 41 FH cases (67%; 3488 Ohms) (P < 0.0001). Comparing NERD to FH, PSPW index was even more pronounced in NERD than in FH: median of 0.56 vs. 0.78. SI values were higher with swallowing peristaltic waves vs. pure reflux episodes (0.886 vs. 0.677, P = 0.005). PSPW index was abnormal preoperatively in 53/53 patients with positive surgical outcome and resulted independent predictor of PPI-refractory GERD at multivariate analysis, (odd ratio 0.6983, P = 0.001).

Conclusion: On-therapy impairment-pH monitoring, impaired chemical clearance and mucosal integrity characterize PPI-refractory typical GERD. PSPW index and MNBI efficiently distinguish PPI-refractory NERD from FH and PSPW index is valid for selecting surgical candidates.

Disclosure of Interest: All authors have declared no conflicts of interest.

A128

OP328 PRELIMINARY RESULTS OF A PROSPECTIVE MULTI-CENTER REGISTRY OF LOWER ESOPHAGEAL SPHINCTER STIMULATION FOR GERD: THE LESS-GERD REGISTRY

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Introduction: Safety and effectiveness of electrical stimulation of the lower esophageal sphincter (LES-ES) using the Endostim® LES Stimulation System (The Hague, The Netherlands) was demonstrated in clinical trials. Limited data available on outcomes in clinical practice.

Aims & Methods: An ongoing, prospective international multi-center web-based registry is collecting data in patients with disruptive GERD symptoms treated with LES-ES in clinical practice at baseline and at routine follow-ups for 5-years.

Demographics, adverse events, GERD symptoms recorded in daily diaries, Demographics, adverse events, GERD symptoms recorded in daily diaries, adverse events, GERD symptoms recorded in daily diaries, and physiological data (esophageal pH / manometry) are collected when available.

Disclosure of Interest: All authors have declared no conflicts of interest.

A128

OP329 SURVEILLANCE OF HIGH-RISK INDIVIDUALS DETECTS RESECTABLE PANCREATIC MALIGNANCIES AND HIGH-GRADE PRECURSORS: RESULTS OF A 16-YEAR EARLY DETECTION PROGRAM FOR FAMILIAL PANCREATIC NEOPLASIA


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Introduction: Endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) screening of asymptomatic individuals (HRI) at high risk for PD to detect for early pancreatic neoplasia can lead to the detection of small pancreatic cancers in almost 40% of cases, with some indication that this may lead to improved survival. However, there is little evidence for which screening tool is best for neoplastic progression and the natural history of low risk detected lesions after baseline screening. The long-term clinical outcomes of radiological surveillance aiming to detect early PD and high-grade precursor lesions (IPMN HGD or PanNET) are poorly understood.

Aims & Methods: To determine the incidence of surveillance-detected pancreatic lesions following baseline screening and calculate the incidence rates of invasive malignancy and high-grade neoplasia in HRI undergoing long-term surveillance. We prospectively enrolled HRI in the surveillance program at the Richard E. Smith Center for Radiological Research (CAPS) from 1998 to 2018 (n = 378) at a tertiary referral academic medical center with a comprehensive multidisciplinary pancreas screening program. HRI consisted of familial PD relatives or patients with a family history of PD (BRCA 1/2, PALB2, p16, PRSS1, STK11) who had a >6-months follow-up of baseline EUS/ERCP (including 5 years of surveillance including 12 months of follow-up imaging after baseline EUS and MRI. HRI with baseline solid masses or prevalent PD were excluded from the surveillance cohort analyses. Radiological progression (progression to high-grade disease or malignant transformation) and worrisome features of progression (IPMN HGD, PanNET, or HPC) were defined. Sendai International Consensus Guidelines (ICG) for pancreatic mucinous cysts were compared to pathologic diagnoses or repeat abdominal imaging according to clinical surveillance protocol.

HRI were screened and underwent follow-up imaging with EUS and/or MRI every 6–12 months (depending on baseline findings), 293 (85%) familial PC relatives and 50 (15%) mutation carriers were studied, mean age 56.4 (range 22-81), 47% male. Mean follow-up time was 5.1 years (range 0.5-15.1). 132/341 (38%) had no pancreatitics at baseline and follow-up, 155 (45%) had a low risk cyst at baseline, and 12 (3.5%) had a solid mass or nodule at baseline. 74 HRI (22%) developed new low risk cysts on follow-up. 34/343 HRI (16%) developed radiological progression, with a new solid mass detected in 58% (n = 19) in 6 months (n = 3) or 12 months (n = 1) by EUS. Baseline EUS was abnormal in 3c m (n = 18) in 6 months (n = 1), 24,7% (n = 5), cyst growth ≥2 mm in 6 months (n = 1), 2 mm in 6 months (n = 1) and 7% (n = 2) at 12 months follow-up. In contrast, none of HRI without detected lesions at baseline or follow-up developed PD (P = 0.002). During surveillance, 13,343 (3.8%) incident PD and 8,343 (2.3%) incident malignant neuroendocrine tumors were detected (all with radiologic progression). An additional 8,343 (2.3%) HRI had HPCls. The incidence of PD was 1/50 (2%) in mutation carriers and 12/293 (4%) in familial PC relatives. Of the 50 patients with pathological diagnoses (45 surgical resection, 5 biopsy), 27 of 29 (93%) with radiological features of progression had a malignancy (PDA = 13 or PanNET tumor = 6), or at least one HPCl (n = 8). 10 of 13 (77%) of incident PDAs were resectable (3 unresectable PDAs were late for surveillance or lost to follow-up). 16,45 (36%) HRI who had surgery had lower grade neoplasms (BD-IPMN LYG/IGD, PanIN2, combined IPMN, SCA, benign neuroendocrine microadenomas). In surgically-treated HRI, the prevalence of IPMN HGD in cysts with mural nodules was 5/7 (71%).
Conclusion: In our 16-year cohort with long-term surveillance, the incidence of PDAC on initially selected but majority of detected cancers were asymptomatic and resectable. Surveillance also detects early stage PanNETs and HPCls. The majority of detected proven malignancies had radiologic progression but more research is needed to improve the selection of patients for surveillance and surgery.

Disclosure of Interest: All authors have declared no conflicts of interest.

Reference


OP330 CLINICAL IMPACT OF ENDOSCOPIC ULTRASONOGRAPHY IMAGING OF CHRONIC PANCREATITIS IN THE PANCREATIC PARENCHYMA IN PATIENTS WITH INTRADUCTAL PapILLARY MUCINOUS NEOPLASMS

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Introduction: The recent guideline for intraductal papillary mucinous neoplasms (IPMNs) focuses on morphological features of the lesion as signs of malignant transformation, but ignores the background pancreatic parenchyma, including features of chronic pancreatitis, a risk factor for pancreatic malignancies. Endoscopic ultrasonography frequently reveals evidence of chronic pancreatitis (EUS-CP findings) in the background pancreatic parenchyma of patients with IPMNs. Therefore, we investigated whether background EUS-CP findings were associated with malignant IPMN.

Aims & Methods: Clinical data for 69 consecutive patients with IPMNs who underwent preoperative EUS and surgical resection between April 2010 and October 2014 were collected prospectively. The association of EUS-CP findings (total number of EUS-CP findings: 0 vs. > 1) with invasive IPMN was examined. The association of EUS-CP findings with pathological changes of the background parenchyma (atrophy/inflammation/fibrosis) was also examined.

Result: Among patients with EUS-CP findings, invasive intraductal papillary mucinous carcinoma (IPMC) was significantly more frequent than among patients without EUS-CP findings (42.5% (17/40) vs. 3.4% (1/29), p = 0.0002). In addition, patients with EUS-CP findings had higher grades of pancreatic atrophy and inflammation than patients without EUS-CP findings (atrophy: 72.5% (29/40) vs. 34.5% (10/29), p = 0.003, inflammation: 45.0% (18/40) vs. 20.7% (6/29), p = 0.04).

Conclusion: In IPMN patients, detection of EUS-CP findings in the background pancreatic parenchyma was associated with a higher prevalence of invasive IPMC. Accordingly, EUS examination should not only assess the morphological features of the lesion itself, but also EUS-CP findings in the background parenchyma.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP331 NEEDLE-BASED CONFOCAL LASER ENDOMICROSCOPY (nCLE) FOR THE DIAGNOSIS OF SOLITARY PANCREATIC CYSTS: A PROSPECTIVE MULTICENTER STUDY

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Introduction: Diagnosis of solitary pancreatic cyst is currently challenging due to the malignant potential of several cyst subtypes. nCLE is emerging as a powerful technique which enables the observation of the inner wall of pancreatic cysts, in vivo and in real-time, during an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). Three clinical trials evaluated the feasibility, the safety and highlighted specific criteria for the characterization of pancreatic cystic lesions. This study aims to prospectively evaluate the diagnostic performance of nCLE procedure on a larger cohort of patients.

Aims & Methods: 217 patients carrying a single large (>2 cm) pancreatic cystic lesion (PCL) without evidence of communication with the main pancreatic duct and scheduled for EUS-FNA procedure were included in five centers. nCLE diagnosis was based on published criteria: “superficial vascular network” for Mucinous Cystic Neoplasms (IPMN), “epithelial border” for Mucinous Cystic Neoplasms (MCN), “dark spots of cell aggregates surrounded by gray areas of fibrosis and vessels” for NeuroEndocrine Neoplasms (NEN), or black particles” for Pseudocyst (PC). In case of doubt between IPMN and MCN, uncertain or poorly determined mucinous cyst (UMC) was proposed. The absence of criteria led to inconclusive nCLE diagnosis considered as false-negative. Nine patients were withdrawn for screen failure (n = 6) or procedure failure (n = 3). Among the 208 analyzable patients, final diagnosis was proven in 90 cases by cytopathological analysis of cystic fluid obtained by FNA (n = 59) or by surgical histopathology (n = 31). Statistical analysis of nCLE performance was done for cysts sufficiently represented.

Result: Among the 217 nCLE procedures, 98.6% were successfully performed. Technical success rate was 2.3% for other significant complication occurred. nCLE was inconclusive in 27 cases. The 90 proven final diagnosis were 32 SCA, 46 Mucinous Lesions (ML) (23 IPMN, 14 MCN and 9 UML), 6 NEN, 2 PC, 1 cystic solid pseudopapillary neoplasm, 1 cystic lymphoma, 1 cystic lymphangiomatosis, 1 primary cystic adenocarcinoma of the congenital pancreatic cyst. These last 6 cysts were underrepresented and therefore withdrawn from statistical analysis. In the remaining 84 patients, nCLE was inconclusive in 5 cases. The performances of nCLE were as follows:

<table>
<thead>
<tr>
<th>Cyst Type</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA</td>
<td>100</td>
<td>57</td>
</tr>
<tr>
<td>ML</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>IPMN</td>
<td>23</td>
<td>95</td>
</tr>
<tr>
<td>MCN</td>
<td>57</td>
<td>100</td>
</tr>
<tr>
<td>NEN</td>
<td>87</td>
<td>88</td>
</tr>
</tbody>
</table>

Conclusion: This large prospective study validates the very high sensitivity and specificity of nCLE for the diagnosis of solitary non communicating PCL which represents the main diagnostic issue. Being able to precisely discriminate between benign (SCA) or premalignant lesions (ML, NEN), the nCLE procedure would significantly improves patient management by avoiding either repeated follow-up procedures or unnecessary resections due to diagnosis uncertainties. nCLE procedures should now be included in the guidelines.

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References


OP332 RISK OF PROGRESSION AMONG LOW RISK IPMNs IN A LARGE MULTICENTER SURVEILLANCE COHORT STUDY

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Introduction: Intraductal papillary mucinous neoplasms (IPMNs) are pancreatic cysts that carry a risk of malignant transformation to pancreatic ductal adenocarcinoma (PDAC). Guidelines have been evolving to best identify which criteria should qualify a patient for resection and which cysts can safely remain under surveillance. Research is needed to improve the selection of patients for surveillance and to determine if current surveillance guidelines should now be included in the guidelines.

Disclosure of Interest: All authors have declared no conflicts of interest.

References


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surveillance. Our aim was to understand which baseline cyst and patient features predict disease progression and malignant transformation.

**Aims & Methods:** Patients with clinically suspected IPMN who did not meet consensus criteria for resection at diagnosis and were surveyed for at least 12 months or underwent surgery after a minimum surveillance of 3 months were included. All patients evaluated by radiologic studies or endoscopic ultrasound between 1998 and 2015 were included. We defined progression as either an increase in size of the dominant cyst ≥20% or ≥2 mm and the development of worrisome features (mural nodule or mass, thick septations, main duct involvement or high-grade dysplasia or cancer on cytology or surgical pathology). Statistical analysis was performed with the Chi square and Fisher exact tests.

**Result:** Statistical analysis was performed with the Chi square and Fisher exact tests.

<table>
<thead>
<tr>
<th>Non-progressors (n = 248)</th>
<th>Progression by cyst size increase (n = 205)</th>
<th>Progression by development of worrisome features (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at 1st study, mean (SD)</td>
<td>65.3 (11.3)</td>
<td>66.6 (10.7)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>95 (38.3%)</td>
<td>80 (39%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>174 (68.6%)</td>
<td>152 (74.3%)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>11 (5.5%)</td>
<td>11 (5.5%)</td>
</tr>
<tr>
<td>Asian, n (%)</td>
<td>9 (4.5%)</td>
<td>8 (4.5%)</td>
</tr>
<tr>
<td>Smoker ever, n (%)</td>
<td>100 (43.1%)</td>
<td>86 (44.1%)</td>
</tr>
<tr>
<td>EthOH use ever, n (%)</td>
<td>108 (47%)</td>
<td>85 (44.7%)</td>
</tr>
<tr>
<td>CF, n (%)</td>
<td>9 (3.7%)</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>AP, n (%)</td>
<td>18 (7.5%)</td>
<td>10 (5.1%)</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td>75 (30.5%)</td>
<td>78 (38.4%)</td>
</tr>
<tr>
<td>Colon, n (%)</td>
<td>3 (1.2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Breast, n (%)</td>
<td>7 (2.8%)</td>
<td>12 (5.9%)</td>
</tr>
<tr>
<td>Prostate, n (%)</td>
<td>6 (2.4%)</td>
<td>12 (5.9%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>56 (23%)</td>
<td>45 (22.4%)</td>
</tr>
<tr>
<td>Family hx of PDAC, n (%)</td>
<td>22 (9.3%)</td>
<td>21 (11%)</td>
</tr>
<tr>
<td>Baseline symptoms, n (%)</td>
<td>71 (28.6%)</td>
<td>60 (29.3%)</td>
</tr>
<tr>
<td>Abd pain, n (%)</td>
<td>65 (26.2%)</td>
<td>49 (23.9%)</td>
</tr>
<tr>
<td>Weight loss, n (%)</td>
<td>11 (4.4%)</td>
<td>18 (8.8%)</td>
</tr>
<tr>
<td>Jaundice, n (%)</td>
<td>1 (0.4%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Serum CEA, median (IQR)</td>
<td>1.6 (1.3)</td>
<td>1.6 (1.2)</td>
</tr>
<tr>
<td>Serum CA 19-9, median (IQR)</td>
<td>13.5 (4.8, 37.3)</td>
<td>17 (8.46)</td>
</tr>
<tr>
<td>Cyst size, mm</td>
<td>11.8 (6.0)</td>
<td>11.1 (6.4)</td>
</tr>
<tr>
<td>Cyst size 0-1 cm, n (%)</td>
<td>100 (40.3%)</td>
<td>94 (45.9%)</td>
</tr>
<tr>
<td>Cyst size 1-2 cm, n (%)</td>
<td>120 (48.4%)</td>
<td>87 (42.4%)</td>
</tr>
<tr>
<td>Cyst size 2-3 cm, n (%)</td>
<td>28 (11.3%)</td>
<td>24 (11.7%)</td>
</tr>
<tr>
<td>Multilocularity, n (%)</td>
<td>95 (38.3%)</td>
<td>73 (35.5%)</td>
</tr>
<tr>
<td>Location</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Head, Uncinate, Neck, n (%)</td>
<td>93 (37.7%)</td>
<td>79 (38.7%)</td>
</tr>
<tr>
<td>Body, n (%)</td>
<td>93 (37.7%)</td>
<td>72 (35.5%)</td>
</tr>
<tr>
<td>Tail, n (%)</td>
<td>61 (24.7%)</td>
<td>53 (26%)</td>
</tr>
<tr>
<td>Cytopathology</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Benign, n (%)</td>
<td>35 (52.2%)</td>
<td>27 (45%)</td>
</tr>
<tr>
<td>Non-malignant n (%)</td>
<td>3 (4.5%)</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td>Atypical, n (%)</td>
<td>3 (4.5%)</td>
<td>4 (6.7%)</td>
</tr>
<tr>
<td>Nondiagnostic, n (%)</td>
<td>26 (38.8%)</td>
<td>24 (40%)</td>
</tr>
<tr>
<td>Cyst CEA, median (IQR)</td>
<td>24 (4.10, 14.5)</td>
<td>101 (14, 333)</td>
</tr>
<tr>
<td>Cyst CEA ≥ 192 ng/mL, n (%)</td>
<td>13 (37.1%)</td>
<td>11 (68.8%) *</td>
</tr>
<tr>
<td>Cyst amylase, median (IQR)</td>
<td>2749 (261, 124527)</td>
<td>8660 (634, 32905)</td>
</tr>
</tbody>
</table>

*Statistically significant difference as compared to non-progressors. We identified 499 patients who met inclusion criteria. Average surveillance time was 47 (+28.7) months. 251 (50%) patients showed progression: 205 (41%) progressed by size alone and 46 (9.2%) developed worrisome features. 55 (11%) met resection criteria and 21 of these went on to surgery. Pathology demonstrated 4 invasive carcinoma, 5 IPMN with high-grade dysplasia, 5 IPMN with low-grade dysplasia, 2 mucinous cystadenoma, 1 serous cystadenoma and 1 neuroendocrine tumor. We then compared predictors of progression. In a univariate analysis, progression to cancer or high-grade dysplasia was associated with male gender, a history of prostate cancer and diabetes, weight loss and initial cyst size >2 cm. A history of prostate cancer and weight loss were the strongest predictors of cyst size increase alone. Baseline characteristics such as race, smoking or alcohol use, a strong family history of PDAC, multifocality and location of cysts were not associated with increased disease progression.

**Conclusion:** In the largest multicenter surveillance study of low risk IPMNs to date, we showed that 41% of suspected IPMNs increased in size only, 9% developed worrisome features and 2% developed high-grade dysplasia or cancer. Among baseline characteristics, none were predictive of size increase. A personal history of prostate cancer and weight loss were the strongest predictors of the development of worrisome features.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**OP333 MULTIMODALITY TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER, INCLUDING FOLFIRINOX CHEMOTHERAPY, SURGICAL EXPLORATION AND IRREVERSIBLE ELECTROPORATION: PROSPECTIVE SERIES OF 132 CONSECUTIVE PATIENTS**

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3Research Unit, Academic Medical Center, Amsterdam/Netherlands
4Gastroenterology, Academic Medical Center, Amsterdam/Netherlands
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7Medical Oncology, Academic Medical Center, Amsterdam/ Netherlands
8Angeodynamics
9Angeodynamics

**Introduction:** Novel treatment options in locally advanced pancreatic cancer (LAPC), including FOLFIRINOX and irreversible electroporation (IRE) have shown promising survival rates. However, outcomes are heavily influenced by selection bias as most studies were retrospective and excluded patients who did not receive FOLFIRINOX or had progressive disease.

**Aims & Methods:** We aimed to describe outcomes of multimodality treatment with chemotherapy, surgical exploration and IRE in a prospective consecutive LAPC-cohort. Patients with histologically proven LAPC (Dutch guideline: ≥90 arterial and/or ≥270 venous involvement) were prospectively registered (September 2013–March 2015). After 3 months of chemotherapy (FOLFIRINOX for WHO physical status 0–1 patients, otherwise gemcitabine), restaging was performed by assessing RECIST 1.1-response, resectability, and IRE-eligibility (tumor ≤5 cm, sufficient vascular patency). All patients with non-progressive disease, eligible for IRE proceeded to laparotomy, regardless of resectability. The study was registered with the Dutch trial registry NTR4320.

**Result:** Of 132 consecutive LAPC-patients, 93 (70%) received chemotherapy (59% (45%) FOLFIRINOX). After 3 months, 59 (45%) had non-progressive disease and 36 (27%) were IRE-eligible and underwent laparotomy, resulting in 14 (11%) pancreatic resections and 15 (11%) IREs. In 36 patients who underwent laparotomy, 14 (39%) suffered from Clavien-Dindo grade ≥3 complications (6/14 resection, 7/15 IRE, 1/7 palliative exploration). Four patients (11%) died within 90 days (1/4 resection, 2/15 IRE, 1/7 palliative exploration). Median overall survival after resection, IRE, in non-progressive disease without resection/IRE and in all 132 patients were 34, 19, 17 and 11 months respectively.

**Conclusion:** This is the first prospective study on multimodality treatment, including FOLFIRINOX and IRE, in a consecutive LAPC-cohort. An 11% resection-rate with a median overall survival of 34 months seems highly promising where no clear survival benefit was seen after IRE. This study highlights the importance of reporting on unselected LAPC-cohorts.

**Disclosure of Interest:** R.C. Martin: Prof. Dr. Marin is a paid consultant for AngeDynamics K.P. van Lienden: Dr. Krijn van Lienden is a paid consultant for AngeDynamics All other authors have declared no conflicts of interest.
**OP334 NATIONALWIDE MULTIDISCIPLINARY ONLINE EXPERTPANEL FOR PANCREATIC CANCER PATIENTS: RESULTS**

J. van Hilten1, M. S. Walma2, J. A. Vogel3, S. J. Romboutz4, B. A. Bonsing5, T. Bollen6, R. Bruinjen7, R. V. Dam8, R. S. Dwarskaping9, C. F. Gerhardi10, J. Groot Koerkamp10, I. D. Hingh11, K. De Jong12, G. Kazemier12, N. C. Krak8, Sprague-Dawley rats were surgically removed and 4 pieces of uterine horn hypothesis in a rat model of endometriosis-induced vaginal hyperalgesia. We hypothesized that linaclotide may be able to similarly function and sensitivity via a proposed mechanism involving viscero-visceral organ cross-talk. We hypothesized that linaclotide may be able to similarly.

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**Introduction:**

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**OP336 ORAL ADMINISTRATION OF THE GUT-RESTRICTED GLUCOSE TRANSPORTER (SGLT) INHIBITOR IN A RAPIDLY PROGRESSING MOUSE MODEL OF BLADDER OVERACTIVITY REVERSES COLITIS-INDUCED CHANGES IN BLADDER NERVE activity, which may reduce intestinal secretion and the anti-nociceptive actions of cGMP compared with healthy controls. Given these changes were apparent in CIC.

**Result:** Oral administration of linaclotide (3 ug/kg/day) on vaginal hyperalgesia were measured after acute (day 1, 2 hours after dosing) and chronic (day 5) dosing, compared to vehicle. Plasma extravasation and EMG measurements were done 10 weeks after the first surgical procedure, when rats were in the proestrus stage of their reproductive cycle. GC-C mRNA expression was determined by qRT-PCR.

**Result:** Chronic oral dosing of linaclotide (n = 12) significantly (P < 0.01) reduced Evans Blue plasma extravasation in the small intestine compared to vehicle (n = 9).

**Conclusion:** Oral administration of linaclotide significantly reduced visceral pain in a rodent model of endometriosis-induced vaginal hyperalgesia. These findings suggest that GC-C agonism, beyond its established effect of improving abdominal pain in IBS-C patients may also be able to alleviate pain in a spectrum of chronic pelvic pain conditions possibly through common sensory peripheral and central inner-pathways.

**Disclosure of Interest:** P. Ge: Employee, stock holder and stock options from Ironwood Pharmaceuticals Inc.

**Aims & Methods:**

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**Disclosure of Interest:** G. Hannig: Employee, stock holder and stock options from Ironwood Pharmaceuticals Inc.
OP357 PATIENTS’ PERCEPTIONS OF CONSTIPATION DIFFER STRIKINGLY FROM THOSE OF GASTROENTEROLOGY SPECIALISTS AND GENERAL PRACTITIONERS, AND THERE IS NO CONSISTENT AGREEMENT WITH THE ROME III CRITERIA

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Introduction: Constipation is a prevalent condition with a huge socioeconomic burden. It is unclear whether patients’ and doctors’ perceptions of the definition of constipation agree with each other or with formal diagnostic criteria proposed by expert committees (e.g. Rome III).

Aims & Methods: A cross-sectional survey was undertaken to compare the symptoms perceived to be important for the diagnosis of constipation within the adult general population (with and without constipation), gastrointestinal (GI) specialists (e.g. gastroenterologists, colorectal surgeons) and general practitioners (GPs) in the UK. Symptoms considered important in diagnosing constipation and their perceived burden, together with 10 case studies based on the Rome III criteria were investigated. Responses were compared between groups using chi squared test.

Result: 2,257 members of the general population (1,623 self-reported constipation) and 365 GI specialists and 411 GPs completed the survey. Only a minority of the general population considered the Rome III symptoms important in diagnosing constipation and their presence a burden. It is unclear whether patients’ and doctors’ perceptions of the definition of constipation was correctly identified in only 60–70% of the four cases with constipation, whereas the presence of constipation was correctly identified in only 60–70% of the four cases with constipation. The GI specialists and general practitioners considered the Rome III symptoms important in diagnosing constipation and their severity burdens.

Table 1: Frequency of symptoms perceived to be important for a diagnosis of constipation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>General Population (With)</th>
<th>General Population (Without)</th>
<th>GI Constipation Constipation Specialists</th>
<th>GPs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rome III symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infrequent bowel movements</td>
<td>28%</td>
<td>26%</td>
<td>65%</td>
<td>41%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hard stool</td>
<td>26%</td>
<td>32%</td>
<td>57%</td>
<td>66%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Straining</td>
<td>43%</td>
<td>40%</td>
<td>53%</td>
<td>61%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sense of incomplete evacuation</td>
<td>15%</td>
<td>24%</td>
<td>21%</td>
<td>13%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Manual disimpaction</td>
<td>14%</td>
<td>15%</td>
<td>32%</td>
<td>34%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-Rome III symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long time on toilet without stool</td>
<td>42%</td>
<td>29%</td>
<td>33%</td>
<td>23%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laxative use</td>
<td>37%</td>
<td>33%</td>
<td>56%</td>
<td>40%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The symptoms most frequently considered to be bothersome were different for each of the groups: manual disimpaction for the constipated general population, bloating for GI specialists and straining for GPs. In the 10 case studies, correct diagnoses were made by doctors (GPs and GI specialists) on 79–80% of occasions. However, on average, the absence of constipation was more frequently identified by doctors in 85–92% of the six cases without constipation, whereas the presence of constipation was correctly identified in only 60–70% of the four cases with constipation.

Conclusion: There are striking differences in the perceived definition and burden of symptoms of constipation between the general population, GI specialists and GPs, and variable agreement with the Rome III criteria. These differences have major implications for patient care, management and satisfaction with treatment. The findings reinforce the need to re-evaluate current diagnostic criteria for constipation in clinical practice and to ensure these are communicated widely.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP358 EFFICACY AND SAFETY OF NALDEMEDINE FOR THE TREATMENT OF OPIOID-INDUCED CONSTIPATION IN SUBJECTS WITH CHRONIC NON-CANCER PAIN RECEIVING OPIOID THERAPY: RESULTS FROM TWO PHASE 3 CLINICAL TRIALS

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Introduction: Opioids effectively treat pain but their use is limited by side effects including opioid-induced constipation (OIC). Naldemedine is an oral, peripherally-acting, mu-opioid receptor antagonist that is being evaluated for the treatment of OIC.

Aims & Methods: Two identical Phase-3, double-blind, randomized, placebo-controlled 12-week studies were conducted. In both studies, subjects 18 to 80 years old, with chronic non-cancer pain and OIC, taking opioids for ≥3 months and on a stable regimen for ≥1 month, not on laxatives, and meeting all other eligibility criteria were randomized (1:1) to naldemedine 0.2 mg taken orally QD or placebo. The primary objective was to evaluate the efficacy of naldemedine vs. placebo as assessed by the proportion of responders. A responder was defined as someone who had ≥9 positive response weeks (PRW) out of 12 weeks and ≥3 PRW out of the last 4 weeks. A PRW was defined as ≥3 spontaneous bowel movements (SBMs)/week and ≥1 SBM/week increase from baseline. The safety and tolerability of naldemedine was also assessed. Studies were approved by an IRB prior to randomization of subjects and conducted in accordance with GCP Guideline (ClinicalTrials.gov identifier NCT01936318 and NCT01993940).

Result: In study 1, 547 subjects were randomized (naldemedine 274; placebo 273) and in study 2, 553 subjects were randomized (naldemedine 277; placebo 276). In both studies, there were a significantly greater proportion of responders with naldemedine relative to placebo (Study 1: naldemedine 47.6%; placebo 34.6%, P = 0.001; Study 2: naldemedine 42.5%; placebo 33.6%, P = 0.001). In both studies, there was a greater increase, relative to the placebo group, from baseline to the last 2 weeks of the study period in the frequency of complete SBMs and the frequency of SBMs without straining. Summary measures of treatment-emergent adverse events (TEAEs) were generally similar between naldemedine and placebo group in both studies. The TEAEs reported by >5% of subjects and at a higher frequency in naldemedine relative to placebo were abdominal pain and diarrhea. In both studies, treatment with naldemedine was not associated with signs or symptoms of opioid withdrawal, and the analgesic effect of opioids was not affected.

Conclusion: Results from two independently designed Phase 3 studies demonstrated a consistent efficacy and safety profile of naldemedine as a treatment for OIC in subjects with chronic non-cancer pain. Naldemedine treatment resulted in a significantly greater proportion of responders than placebo, with improvement early on and throughout the 12-week study period. Naldemedine was generally well tolerated in these two studies.

Disclosure of Interest: M.E. Hale: I was a Principle Investigator for the Clinical Trials, and a consultant for Shionogi J. Wild: 1) I was a Principal Investigator on Composel trial and 2) I did receive a stipend from Shionogi for clinical study review. Otherwise I have no relationship with the company. J. Reddy: Employee of Shionogi T. Yamada: Employee of Shionogi J.C. Arjona Ferreira: Employee of Shionogi

OP359 PILOT STUDY COMPARING THREE METHODS OF SCREENING FOR FECAL INCONTINENCE

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2Shionogi Inc, Florham Park/United States of America/FL
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Introduction: Fecal incontinence (FI) affects 8% of US adults overall including 15% over age 70. However, less than 1/3 of people with FI have discussed this problem with their physicians, and most of these report that they were not screened but volunteered this symptom. This suggests many physicians are not screening for FI.

Aims & Methods: The goal of this study was to provide preliminary information on the effectiveness of 3 simple screening interventions for increasing screening rates in a Geriatric Medicine Clinic (GMC) at the University of North Carolina: a gastrointestinal (GI) symptom checklist distributed in the clinic waiting room, screening by the clinic nurse, and screening by the medical provider. The GI symptom checklist included fecal incontinence [accidental bowel leakage] and 7 other common GI symptoms. Patients checked all they had experienced in the last month, and gave the checklist to the clinic nurse. To facilitate screening by nurses, the GMC was asked to suggest three screening questions. We also gave...
providers and nurses a modified Fecal Incontinence Severity Inventory (FISI) to help them decide whether FI was severe enough to warrant referral to a specialist, and instructions on how to refer to the GI Medicine Clinic. All patients attending the GMC during 4 two-week periods were considered subjects. After an initial two-week baseline, all patients were exposed to the screening methods in the same sequence for two weeks each: GI symptom checklist, provider screening, and nurse screening. Three types of outcome data were collected: (1) A limited review of electronic medical records of all patients seen during these 4 two-week periods was used to identify the number of new FI diagnoses during these 4 periods. (2) Following the last screening intervention, all 11 clinic providers rated the effort required by each intervention and indicated whether they believed the benefit outweighed the burden. (3) Telephone interviews were conducted 2-4 weeks after the index clinic visit to determine what proportion of patients had been screened during their clinic visit. A p-value of <.10 accepted as significant in this small pilot study.

Result: 1034 unique patients were seen during the 4 two-week periods: 60 had a diagnosis of FI somewhere in their medical record, and 24 had a diagnosis of FI at their index clinic visit, including 6 new FI diagnoses. Three of the 6 new diagnoses occurred during the GI checklist intervention and 3 during provider screening (p < .10). None occurred during nurse screening. The GI symptom checklist was rated the least burdensome by the 11 providers (p = .09). Five of 11 providers said the benefits of screening outweighed the burden, 4 were undecided, and 2 rated screening as too burdensome (p = .001). Phone interviews were completed by 88 patients: 33/88 (37.5%) confirmed they were screened by their doctor or nurse, 55.7% said no, and 6.8% said they did not know or declined to answer.

Conclusion: Systematically encouraging gastrointestinal medicine providers to screen for FI significantly increased the number of patients receiving a new diagnosis of FI compared to baseline care. The benefits outweighed the burdens for the majority of providers. Future research could examine how providers and their patients are managing their FI.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP340 COPING WITH FAECAL INCONTINENCE: A POPULATION STUDY

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2UNC Center For Functional GI And Motility Disorders, University of North Carolina at Chapel Hill, Chapel Hill/United States of America/NC
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Introduction: Faecal incontinence (FI) is a common and devastating condition that affects quality of life. Many individuals suffer in silence and population surveys report that fewer than 30% of those affected consult a physician. Little is known about how people prevent or cope with symptoms in the community.

Aims & Methods: This study aimed to describe the most common coping strategies, the impact of FI severity on ways of coping, whether those under a physician’s care cope differently and the perceived overall effectiveness of individuals’ coping efforts. A 54-question survey was designed and distributed online (Qualtrics, UT, USA) to individuals in the US general population in March 2016 who reported symptoms of FI occurring at least twice per month.

Conclusions: A total of 254 complete datasets were received, of which 182 (72%) met the eligibility criteria (mean age 56.6 ± 13.2 years, 54% male). The demographic characteristics of the sample were similar to those of community-dwelling older adults in the United States. The average number of coping strategies was 3.86 (2.61) (5th to 95th percentiles: 2.00–5.30). A positive preventive strategies such as the use of medication and scheduling bowel movements.

Table 1: Prevalence of Coping Strategies and Impact of Faecal Incontinence Severity on Coping

<table>
<thead>
<tr>
<th>Coping Strategy</th>
<th>% who use</th>
<th>Effect of FI Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wear pads</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Food avoidance</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Anti-diarrhoeal drug</td>
<td>43</td>
<td>0.029</td>
</tr>
<tr>
<td>Avoid clothing</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Avoid going out</td>
<td>19</td>
<td>0.018</td>
</tr>
<tr>
<td>Avoid physical activity</td>
<td>19</td>
<td>0.024</td>
</tr>
<tr>
<td>Avoid eating</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Avoid sex</td>
<td>14</td>
<td>0.026</td>
</tr>
<tr>
<td>Avoid leaving</td>
<td>12</td>
<td>0.047</td>
</tr>
<tr>
<td>Shop/food</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Discourage visits</td>
<td>04</td>
<td></td>
</tr>
<tr>
<td>Average number of coping strategies</td>
<td>3.86 (2.61)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 08:30-10:00
NEW INSIGHTS IN UPPER GI ENDOSCOPY TECHNIQUES - ROOM LT

OP341 NOVEL ENDLOOP VS OVER-THE-SCOPE-CLIP (OTSC) IN ENDOSCOPIC CLOSURE OF GASTRIC FULL-THICKNESS DEFECT: A MULTI-CENTER STUDY

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Introduction: Endoscopic full-thickness resection (EFTR) of the gastric lesion using a snaring technique has been applied for gastric subepithelial tumors. We identified criteria for the use of a novel type of nylon loop device vs. traditional ‘Over the scope’-clip (OTSC) for containing artificial submucosal lesions.

Aims & Methods: One hundred and twenty-eight patients with submucosal tumors in gastric fundus were randomly divided into two groups, study group with 56 patients and control group with 72 patients, all patients were treated with endoscopic full-thickness resection. After the resection, novel LetCampTM endo-loop device and OTSC were used respectively to close the gastric defects in the study group and control group. The closure success rate, closure time, complications and the wound-healing rate were compared.

Result: All lesions were removed by using EFTR technique. The closure success rates of the two groups were both 100%. Of the total of 128 patients, 1034 unique patients were seen during the 4 two-week periods was used to identify the number of new FI diagnoses during these 4 periods. (2) Following the last screening intervention, all 11 clinic providers rated the effort required by each intervention and indicated whether they believed the benefit outweighed the burden. (3) Telephone interviews were conducted 2-4 weeks after the index clinic visit to determine what proportion of patients had been screened during their clinic visit. A p-value of <.10 accepted as significant in this small pilot study.

Conclusion: Systematically encouraging gastrointestinal medicine providers to screen for FI significantly increased the number of patients receiving a new diagnosis of FI compared to baseline care. The benefits outweighed the burdens for the majority of providers. Future research could examine how providers and their patients are managing their FI.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:

ADENOMA: COMPLICATION RATE AND FOLLOW UP OF 38 CASES

Disclosure of Interest: None.

Conclusion: Heruntergeladen von http://dx.doi.org/10.1155/2015/692492. 4 pages

References

1. Joana Marques, Francisco Baldaque-Silva, Pedro Pereira, Urban Arnelo, Naohisa Yahagi, Guilherme Macedo. Endoscopic mucosal resection and clinical outcome of ESD/HER compared to EMR in our cohort of patients. Aims & Methods: In a single tertiary center, we cross-examined our database of endoscopic procedures to identify patients with duodenal adenoma treated by ESD, HER and EMR between 2006 and 2016. We included patients with non-ampullary lesions and familial adenomatous polyposis. Procedure was qualified as ESD when an endoscopic knife was used. When resection was achieved with an endoscopic knife and resection loop, the procedure was considered as HER. We divided complications in 3 groups (ASGE and ESGE recommendations): intra-procedural, early complications (occurring within 15 days) and late complications (occurring after 15 days). Results: Thirty-eight patients underwent ESD/HER procedure out of a total of 111 patients. The resection was complete in 38/39 lesions in ESD/HER group, with Student’s t-test, Pearson’s chi-squared test.

Results: Thirty-eight patients underwent ESD/HER procedure out of a total of 111 patients. The resection was complete in 38/39 lesions in ESD/HER group, and 141/149 lesions in EMR group (p = 0.182). Histological finding showed 45% adenocarcinomas, 34% HGD, and 60% LGD. No significant differences were observed in terms of age, sex, location of lesions or length of hospitalization. There were no significant differences in the procedure time (108 min ESD/HER, 79 min EMR), intra-procedural complications (46% ESD/HER, 23% EMR) and early complications (23% ESD/HER, 9% EMR). Intra-procedural complications occurred in 46% of ESD/HER vs 23% in EMR (p = 0.015), including haemorrhage (25.6%, 6% EMR 20.1%) and perforation (ESD 20.5%, EMR 3.4%, p = 0.07). In HER, perforations occurred between 2006 and 2010. Early complications (Haemorrhage, perforation, pancreatitis) occurred in 23% ESD vs 9% in EMR (p = 0.001), managed either by medical treatment. Five cases of perforation occurred (4 ESD/HER, p = 0.001) and 2 cases needed surgery. Three cases of late complications (stenosis) occurred in the EMR group. No mortality reported during the study.

Conclusion: There is a higher rate of intra-procedural and early complications in the EMR HER group, especially in case of perforation. These events can be well managed in a tertiary center, experienced in ESD and HER. Perforation rate tends to decrease over time, reflecting the experience acquired in our team. This highlight the importance of a learning process in ESD/HER procedure, which results in better adaptation of intra-procedural and early complications.

Disclosure of Interest: All authors have declared no conflicts of interest.

References


OP343 ENDOSCOPIC SUBMUCOSAL DISSECTION FOR DUODENAL ADENOMA: COMPLICATION RATE AND FOLLOW UP OF 38 CASES

Disclosure of Interest: None.

Conclusion: Heruntergeladen von http://dx.doi.org/10.1155/2015/692492. 4 pages

References

1. Joana Marques, Francisco Baldaque-Silva, Pedro Pereira, Urban Arnelo, Naohisa Yahagi, Guilherme Macedo. Endoscopic mucosal resection and clinical outcome of ESD/HER compared to EMR in our cohort of patients. Aims & Methods: In a single tertiary center, we cross-examined our database of endoscopic procedures to identify patients with duodenal adenoma treated by ESD, HER and EMR between 2006 and 2016. We included patients with non-ampullary lesions and familial adenomatous polyposis. Procedure was qualified as ESD when an endoscopic knife was used. When resection was achieved with an endoscopic knife and resection loop, the procedure was considered as HER. We divided complications in 3 groups (ASGE and ESGE recommendations): intra-procedural, early complications (occurring within 15 days) and late complications (occurring after 15 days). Results: Thirty-eight patients underwent ESD/HER procedure out of a total of 111 patients. The resection was complete in 38/39 lesions in ESD/HER group, with Student’s t-test, Pearson’s chi-squared test.

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Conclusion: There is a higher rate of intra-procedural and early complications in the ESD HER group, especially in case of perforation. These events can be well managed in a tertiary center, experienced in ESD and HER. Perforation rate tends to decrease over time, reflecting the experience acquired in our team. This highlight the importance of a learning process in ESD/HER procedure, which results in better adaptation of intra-procedural and early complications.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

Introduction: Esophageal endoscopic submucosal dissection (ESD) is technically difficult because of narrow working spaces and ease of perforation due to the lack of serosa. HybridKnife® is a recently developed ESD device that is combined with the high-pressure waterjet ERBEJET® 2 system to lift mucosa. We hypothesized that this waterjet could make submucosal dissection safer and studied this in porcine esophagus.

Aims & Methods: Water pressures of 30–70 bar were tested to determine the appropriate waterjet ESD with HybridKnife® (WJ-ESD) pressure in one pig. Water pressures of 70, 40, and 20 bar for three ESD procedures were compared with HybridKnife ESD using DualKnife® (C-ESD). Each of 3 virtual esophageal lesions in 2 pigs were resected alternatively using both methods from the lower to upper esophagus. For WJ-ESD, the submucosa, except for hard fibrous tissues, was dissected using water pressure alone.

Results: Using 50 bar of water pressure resulted in the best balance between dissection speed and view-disturbing water buckflow. The dissection speeds for the lower, middle, and upper esophagus were 0.2, 0.9, and 0.2 cm/min in 50 bar WJ-ESD and 1.1, 0.5, and 1.0 cm/min in C-ESD, respectively. Minor bleeding when over three-quarters of the circumference of the esophagus is dissected, has been widely accepted in last decade; however, it often causes postoperative stricture. T. Mizushima, 1.1, 0.5, and 1.0 cm2/min in C-ESD, respectively. Minor bleeding

Conclusion: WJ-ESD spent longer dissection time, but damaged less muscle layer. It can be combined with electrocautery ESD.

Disclosure of Interest: All authors have declared no conflicts of interest.

References:

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Disclosure of Interest: All authors have declared no conflicts of interest.

References:
Phenotypically, HPCs express both markers of (immature) hepatocytes (e.g. oval nucleus and a scanty cytoplasm situated in the canals of Hering) and markers of cholangiocytes (e.g. cytokeratin K7 and K19). The method is the SP which is based on the efflux capacities of the progenitor cells of HPC-enriched cells were obtained via three different isolation methods. A first human liver tissue was collected from alcoholic steatohepatitis explant livers, and enriched cell populations from adult human liver tissue using different isolation methods indicated some slight differences between the different HPC populations, e.g. the ErbB signalling path- way is activated in the TROP-2 positive cells while this is not the case in the EpCAM-positive or SP cell populations. Our results indicate that gene signatures of human HPCs are enriched in pathways already known to be involved in HPC activation in human and in animal models, but we also identify previously unknown pathways like TNF, IL17A and ErbB signalling pathways. Comparison of the 3 isolation methods sheds light on the possible existence of different HPC populations exist- ing in the human liver. The isolated HPC populations will be used to further characterize human HPCs and to understand the molecular mechanisms underlying their activation and differentiation, with the ultimate goal of using HPCs for the treatment of liver diseases.

Disclosure of Interest: All authors have declared no conflicts of interest.

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of necroptosis in the pathogenesis of cholestatic liver injury has been poorly understood. We have previously demonstrated that the necroptosis pathway is activated in primary biliary cirrhosis (PBC) patients, correlating with tumor stage and metastatic burden in various cancers including hepatocellular carcinoma (HCC) [2–4].

Introduction: Necroptosis represents a form of programmed cell death that is initiated by death receptor activation, leading to the activation of caspase-8, RIP1, and RIP3, which in turn can activate the RIP3-MLKL (mixed lineage kinase domain-like) kinase complex, leading to the promotion of necroptosis. The role of necroptosis in the pathogenesis of cholestatic liver injury has been poorly understood. We have recently demonstrated that cell cycle-related kinase (CCRK) acts as a new oncogenic signaling hub in hepatocellular proliferation and transformation [2–4].

Aims & Methods: To investigate whether CCRK regulates tumor microenvironment in hepatocarcinogenesis, we determined the role of CCRK signaling in the crosstalk between HCC cells and MDSCs. We have used a liver-specific CCRK transgenic mouse model and HCC orthotopic model in C57/BL6 immunocompetent mice. Molecular techniques including co-immunoprecipitation and ChIP assay were used to investigate the underlying mechanisms.

Results: Transgenic over-expression of CCRK in murine liver led to expansion of RIP3+ and MLKL in the insoluble protein fraction of the liver. Thus, RIP3 and MLKL are activated as evidenced by increased RIP3 expression and activity and sequestration of RIP3 and MLKL in the insoluble protein fraction of the liver. Remarkably, RIP3 deficiency blocked BDL-induced necroinflammation at 3 and 14 days post-BDL. Serum hepatic enzymes, fibrogenic liver gene expression and oxidative stress decreased in RIP3+ mice at 3 days after BDL. However, at 14 days, cholestasis aggravated and fibrosis was not ameliorated. RIP3 deficiency was further associated with increased hepatic expression of heme oxygenase-1 (HO-1) and accumulation of iron in BDL mice. The functional link between HO-1 activity and bile acid toxicity was established in RIP3-deficient primary hepatocytes. The CCRK-deficient cells and 14% CCK activity increased after 14 days after BDL in both WT and RIP3+ mice, while remaining at basal levels at day 3, indicating that apoptosis is activated at late time-points in the BDL murine model, reflecting the peak of liver fibrosis.

Conclusion: In conclusion, necroptosis is triggered in PBC patients and mediates hepatic necroinflammation in BDL-induced cholestasis. Targeting necroptosis may provide an opportunity to develop novel therapeutic strategies to attenuate acute cholestatic liver injury. However, therapeutic strategies to inhibit RIP3-dependent signaling during chronic cholestasis should be undertaken with a complete understanding of the potential duality of this pathway. (Supported by HSMP-ICT/008/2011, SFRH/BD/91192/2011, SFRH/BD/88212/2012 and SFRH/BD/104160/2014, FCT, Portugal).

Disclosure of Interest: All authors have declared no conflicts of interest.

References
to liver injury and fibrosis suggesting the beneficial role of intestinal microbiota in preventing disease.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

OP352 IMPROVING METABOLIC PARAMETERS IN NAFLD BY TARGETING NUCLEAR RECEPTORS

P.M. Rodrigues1, M.B. Afonso1, A. Simão1, M. Cardade1, C. C. Carvalho2, A. Trindade1, A. Duarte3, P. M. Machado4, H. Cortez-Pinto5, C. M. P. Rodrigues1, R. E. Castro1
1Research Institute for Health Sciences (Med/ULisboa), Faculty of Pharmacy. Universidade de Lisboa, Lisbon/Portugal
2Reproduction and Development, Interdisciplinary Centre of Research in Animal Health (CIHSA), Faculty of Veterinary Medicine, Universidade de Lisboa, Lisbon/Portugal
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Contact E-mail Address: pmvrodriques@ff.ul.pt

Introduction: Non-alcoholic fatty liver disease (NAFLD) pathogenesis and treatment remain unsolved. microRNAs and bile acids were recently suggested to participate in disease pathogenesis and, as such, constitute potential therapeutic tools and targets. Moreover, nuclear receptors, namely peroxisome proliferator-activated receptor (PPAR) and the farnesoid X-receptor (FXR) are currently under scrutiny as modulators of lipid and glucose metabolism in non-alcoholic steatohepatitis (NASH).

Aims & Methods: We aimed to elucidate the role of miR-21 in PPAR-β/δ pathway in liver and muscle tissues of murine NASH models and ascertain the therapeutic potential of miR-21 abrogation alone or in combination with obeticholic acid (OCA). Wild-type (WT) and miR-21 KO mice were fed with chow (n = 10) or methionine and choline-deficient (MCD; n = 10) diets for 2 and 8 weeks. Alternatively, mice were fed either chow (n = 12) or fast food diet (FF; n = 12) for 25 weeks. Six animals from each group had their diet supplemented with OCA 10 mg/kg/day (Intercept Pharmaceuticals, Inc.). Human liver biopsies were obtained from morbid obese NAFLD patients (n = 28). Liver/muscle samples were collected for histological analysis and assessment of miR-21, pro-inflammatory/pro-fibrogenic cytokines, PPARα and metabolic relevant genes, by qRT-PCR and immunoblotting. A Taqman® Array was performed to evaluate modulation of lipid regulated genes. ROS levels were analysed through the use of 2′,7′-dichlorodihydrofluorescein diacetate.

Results: WT mice fed with the MCD diet developed steatohepatitis and fibrosis, displaying increased levels of apoptosis, necroptosis and serum ALT and AST. In contrast, miR-21 KO mice displayed a significant decrease in steatosis severity, liver inflammation and fibrosis (MCD-fed) and did not develop fibrosis. WT-fed mice developed hepatomegaly, macrovesicular steatosis, inflammatory infiltrates and increased oxidative stress. miR-21 levels were increased in WT FF-fed mice, in both liver and muscle, concomitantly with decreased expression of PPARα, a key mediator of lipid metabolism, and increased expression of miR-21 in FF-fed mice. The PPARα inhibitor, Wy-14643, significantly reduced the levels of both liver and muscle miR-21 whereas the levels of miR-21 were not affected by the treatment with OCA.

Conclusion: In conclusion, activation of PPAR-β/δ as a result of miR-21 abrogation, together with FXR activation by OCA, significantly improves metabolic parameters in NASH, highlighting the therapeutic potential of multi-targeting therapies for NAFLD. (Supported by PTDC/BIM-MEC/087532/2012, SFRH/BD/88212/2012, FCT, Portugal).

Disclosure of Interest: All authors have declared no conflicts of interest.

EASTERN WEDNESDAY, 19 NOVEMBER 2016 08:30-10:00
MURINE MODELS OF INTESTINAL INFLAMMATION – ROOM 1.86

OP353 AN AUTOMMUNITY-ASSOCIATED VARIANT IN PTTPN22 PROTECTS FROM DISEASE ONSET IN MOUSE MODELS OF COLITIS

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1Gastroenterology And Hepatology, University Hospital Zurich, Zurich/ Switzerland
2Division Of Gastroenterology And Hepatology, University Hospital Zurich, Zurich/ Switzerland
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Introduction: Presence of the single nucleotide polymorphism (SNP) rs2476601 in the gene encoding protein tyrosine phosphatase non-receptor type 22 (PTPN22) results in an altered-function PTPN22 protein product and is associated with increased risk to develop autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus. However, the same variant reduces the risk for Crohn’s disease (CD) onset. We have previously shown that protein and mRNA levels of PTPN22 are reduced in intestinal biopsies from CD patients, and that loss of PTPN22 results in enhanced inflammatory cytokine secretion from mononuclear cells treated with interferon-gamma or the bacterial product muramyl dipeptide.

Aims & Methods: In this study, we addressed how presence of the altered-function PTPN22 in inflamed intestinal tissue may modulate the susceptibility to intestinal inflammation in mouse models of colitis. For this aim, colitis was induced in 10-12 week old female mice by administration of 2% DSS for 7 days (acute DSS colitis), administration of four cycles of DSS (1.5% DSS for 7 days, followed by 10 days normal diet during each cycle; chronic DSS colitis), or by transferring naïve PTPN22-deficient (PTPN22-/-) or PTPN22 deficient (PTPN22-/-) naive T cells into Rag2/-/- recipients. PTPN22 deficient (PTPN22-/-) mice, or mice expressing the IBD-associated variant in PTPN22 (PTPN22-619W mice), and their respective wild-type (WT) littermates were used for the study.

Result: PTPN22-/- mice suffered from aggravated acute DSS colitis as characterized by pronounced weight loss, increased endoscopic and histologic colitis scores (p < 0.05 each), while PTPN22-619W mice reacted only weak only to the DSS treatment when compared to WT littermates (p < 0.05 for weight development, p < 0.05 for other parameters). In chronic DSS colitis however, PTPN22-/- mice suffered from a milder disease course (reduced weight loss [p < 0.05], decreased histological severity [p < 0.05]) from the third cycle onwards. PTPN22-619W mice prolonged survival compared to WT mice and showed a milder DSS colitis course in the later phase. In the T cell transfer model, PTPN22-/- T cells induced an enhanced histological pathology (p < 0.05), while weight loss was not affected when compared to mice receiving WT T cells. In contrast, mice co-transferred with PTPN22-619W T cells were protected from DSS-induced disease in the first weeks, and later on developed only a mild disease (moderate weight loss [p < 0.01], reduced shortening of the colon [p < 0.05], low histological disease scores [p < 0.05]) when compared to mice receiving WT T cells.

Conclusion: Taken together, we here describe for the first time how the IBD-associated variant in PTPN22 affects colitis development. This helps to explain why this variant is associated with a reduced risk for CD onset, although it increases the risk to develop classical autoimmune disorders.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP354 TOLL LIKE RECEPTOR 2 MODULATES THE INHIBITORY MOTOR RESPONSE INDUCED BY HYDROGEN SULPHIDE IN MOUSE COLON

R. Forcen García1, E. Layunta1, J. Pardo1, J.E. Mesonero1, L. Grasa1
1Pharmacology And Physiology Department, University of Zaragoza, Zaragoza/Spain
2Biochemistry And Molecular And Cellular Biology Department, University of Zaragoza, Zaragoza/Spain
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Introduction: The recognition of intestinal microbiota is in part carried out by toll-like receptors (TLR), which are responsible for initiating the innate immune response. Alterations in the intestinal microbiota and its recognition may contribute to the development of intestinal inflammatory pathologies. Otherwise, hydrogen sulphide (H2S) is an endogenous gaseous signalling molecule and it potentially plays a relevant role in the intestinal motility. In mammals, two pyridoxalphosphate-dependent enzymes are responsible for H2S synthesis: cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). The aim of this study was to investigate the influence of TLR2 on the motor response induced by H2S and the enzymes responsible for H2S synthesis (CBS and CSE) in mouse colon. Colon strips from male C57BL/10 wild-type (WT) and TLR2-/- mice of 8–12 weeks old were suspended in an organ bath in the direction of circular smooth muscle. We studied the effect of NaHS (10 μM–1 mM), DL-propargylglycine (PAG, 10 μM–10 mM), an inhibitor of CSE, and amino-oxyacetic acid (AOAA, 10 μM–10 mM), an inhibitor of CBS, on WT and TLR2-/- mice colonic motility. Gene expression (mRNA) of CSE and CBS were determined by real-time PCR and protein expression of CSE and CBS were quantified by Western blotting in colon from WT and TLR2-/- mice.

Results: The NaHS, as a source of exogenous H2S, reduced the frequency but not the amplitude of the spontaneous contractions in colon from WT mice. The inhibition of CSE or CBS with PAG or AOAA, respectively, increased the frequency but not the amplitude of the spontaneous contractions in colon from WT mice. The NaHS induced a higher reduction of the frequency of the spontaneous contractions in TLR2-/- mice compared with WT mice. The PAG and AOAA did not modify the spontaneous contractions in colon from TLR2-/- mice. The mRNA and protein expression of CBS resulted decreased in colon of TLR2-/- compared with WT mice. The mRNA but not the protein expression of CSE resulted decreased in TLR2-/- compared with WT mice.

Conclusion: These results suggest that the exogenous and endogenous H2S may regulate the colonic spontaneous contractions in WT mouse, reinforcing the hypothesis that H2S is a gaseous inhibitory mediator of intestinal motility.
HPLC system measuring the degradation rate of endorphin-2 (EM2, natural DPD IV substrate) in the presence of EMDB-1. The inhibitory effect of EMDB-1 on DPP IV activity was characterized in vivo in the colon of acute and semi-chronic colitis induced by trinitrobenzenesulfonic acid (TNBS). Body weight, macroscopic score, ulcer score, colon length and thickness, as well as myeloperoxidase (MPO) activity were recorded. A significant inhibition was observed.

Results: EMDB-1 is a potent and specific DPP IV inhibitor as shown by significantly decreased degradation rate of EM2 by DPP IV (t1/2 = 1.73 vs. 3.60 min in the absence and the presence of EMDB-1, respectively). The intracolonic (i.c.) administration of EMDB-1 (0.1, 1 and 3mg/kg, twice daily) attenuated both acute and semi-chronic TNBS-induced colitis in mice in a dose-dependent manner, as indicated by significantly reduced macroscopic parameters and MPO activity. Anti-inflammatory effect of EMDB-1 was not blocked by nalox-one, thus the opioid receptors were not involved in its mechanism of action.

Conclusion: EMDB-1 is a potent inhibitor of DPP IV in vitro and exhibits substantial anti-inflammatory activity in the GI tract in vivo. Results of this study validate the EMDB-1 backbone for further development of peptide DPP IV inhibitors and suggest their potential use in the treatment of colitis.

Disclosure of Interest: All authors have declared no conflicts of interest.
Introduction: The adaptive immune system plays a crucial role in the pathogenesis of inflammatory bowel diseases (IBD). Inactivation of IFN-γ in T-cells was rarely detected in colonic tissue of TDAG8-/- in comparison to the WT group. Downregulation of mRNA expression of pro-inflammatory cytokines (IFNy, TNF, IL17A) was observed in the TDAG8-/- group in comparison with the WT group. No significant differences were observed in mRNA expression levels of Fop1, RORγ and IL18.

Conclusion: Our data demonstrate that TDAG8-deficiency in T-cells ameliorates the development of colitis suggesting an important physiological role of this pH receptor.

Disclosure of Interest: All authors have declared no conflicts of interest.

Wednesday, October 19, 2016 10:30-12:00 Surgery meets endoscopy in the colon – Room F1

OP359 TRANSACTIONAL ENDOSCOPIC MICROSURGERY VERSUS ENDOSCOPIC MUSCULAR RESECTION FOR LARGE RECTAL ADENOMAS (TREND-STUDY)


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Introduction: Non-randomized studies suggest that endoscopic mucosal resection (EMR) is usually effective in removing large rectal adenomas as an alternative to endoscopic submucosal dissection (ESD) for the treatment of rectal adenomas. The aim of this study was to evaluate the safety and efficacy of EMR versus EMDR for the treatment of large rectal adenomas in patients with similar expertise of TEM and EMR.

Methods: We investigated the role of TDAG8 in T-cell-mediated pathogenesis in intestinal inflammation using a murine adoptive transfer colitis model. Naïve T-cells (CD4+CD25L-), from WT and TDAG8-/- donor mice, were injected into Rag2-/- recipient mice. Injection of PBS was used as a control group. The results of colitis were evaluated by weight change, colonoscopy score, spleen weight, H&E staining, IHC and mRNA expression.

Results: Induction of colitis was observed after 3 weeks by weight loss, diarrhea and bloody stool. The WT group showed severe weight loss (P < 0.013), whereas the TDAG8-/- group displayed only a minor delay in weight gain. No significant differences were observed in colon length, spleen weight and colonoscopy score between PBS and the TDAG8-/- groups. H&E staining of distal and proximal parts of the colon revealed severe infiltration and crypt damage in the WT group. The TDAG8-/- group displayed significantly less histopathological signs of colitis compared to PBS and WT groups. CD3+ and IL-17A immunoreactive cells were rarely detected in colonic tissue of TDAG8-/- in comparison to the WT group. Expression of mRNA expression of pro-inflammatory cytokines (IFNy, TNF, IL17A) was observed in the TDAG8-/- group in comparison with the WT group. No significant differences were observed in mRNA expression levels of Fop1, RORγ and IL18.

Conclusion: Our data demonstrate that TDAG8-deficiency in T-cells ameliorates the development of colitis suggesting an important physiological role of this pH receptor.

Disclosure of Interest: All authors have declared no conflicts of interest.

Wednesday, October 19, 2016 10:30-12:00 Upper GI bleeding – Room M

OP361 MEDIUM- AND LONG-TERM RESULTS OF TREATMENT WITH LANREOTIDE IN CASES OF CHRONIC OR RECURRENT OBSCURE GASTROINTESTINAL BLEEDING OR DUE TO GASTROINTESTINAL ANGIODYSPASIAS

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Introduction: Somatostatin analogues have been proposed as a rescue therapy in cases of chronic or recurrent obscure gastrointestinal bleeding (GB) or attributable to gastrointestinal angiodyspasias (GIADs). The long-term results with lanreotide are still very scarce.

Methods: Our aim is to determine the medium and long-term benefit of lanreotide in cases of chronic or recurrent refractory obscure gastrointestinal bleeding or due to gastrointestinal angiodyspasias, in terms of savings of health resources. This was a retrospective single-center study conducted under conventional clinical practice, following a defined management protocol, between 2003 and 2012. Patients with chronic or recurrent obscure GB or due to GIADs, refractory to or not candidates for iron therapy, endoscopic, surgical or angiographic treatments, were included. Cirrhotic patients and those ones with very severe co-morbidities (IVX 60/90, the American Society of Anesthesiologists Classification-ASA) were excluded. The protocol included upper and lower endoscopy, abdominal computed tomography, video capsule endoscopy and/or single balloon enteroscopy. Lanreotide 60 or 90 mg was administered monthly, for at least 6 months. During the previous year and 36 months after starting the drug it was recorded demographics data, comorbidities, chronic use of antplatelets and anticoagulants, hemostatic treatments, side effects, hospitalization, transfusion of tranfused red cells units, intravenous
iron doses, and non-diagnostic endoscopies. Differences between data from one year before and each one of the three years after starting lanreotide were evaluated using Wilcoxon test with significance level of p < 0.05.

Results: Twenty-two patients (median age 76.1 years, range 56–90; 50% male sex) were included. Before starting treatment 19 were ASA III, 22.7% consumed anticoagulants and 31.8% anticoagulants. At the end of follow-up only one patient had stopped the anticoagulant. The bleeding was attributed to GIAD in 77.3% and 22.7% was obscure. The bleeding was overt in 68.2% and occult in 31.8%. Before starting lanreotide 4 patients had received endoscopic treatment using argon plasma coagulation (APC), 2 hormonal therapy and 1 thalidomide. Two patients received APC concomitant to lanreotide, and 1 hormonal therapy after stopping this one without reaching bleeding cessation. The average duration of treatment with lanreotide was 28.4 months (range 6–36). Mean follow-up was 32.4 months (range 9–36), with the results shown in the table. Five patients did not complete the follow-up for not related to GIB deaths. No side effects forced to suspend lanreotide.

Conclusion: The use of lanreotide for at least 6 months in patients with chronic or recurrent obscure gastrointestinal bleeding or from gastrointestinal angiodysplasia, refractory to or not candidates for other therapies, is safe and is associated with a decrease in consumption of medical resources within the three years following its indication.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP361 SOMATOSTATIN ANALOGUES ARE LESS EFFECTIVE IN PATIENTS WITH ANGIODYSPLASIAS AT MULTIPLE SITES OR LOCATED IN THE COLON: A POOLED ANALYSIS OF INDIVIDUAL PATIENT DATA


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Introduction: Cohort studies have shown a beneficial effect of octreotide in decreasing the rebleeding rates in patients with gastrointestinal angiodysplasias, however with large variation among individuals. Most studies have a small sample size and different primary outcomes, such as haemoglobin and rebleed, which makes it difficult to estimate the true effect on clinical relevant outcomes such as transfusion dependency and to investigate predictors for good clinical response.

Aims & Methods: The aim of this individual patient data meta-analysis is to investigate efficacy of SST on transfusion dependency and identify subgroups of patients that benefit most from SST. A systematic review was performed to identify articles reporting the effect of SST in gastrointestinal angiodysplasias. We collected individual patient data of included articles. Patients with only oral iron dependency were excluded. The primary outcome was response to SST, defined as good: >50% reduction of parenteral iron and/or red blood cell (RBC) transfusions; or poor: <50% reduction of parenteral iron and/or RBC transfusions. We used univariate logistic regression to determine the effects of patient and disease characteristics on SST. The variable “study” was included in the univariate analysis to correct for study-effect.

Results: We identified 7 studies and obtained individual data from 6 (n = 180) studies. We analyzed data of 159 patients (mean age 70 years, 56% men) with transfusion dependency due to gastrointestinal angiodysplasia bleeding that were treated with SST. Fifty percent of patients had angiodysplasias at multiple sites (small bowel (75%), stomach (45%), and colon (45%)). Endoscopic treatment prior to SST was started in 48%. Octreotide LAR 20 mg was the most frequent prescribed (81%). Side-effects occurred in 31% (41/131) of the patients, with gastrointestinal symptoms (19.8%) and erythema / pain at the injection site (8%) the most frequent. In 8 patients (6%) SST was discontinued due to side-effects. There was a high SST response with 99% of the patients having >50% reduction of their parenteral iron and/or RBC transfusion dependency. Sex, age, small bowel and stomach localization, the use of anticoagulants, dose, only parenteral iron dependent and prior endoscopic treatment were not associated with treatment response. Angiodysplasia localization in the colon (OR 0.28, 95% CI 0.09–0.88, p = 0.03) and at multiple sites (OR 0.37, 95% CI 0.17–0.77, p = 0.008) were negatively associated with a good response.

Conclusion: Based on this pooled analysis of data from individual patients with transfusion dependent angiodysplasia bleeding, SST is effective and safe in the majority of patients. A decreased SST response is found in patients with angiodysplasias located at multiple sites or in the colon.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP363 ESOPHAGEAL VARICES POST BANDING ULCER BLEEDING - DETERMINANTS AND IMPACT IN MORTALITY

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Introduction: Esophageal band ligation (EBL) is the choice for both prophylaxis and treatment of esophageal varices hemorrhage. Post-EBL ulcer bleeding is a deemed complication for which risk factors and impact in mortality are not clearly understood.

Aims & Methods: We aimed at identifying risk factors for variceal post-EBL ulcer bleeding and determine its impact in short and long-term mortality. We conducted a case control study. Cases: all admissions for post-EBL ulcer bleeding, in a tertiary gastroenterology service, from January 2003 to December 2015. Controls: EBL treated patients without post-therapeutic ulcer bleeding. Matching was made for Child-Pugh-Turcotte (CPT) score and indication (bleeding vs elective) in a 1 case for 2 controls ratio. Patient’s demographics, comorbidities and endoscopic findings were reviewed from medical records. Endpoints were re-bleeding from post therapeutic ulcer and mortality assessed at 28, 90, 180 and 360 days post-therapeutic.

Results: A total of 50 post-EBL ulcer bleeding cases and 100 controls were included. Mean age (57.1 ± 12.0); male:female ratio (4:1). Cirrhosis etiologies: alcoholic (30.7%), HCV (29.5%) and HBV (15.7%). CPT distribution: A (17.3%) B (46%) and C (36.7%); mean MELD was 14.5 ± 6.1. All patients underwent EBL and 7.3% also received a sclerosing agent. Mean time to rebleed: 12.6 ± 5.4 days. A higher number of rubber bands (5.8 ± 1 vs 5.2 ± 1, p = 0.003), lower baseline hemoglobin (10.7 ± 1.5 vs 11.5 ± 2.1 g/dl, p = 0.007), hemodynamic instability (OR:2.0 p = 0.048) portal vein thrombosis (OR:2.8, p = 0.022), HBV cirrhosis (OR:6.2, p = 0.007), and endoscopic stigmata of active or recent bleeding (OR:5.0 p < 0.001) correlated with rebleeding. In multivariate logistic regression analysis HBV cirrhosis, multiple concomitant aetologies of cirrhosis and endoscopic stigmata of recent bleeding were independently associated with rebleeding. Post-EBL ulcer bleeding did not significantly impacted overall short and long term mortality. However CPT class B patients with post-EBL ulcer bleeding showed a trend for lower survival which was significant at 180 days (16% vs 6% log rank p = 0.04).

Conclusion: We identified both patient’s and endoscopic features correlating with post-EBL ulcer bleeding, namely HBV infection related cirrhosis, higher number of concomitant aetiologies/aggressors, and endoscopic stigmata of recent/active bleeding. Though overall patient’s short and long-term mortality was not affected by post-EBL ulcer bleeding, CPT class B patients showed a trend for
lower survival. Thus, we hypothesize that CPT class B patients may be a cluster of patients with low hepatic reserve, to whom post-EBL bleeding may impose an additional risk for disease progression, that can significantly impact on survival.

Disclosure of Interest: All authors have declared no conflicts of interest.

References


OP364 INTERNATIONAL PROSPECTIVE STUDY OF UPPER GI HEMORRHAGE: DOES WEEKEND ADMISSION AFFECT OUTCOME?
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Introduction: Weekday admissions have been associated with higher mortality. For upper gastrointestinal haemorrhage (UGIH) some studies show significantly increased mortality1 and delayed endoscopy while the UK UGIB audit reported no difference.2 We studied whether out of hours (OOH) admissions had more morbidity, were less stable and/or had higher mortality.

Aims & Methods: Prospective study over 12 months (from March 2014) from 2 UK and 2 international centres. Admission time, demographics, pulse, BP, lab results, endoscopy findings, further procedures and 30d mortality were recorded. 3 pre-endoscopy scores (Glasgow Blatchford (GBS), AIMS65 and admission Rockall scores) and 2 post-endoscopy scores (PNED and full Rockall scores) were determined. Chi-squared, Fisher’s exact and Kruskal-Wallis tests were used as appropriate. A two-tailed significance level of 5% was used.

Results: 2181 consecutive patients, 60% male, median age 66 years were seen. There were no significant differences in mortality, need for endoscopic therapy, shape of ulcer or delayed endoscopy within in both UK and non-UK centres. There were no differences in comorbidity, median ASA 2.3, pulse or BP although weekday admissions had a lower Hb (110 [±11] vs 118 [±11] weeknight) and 117 [±11] weekend p < 0.001 and higher GBS (p = 0.05). No difference in peptic ulcer disease or varies incidence between periods although more weekday admissions had normal endoscopy(=0.002). OOH admissions were less likely to have an endoscopy (30% not endoscoped vs 23% for weekday admission p = 0.005). Time to endoscopy was less for weekend admissions (15% vs 17h for weekend and 20h for weekdays, OR=0.0001). 67% weeknight vs 75% weekend and 60% weekend admissions had their endoscopy within 24 hours

Outcome of patients with UGIH and time of presentation

<table>
<thead>
<tr>
<th>Weekdays: working time</th>
<th>Weekdays: overnight</th>
<th>Weekdays: Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>858</td>
<td>603</td>
</tr>
<tr>
<td>Units blood transfused</td>
<td>1.4 [±0.6]</td>
<td>1.3 [±0.6]</td>
</tr>
<tr>
<td>Endoscopic therapy</td>
<td>185 (22)</td>
<td>116 (19)</td>
</tr>
<tr>
<td>Surgery/endoscopy</td>
<td>4 (0.5)</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>49 (5.8)</td>
<td>33 (5.7)</td>
</tr>
<tr>
<td>30d mortality</td>
<td>61 (7.1)</td>
<td>43 (7.1)</td>
</tr>
</tbody>
</table>

2181 consecutive patients admitted March 2014-March 2015 from Glasgow (600), Truro (544), Odense (541) and Singapore (433). Data shown are mean [95% CI] or number (%).

Conclusion: There is no difference in mortality in patients admitted with UGIH OOH compared to weekday admissions although weekday admissions had a lower haemoglobin and higher GBS. There was no evidence of delay in time to endoscopy with OOH admissions. The severity of UGIH was not related to time of admission. Similar findings were noted in all four centres.

Disclosure of Interest: All authors have declared no conflicts of interest.

References


OP366 A HISTORY OF ISCHEMIC HEART DISEASE, HIGH BLOOD UREA NITROGEN AND C-REACTIVE PROTEIN LEVELS, AND LOW HOMOGLBIN LEVELS: AS PREDICTIVE CLINICAL FEATURES FOR EARLY DEATH AFTER PERCUTANEOUS ENDOSCOPIC GASTROSTOMY

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Introduction: Percutaneous endoscopic gastrostomy (PEG) is accepted as the method that enables enteral feeding in patients with swallowing difficulties. However, complications and early death are considerably prevalent after PEG. To decrease the incidence of early mortality after PEG, it is very important to identify risk factors of this procedure.

Aims & Methods: The aim of our study was to determine factors that could predict early death within 30 days following PEG. A retrospective analysis of the records of all patients who underwent PEG at Kure Medical Center and Chugoku Cancer Center from April 2008 to March 2010 was performed. The examined clinical and preparatory laboratory data and extracted predictive factors of early death after PEG by using univariate and multivariate analyses.

Results: A total of 1077 patients [502 female (46.7%) and 575 male (53.3%); mean age 78.0 (s) years] were assessed. Predictors of poor survival after PEG included history of ischemic heart disease (odds ratio [OR] 2.32, 95% confidence interval [CI] 1.2-4.3, P < 0.01), blood urea nitrogen level ≥30 mg/dl (OR 3.14, 95% CI 1.8-5.5, P < 0.0001), C-reactive protein level ≥2.0 mg/dl (OR 4.04, 95% CI 2.2-7.3, P < 0.0001), albumin level ≤2.7 mg/dl (OR 4.2, 95% CI 1.3-12.2, P < 0.001), and hemoglobin level ≤11.2 g/dl (OR 4.0, 95% CI 2.0-8.0, P < 0.0001).

Multivariate analysis on predictive factors of early death revealed a significant correlation between early death and each of the following: history of ischemic heart disease, high blood urea nitrogen level, C-reactive protein level, low hemoglobin level, and low homologbin level.
Aims & Methods: Metabolic dependencies of KRAS mutant CRC cell lines were assessed by colony formation and apoptosis assays. Glutamine metabolism in KRAS mutant CRC cells were traced using stable U-13C-glutamine labeling and Ultra-High Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS). Role of glutaminase (GLS1) and the mitochondrial glutamate transporter (SLC25A22) in mediating glutaminolysis was evaluated. Finally, the functional effect of glutaminolysis inhibition (via GLS1 or SLC25A22 blockades) on cell viability and chemotherapeutic agents was tested.

Results: Deprivation of glucose, glutamine or their combination in six KRAS mutant CRC cell lines (CACO-2, COLO205, HT29 and SW480) revealed that KRAS mutant CRC cells were profoundly sensitive to glutamine depletion as compared with KRAS wild type CRC cells; whilst exhibiting resistance to glucose depletion. This indicates that supply of glutamine is obligatory for KRAS mutant CRC survival. U-13C5-glutamine labeling in DLD1 cells and UPLC-MS revealed that a majority of glutamine was metabolized into glutamate, aspartate and the intermediates of the tricarboxylic acid (TCA) cycle, indicating that glutamine-derived carbons were channeled to the mitochondria for the replenishment of TCA cycle (a process known as glutaminolysis). We further revealed that glutamine was first converted to glutamate by GLS1 at the outer side of inner mitochondrial membrane, which is coupled to SLC25A22 for the import of glutamate into the mitochondrial matrix. Consistent with this model, the silencing of GLS1 or SLC25A22 significantly suppressed cell proliferation in KRAS mutant CRC cells, indicating that their coupled action is indispensable for cell growth. U-13C5-glutamine tracing in DLD1 cells with SLC25A22 knockdown showed an attenuated entry of glutamine-derived carbon backbone into TCA cycle, confirming its involvement in glutaminolysis. Inhibition of SLC25A22-dependent glutaminolysis triggered metabolic stress, suppressed ATP production and promoted oxidative stress. Moreover, a combinatorial approach utilizing SLC25A22-shRNA plus 5-Fluorouracil synergistically suppressed the proliferation of KRAS mutant CRC in vitro and in subcutaneous xenograft models.

Conclusion: A history of ischemic heart disease and laboratory data, such as high blood urea nitrogen and high C-reactive protein levels and low hemoglobin may be useful predictive clinical factors for early death after PEG. If patients have a history of ischemic heart disease, high blood urea nitrogen, high C-reactive protein, or anemia, PEG should be considered carefully.

Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 10:30-12:00
IMMUNOTHERAPY IN CANCER – ROOM 1.61/1.62

OP367 GLUTAMINOLYSIS INHIBITION AS A THERAPEUTIC STRATEGY IN GLUTAMINE-ADDICTED KRAS MUTANT COLORECTAL CANCER

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Introduction: Colorectal cancer (CRC) with KRAS mutations represents an urgent clinical need due to the lack of effective therapies. A defining characteristic of oncogenic KRAS-driven cancers is an altered cellular metabolism, in which glucose and glutamine metabolism are extensively rewired to satisfy their anabolic needs. In this study, we investigated the metabolic dependencies of KRAS-mutant CRC, established the role of glutaminolysis in KRAS-mutant CRC survival. U
2
1

Conclusion: A history of ischemic heart disease and laboratory data, such as high blood urea nitrogen and high C-reactive protein levels and low hemoglobin may be useful predictive clinical factors for early death after PEG. If patients have a history of ischemic heart disease, high blood urea nitrogen, high C-reactive protein, or anemia, PEG should be considered carefully.

Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016 10:30-12:00
COMPLICATIONS OF LIVER CIRRHOSIS: BEYOND BLEEDING AND ASCITES – ROOM N1

OP369 RANDOMIZED CONTROLLED TRIAL OF BACLOFEN IN THE TREATMENT OF MUSCLE CRAMPS IN PATIENTS WITH LIVER CIRRHOSIS

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Introduction: Muscle cramps adversely influence the quality of life of patients with liver cirrhosis. However, despite the obvious association of muscle cramps with liver disease, there is a paucity of information regarding pathogenesis and treatment in these patients.

Aims & Methods: This is the first randomized placebo controlled trial of baclofen in the treatment of muscle cramps in patients with liver cirrhosis. One hundred patients with liver cirrhosis and suffering from muscle cramps signed informed consent to participate in this study. They were recruited from Department of Tropical Medicine-Tanta University hospital. They were randomized to receive either baclofen or placebo for 3 months. Patients were followed monthly and one month after withdrawal. Each visit, the clinico-epidemiological data were recorded, muscle cramp questionnaire was filled, and any drug related side effects were reported.

Results: In the baclofen group, the frequency of muscle cramps was significantly decreased after one and three months of treatment (p < 0.005), with a significant rebound after withdrawal (p < 0.001). Patients receiving baclofen had a significant reduction in the severity of muscle cramps (P < 0.001). After three months of baclofen therapy at dose of 30 mg/day, muscle cramps disappeared completely in 72%, reduced in 20%, and no change in 8% of patients. No significant changes in the frequency, severity and duration of muscle cramps were observed in the placebo group. There were few but non-significant side effects in the baclofen group when compared to placebo group.

Conclusion: Baclofen was well tolerated, safe, and effective in the treatment of muscle cramps in Egyptian patients with post-hepatisitis C liver cirrhosis.
Disclosure of Interest: All authors have declared no conflicts of interest.

References

OQ370 SPONTANEOUS BACTERIAL PERITONITIS – DOES THE INFECTION ACQUISITION SITE MATTER?

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Introduction: Spontaneous bacterial peritonitis (SBP) develops in up to 25% of patients with cirrhosis and is associated with significant short and long-term morbidity and mortality. With the amelioration of medical care, the use of antibiotics for primary and secondary prophylaxis of SBP, there is some controversy concerning whether the acquisition site of the infection has an effect on the prognosis of SBP and if the international guidelines for antibiotic therapy (mainly based on the acquisition site) are still considered to be the best practice. Aim: To compare clinical, laboratory and microbiological characteristics between nosocomial and community-acquired SBP; to assess the influence of the infection acquisition site when evaluated in hospital mortality and 1 year-mortality. Retrospective cohort study, conducted in 3 tertiary centers that evaluated all cases of SBP between 2010 and 2014. Medical records and laboratory data were reviewed. For defining the acquisition site of the infection, we followed the criteria described by European Center for Disease Prevention and Control (ECDC). Healthcare-Associated infections and Nosocomial infections were analyzed as the same variable. Multiresistant bacteria (MDR) was defined according to the ECDC criteria (resistant to 3 antibiotic families, including beta-lactam antibiotics).

Results: We identified 222 episodes of SBP, from which 110 were considered as community-acquired and 112 as nosocomial infection. The nosocomial infections were more frequently by gram positive bacteria (p = 0.003); SBPs secondary to nosocomial infection were associated with a worse prognosis (63.0 vs 51.7%; p = 0.007). Likewise, proximal lesion detection rates rose from 15.8% (SD 9.8%) to 21.7% (SD 13.3%; p = 2.5% per two-year-period, 95% CI: +1.9%, +3.1%, p < 0.001). Adverse events occurred in 0.3%, 63% thereof were associated with polyplectomy. There was a decline in complication rates of −7.3 per 10,000 endoscopies per two-year-period (95% CI: −13.1, −1.5 per 10,000 endoscopies per two-year-period, p = 0.013). Sedation increased the probability of adverse events (0.24% in sedated and 1.16% in unsedated patients, p = 0.025). Notably, all perforations occurred under sedation.

Conclusion: This study showed a strong improvement in quality of screening colonoscopy performed within a quality assurance program in Austria between 2011 and 2014. Both overall adenaoma detection rate and detection rate of proximal lesions increased strongly in the investigated study period. Interestingly, the detection rate of advanced adenomas decreased.

Disclosure of Interest: All authors have declared no conflicts of interest.

OQ372 ENDORNGS™ INCREASES ADR EVEN IN HIGH-RISK SCREENING COLONOSCOPY – RESULTS OF A SINGLE CENTRE PILOT STUDY

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Introduction: Colonoscopy remains the gold standard procedure for screening and polyp detection, with adenoma detection rate (ADR) being a widely accepted key performance indicator (KPI). It has long been recognised that even experienced endoscopists incur an appreciable ‘miss-rate’ and a number of novel devices have been marketed to assist this aspect of practice. The Endorings™ device is a simple soft silicone, single-use device consisting of a series of rings arranged around a central tubular core. As the colonoscope is inserted it allows inflation and flare on withdrawal to flatten colonic folds and aid inspection.

Aims & Methods: This was a single-centre pilot study to determine the effect of Endorings used in a high-risk cancer screening population (national), when used by experienced endoscopists already familiar with their use, in improving ADRs. Data was collected during screening colonoscopy (performed by two accredited ADR) by experienced operators with an established ADR already established at the time of data collection. Prospective data was collected during screening colonoscopy (performed by two accredited endoscopists) when the Endorings™ device was used and compared the results to outcomes from the previous few months, for the same (two colonoscopists) when the device was not in use (ie. historical controls).

Results: The ADR without Endorings (n = 85) was 49.4% with a per-procedure detection rate (ppr) of 0.97. With the device (n = 66), ADR was 66.7% (p = 0.0006) with ppr of 1.625. This represents a 35% increase in ADR and a 68% increase in the number of polyps detected at any given procedure. There were no significant differences in completion rates, withdrawal time, use of sedation or comfort scores. The device was removed in 5/6 procedures due to interference with intubation (in the presence of either an angulated sigmoid or difficult console). No complications were recorded.

Conclusion: Use of the Endorings™ device was associated with a significant increase in ADR. Qualitatively, the three-ring design was felt to interfere with normal intubation such that insertion technique had to be modified. An updated design is in production with two rings in slightly different positions along the central tube, has been produced and appears to offer a significant advantage in this regard. Furthermore, the central tube can be pushed further along the distal part of the colonoscope to allow the terminal ileum to be intubated with the device in place. The Endorings™ may offer an advantage in screening colonoscopy and, in this cohort, further prospective investigation is warranted. Disclosure of Interest: All authors have declared no conflicts of interest.

OQ373 THE FIRST RANDOMISED CONTROLLED TRIAL OF ENDOCUFF VISION®-ASSISTED COLONOSCOPY VERSUS STANDARD COLONOSCOPY FOR POLYP DETECTION IN BOWEL CANCER SCREENING PATIENTS (E-CAP STUDY)

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Introduction: Up to 25% of colorectal polyps are missed during colonoscopy. The Endocuff Vision® is a cap with soft flexible arms which attaches to the end of a colonoscope and improves views during withdrawal. We have performed the first randomised controlled trial to identify the role of Endocuff Vision® in improving polyp detection.

Aims & Methods: Our aim was to investigate the impact of Endocuff Vision®-assisted colonoscopy on polyp detection, as compared to standard colonoscopy, in the UK Bowel Cancer Screening Programme (BCSP). This was a single-centre, randomised controlled trial. Ethics approval was obtained (ref: E1216).
E-CAP results
cant difference was found between the 2 study arms for any of the study endpoints. Endpoints were also evaluated separately for: screening group, surveillance group, and the individual endoscopists. In all these analyses, no significant difference was found between the 2 study arms for any of the study endpoints.

Result: 534 patients were recruited from Sep 2014 to Sep 2015. 3 were excluded due to new diagnosis of polyposis syndrome, to avoid skewing of results. 531 were included and randomised to the 2 study arms. No significant difference was seen between the 2 groups for the primary endpoint of number of polyps per patient. Secondary endpoints: No significant difference was observed between the 2 groups for adenoma detection rate (ADR) or number of adenomas per patient (Table 1). Endpoints were also evaluated separately for: screening group, surveillance group, and the individual endoscopists. In all these analyses, no significant difference was found between the 2 study arms for any of the study endpoints. No significant adverse events were encountered during the study in either arm. The mean intubation time was not prolonged and patients did not experience any additional discomfort due to the Endocuff Vision.

Table 1: E-CAP results

<table>
<thead>
<tr>
<th>Endocuff</th>
<th>Standard</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>265</td>
<td>266</td>
</tr>
<tr>
<td>Polyps</td>
<td>470</td>
<td>436</td>
</tr>
<tr>
<td>Polyps/patient</td>
<td>1.77</td>
<td>1.64</td>
</tr>
<tr>
<td>Adenomas</td>
<td>359</td>
<td>336</td>
</tr>
<tr>
<td>Adenomas/patient</td>
<td>1.35</td>
<td>1.26</td>
</tr>
<tr>
<td>PDR</td>
<td>185/265 = 69.8%</td>
<td>187/266 = 70.3%</td>
</tr>
<tr>
<td>ADR</td>
<td>167/265 = 63%</td>
<td>162/266 = 69.9%</td>
</tr>
<tr>
<td>Cancer detection rate</td>
<td>15/265 = 5.7%</td>
<td>14/266 = 5.3%</td>
</tr>
</tbody>
</table>

Conclusion: In the UK, bowel cancer screening is performed by highly experienced endoscopists with special accreditation. Our results suggests that in expert hands, ADR exceeds 60% even without Endocuff. In such settings, Endocuff Vision did not improve polyp detection rates (PDR) or ADR. However, Endocuff did not cause any adverse events, prolong procedure duration or cause additional discomfort. These data demonstrate the safety and feasibility of Endocuff. However, no additional gain was demonstrated in expert hands.

Disclosure of Interest: All authors have declared no conflicts of interest.


disclosure

OP374 INCREASED ADENOMA DETECTION RATE BY G-EYE HIGH DEFINITION COLONOSCOPY IN COMPARISON TO STANDARD HIGH DEFINITION COLONOSCOPY: A PROSPECTIVE RANDOMIZED MULTICENTRE STUDY


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Introduction: Colorectal cancer (CRC) detection is attributed to the early detection and removal of polyps and adenomas during colonoscopy procedures. Although colonoscopy is considered to be the ‘gold standard’ for CRC prevention, a significant number of polyps and adenomas go undetected during standard procedures. This is largely due to polyps that are hidden behind colonic folds that obscure endoscopic optics and result in interval cancers. The G-EYE colonoscopy system (Norgine, Harefield, United Kingdom) comprises a standard forward-viewing endoscope with a permanently integrated balloon at the distal end. Upon withdrawal of the endoscope, the G-EYE balloon is inflated to a forward-viewing endoscope with a permanently integrated balloon at the distal end. Upon withdrawal of the endoscope, the G-EYE balloon is inflated to a forward-viewing endoscope with a permanently integrated balloon at the distal end. Upon withdrawal of the endoscope, the G-EYE balloon is inflated to a forward-viewing endoscope with a permanently integrated balloon at the distal end. Upon withdrawal of the endoscope, the G-EYE balloon is inflated to a forward-viewing endoscope with a permanently integrated balloon at the distal end. Upon withdrawal of the endoscope, the G-EYE balloon is inflated to a forward-viewing endoscope with a permanently integrated balloon at the distal end. Upon withdrawal of the endoscope, the G-EYE balloon is inflated to a forward-viewing endoscope with a permanently integrated balloon at the distal end. Upon withdrawal of the endoscope, the G-EYE balloon is inflated to a forward-viewing endoscope with a permanently integrated balloon at the distal end.

Conclusion: Our study shows that the G-EYE endoscope can substantially improve ADR when compared to SC. In addition to diminutive and small adenomas, the G-EYE endoscope detects a larger number of advanced and large-size adenomas. Consequently, we conclude that the G-EYE endoscope can significantly enhance the quality of CRC screening and thus reduce colonic mass rates and interval cancer incidents.

Disclosure of Interest: H. Jacob: Board of directors

All other authors have declared no conflicts of interest.

OP375 EFFICACY AND SAFETY OF THE NOVEL II. PEG AND ASCORBATE BOWEL PREPARATION NER1006 VERSUS TRISULFATE SOLUTION IN OVERNIGHT SPLIT-DOSING ADMINISTRATION: RESULTS FROM THE PHASE 3 STUDY NOCT221

M. Demico1, L. B. Clayton2, R. Ng Kwet Shing3, M. Epstein1

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Introduction: Successful colon cleansing enables effective colonoscopy. PEG based split dosing preparations are traditionally seen as the gold standard in cleansing, but many still require a high preparation volume intake. NER1006 is a proprietary 1L PEG3350 ascorbate bowel preparation, currently under 3 clinical development. The low volume of NER1006 is achieved through the use of ascorbate in the second dose only.

Aims & Methods: This phase 3, randomised, multicentre, colonoscopist-blinded, non-inferiority study assessed the efficacy, safety and tolerability of a 2-day overnight split-dosing regimen of either NER1006 (N2D) or trisulfate solution (TS) in patients undergoing colonoscopy. Two alternative primary endpoints were utilized: overall bowel cleansing success and an ‘Excellent plus Good’ cleansing rating in the colon ascendens using the Harefield Cleansing Scale (HCS). Secondary endpoints included hierarchical evaluation of lesion detection rates (key), and cleansing assessment using the Boston Bowel Preparation Scale (BBPS; supportive). Patient tolerability, acceptability and compliance were assessed using questionnaires. Safety was monitored through adverse events and clinical laboratory evaluation. The threshold for statistical significance in this study was P < 0.025. The confidence interval (CI) for the difference between the groups used a 10% margin to demonstrate non-inferiority vs TS.

Result: Patients were randomised to receive either N2D (n = 310) or TS (n = 311). For N2D and TS, respectively, the mean age (SD) was 57.7 (10.36) and 57.3 (10.56) years. The distribution of males vs. females was 158 (51.0%) vs. 152 (48.9%). The mean age (SD) was 57.7 (10.36) and 57.3 (10.56) years. The distribution of males vs. females was 158 (51.0%) vs. 152 (48.9%).

Conclusion: For NER1006 and TS, respectively, the mean age (SD) was 57.7 (10.36) and 57.3 (10.56) years. The distribution of males vs. females was 158 (51.0%) vs. 152 (48.9%). The mean age (SD) was 57.7 (10.36) and 57.3 (10.56) years. The distribution of males vs. females was 158 (51.0%) vs. 152 (48.9%).

Disclosure of Interest: All authors have declared no conflicts of interest.

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1L. NER1006 showed high efficacy and safety in overnight split-dosing administration.


Table 1 (OP375): Efficacy and safety endpoints

<table>
<thead>
<tr>
<th>Abstract legend</th>
<th>NER1006 2-day split-dosing</th>
<th>Comparator: trisulfate solution</th>
<th>CI for the difference [P value]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY</td>
<td>Primary analysis set, n = 276</td>
<td>Primary analysis set, n = 280</td>
<td>#8.15%* [0.528]</td>
</tr>
<tr>
<td>Primary endpoint: Patients with successful overall bowel cleansing efficacy (HCS) [n]</td>
<td>235 (85.1%)</td>
<td>238 (85.0%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Supportive secondary endpoint: Patients with successful overall bowel cleansing efficacy (BBPS) [n]</td>
<td>228 (82.6%)</td>
<td>227 (81.1%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Primary endpoint: Excellent plus Good cleansing rate in colon ascends [n]</td>
<td>99 (35.9%)</td>
<td>82 (29.3%)</td>
<td>#1.69%* [0.059]</td>
</tr>
<tr>
<td>Key secondary endpoint: Adenoma detection rate, colon ascends</td>
<td>14.1%</td>
<td>17.1%</td>
<td>#11.36%, #2.82%* [0.863]</td>
</tr>
<tr>
<td>Key secondary endpoint: Adenoma detection rate, overall colon</td>
<td>33.7%</td>
<td>35.0%</td>
<td>n.a.</td>
</tr>
<tr>
<td>Key secondary endpoint: Polyp detection rate, colon ascends</td>
<td>18.5%</td>
<td>23.9%</td>
<td>n.a.</td>
</tr>
<tr>
<td>Key secondary endpoint: Polyp detection rate, overall colon</td>
<td>45.7%</td>
<td>48.6%</td>
<td>n.a.</td>
</tr>
<tr>
<td>Compliance rate (min 75% of both doses taken) [n]</td>
<td>255 (92.4%)</td>
<td>255 (91.1%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>BOCLIR score [mean (SD)]</td>
<td>39.9 (17.70)</td>
<td>39.6 (17.51)</td>
<td>n.a.</td>
</tr>
<tr>
<td>All treatment-emergent adverse events [n]</td>
<td>118</td>
<td>67</td>
<td>n.a.</td>
</tr>
<tr>
<td>Patients with any related treatment-emergent adverse event [n]</td>
<td>39 (14.9%)</td>
<td>25 (9.4%)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

* #97.5% 1-sided CI; ** #95% 2-sided CI; n.a. = not applicable

Reference

WEDNESDAY, OCTOBER 19, 2016
10:30-12:00

BURDEN OF LIVER DISEASE – ROOM LT7

OP377 THE BURDEN OF OVERT AND OCCULT LIVER CIRRHOSIS IN PATIENTS WITH METABOLIC SYNDROME: ANALYSIS FROM A LARGE GENERAL PRACTITIONERS DATABASE

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Introduction: Liver cirrhosis represents the end stage of chronic liver disease, characterized by high mortality and morbidity (1.2) with relevant health and social costs (3). Metabolic syndrome represents one of the major risk factors of liver disease in western countries (4). The real prevalence of this condition is difficult to assess, since liver disease is silent until clinical decompensation of cirrhosis occurs.

Aims & Methods: The aim of this study was to estimate the prevalence of occult liver disease in the Veneto region and to compare the results with the burden of liver disease in western countries (4). The real prevalence of this condition is difficult to assess, since liver disease is silent until clinical decompensation of cirrhosis occurs.

Results: During the study period (January–April 2016), 286 patients were enrolled (mean age 59.8±7, males 53.7%), 143 in group A and 143 in group B; of them 266 have undergone colonoscopy (group A: 130, group B: 136). The two groups were well balanced as concerns age, gender, education, employment and marriage status. Split-dose was adopted by 106/130 and by 118/136 patients in group A and B, respectively (81.5% vs 86.8%, p = 0.317). Among patients who complied with split-dose the quality of bowel cleansing was adequate (BBPS ≥ in each segment of the colon) in 215/224 (96.0%). No significant differences between group A and B were observed with regards to adherence to preparation scheme, which were both optimal, (98.1% vs 97.5%, p = 0.693) and to the adequacy of bowel prep (BBPS > 2 in each segment) (97.2% vs 94.9%, p = 0.785). No variable was significantly associated with split-dose uptake at logistic regression analysis.

Conclusion: Present data show an excellent compliance with split-dose prescription for early morning colonoscopy in both written only and oral and written instruction groups, leading to very satisfactory levels of colon cleansing. This finding underlines that the adoption of a self-explanatory booklet clearly describing the benefits of split-dose marginalizes the need of additional oral instructions. This result is relevant in an open-access system, where routine oral education is unfeasible, and does not support ESGE indications, which recommend both oral and written explanation by healthcare professionals.

Disclosure of Interest: All authors have declared no conflicts of interest.
was recorded. Sex distribution of these patients was similar to that of the patients with cirrhosis, without differences in enzyme alterations (M:F=90:1 vs 0.9, respectively), while age was higher in patients with elevated transaminases (mean age (yrs) = 55.5 vs 48.9, p < 0.0001). Patients with overt diagnosis of cirrhosis were 0.3% of the overall population, while thrombocytopenia, as indicator of occult cirrhosis, was detected in 1.3% of the remaining patients. The epidemiological profile of these two groups was similar [M:F=1:1.59; mean age (yrs)=60.5 vs M:F=1.67; mean age (yrs)=65, p = ns], but significantly different (p < 0.0001) compared to the normal population and to subjects with only liver enzyme alterations. Patients with occult and overt cirrhosis presented a similar prevalence of a metabolic syndrome profile (49% and 56% respectively), while these figures were lower in patients without signs of liver disease (33%, p < 0.0001).

Conclusion: In conclusion, a large proportion of patients with biochemical signs of chronic hepatitis and cirrhosis are still undiagnosed. Metabolic syndrome seems to be the major risk factor that characterizes patients with more severe liver disease.

Disclosure of Interest: All authors have declared no conflicts of interest.

References

Table 1 (OP379): All-cause resource use pre- and post-RFX initiation

<table>
<thead>
<tr>
<th>Resource Use</th>
<th>Pre-RFX</th>
<th>Post-RFX</th>
<th>P</th>
<th>Pre-RFX</th>
<th>Post-RFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalisations with overnight stay per patient</td>
<td>101</td>
<td>2.2 (1.9)</td>
<td>0.99</td>
<td>2.7 (2.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total bed days</td>
<td>101</td>
<td>2890</td>
<td>1206</td>
<td>-</td>
<td>1621</td>
</tr>
<tr>
<td>Total bed days per inpatient</td>
<td>101</td>
<td>28.6 (31.4)</td>
<td>&lt;0.001</td>
<td>99</td>
<td>31.7 (35.9)</td>
</tr>
<tr>
<td>Critical care bed days per inpatient</td>
<td>19</td>
<td>7.9 (10.1)</td>
<td>0.018</td>
<td>11.3 (11.8)</td>
<td>0.017</td>
</tr>
<tr>
<td>Critical care bed days per inpatient</td>
<td>19</td>
<td>7.9 (10.1)</td>
<td>0.018</td>
<td>11.3 (11.8)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Disclosure of Interest: R. Aspinall: Consultant and UK advisory board member for Norgine
A. Radwan: Employee of Norgine
G. Shaya: Employee of Norgine
H. Sodatonou: Consultant for Norgine
R. Cipelli: Consultant for Norgine. Employee of pH Associates which was commissioned by Norgine to provide support with study design and data management, and scientific editorial services.
M. Hudson: Consultant for Norgine. Attended advisory board and has given sponsored lectures (national or international) on behalf of Norgine.
Results: 56 patients with CD (mean age 41 [range 21–76] y, 27 females), 45 with biopsy samples.

The recently recognised alternative RAS axis comprising angiotensin converting enzyme 2 (ACE2) protein may play an important role in physiology, especially in epithelial cells. Circulating and mucosal components of the alternative RAS axis are up-regulated in patients with IBD, but mucosal Ang (1–7) is reduced, suggesting dysregulation and a potential role of the RAS in pathogenesis or perpetuation of inflammation in IBD. Novel therapies that increase mucosal Ang (1–7) may have a role in IBD.

Disclosure of Interest: All authors have declared no conflicts of interest.

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Introduction: The anti-CD47 antibody vedolizumab (VDZ), which inhibits homing of lymphocytes via interaction of α4β7 with MAdCAM-1, has greatly increased therapeutic options in patients with IBD. However, lymphocyte homing may also occur via other homing molecules like the α4β7 integrin and a considerable portion of patients does not respond to VDZ therapy. The anti-CD47 antibody etrolizumab (ETZ) is currently tested in phase III trials and additionally blocks the binding of αEβ7 to E-Cadherin, which is believed to mediate epithelial retention of homed lymphocytes.

Aims & Methods: We aimed to compare lymphocyte trafficking upon blockade of αEβ7 by etrolizumab and α4β7 by vedolizumab.

Results: αEβ7 expression was significantly higher on CD4+ lymphocytes both in the peripheral blood and the gut. Among both subsets αEβ7 expression was correlated with IL-9 secretion, while CD4+IL-9 cells expressed less αEβ7 than other CD4+ subsets. At the same time, CD8+ cells exhibited a notably greater potential to increase αEβ7 expression upon T cell stimulation and TGF-β treatment, while butyric and retinoic acid decreased αEβ7 expression on CD8+ cells. ETZs markedly inhibited binding of αEβ7 to E-Cadherin and blocked the adhesion of CD4+ and CD8+ lymphocytes to MAdCAM-1 and E-Cadherin. To put it simply, CD8+ cells from IBD patients treated with VDZ had a reduced potential of VDZ and the ETZ surrogate antibody FB504 (ETZs) were tested. Finally, lymphocytes from UC patients were treated with either of the compounds. Fluorescence labelled and injected into the ileoceleic artery of immunocompromised mice. Gut homing was assessed by in vivo confocal microscopy and flow cytometry of lamina propria cells.

Conclusion: VDZ may not equally cover all pathogenetically relevant lymphocyte trafficking and therapeutic response in UC and CD patients, and healthy donors by flow cytometry or immunofluorescence staining, respectively. The regulation of αEβ7 expression upon lymphocyte stimulation and incubation with cytokines was studied. In vitro adhesion assays the adhesive capacity of lymphocytes to MAdCAM-1 and E-Cadherin. Humanized mouse model the portion of human CD8+ cells in the murine gut significantly reduced three hours after injection when cells were treated with ETZs vs. VDZ. Among CD4+ cells, the fraction of T11 cells was decreased. The expression of αEβ7 on CD8+ cells from IBD patients treated with VDZ was higher in the maintenance than in the induction phase of treatment.

Disclosure of Interest: S. Zandler: The etrolizumab Surrogate antibody was produced by Genentech. Sanofi is a shareholder (p = 0.002). Sz. The etrolizumab Surrogate antibody was produced by Sanofi, USA. CA, USA.

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Discussion: VDZ seems to offer superior reduction of intestinal lymphocyte infiltration especially concerning CD8+ and T9 cells.

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Results: αEβ7 expression was significantly higher on CD4+ lymphocytes both in the peripheral blood and the gut. Among both subsets αEβ7 expression was correlated with IL-9 secretion, while CD4+IL-9 cells expressed less αEβ7 than other CD4+ subsets. At the same time, CD8+ cells exhibited a notably greater potential to increase αEβ7 expression upon T cell stimulation and TGF-β treatment, while butyric and retinoic acid decreased αEβ7 expression on CD8+ cells. ETZs markedly inhibited binding of αEβ7 to E-Cadherin and blocked the adhesion of CD4+ and CD8+ lymphocytes to MAdCAM-1 and E-Cadherin.

Discussion: VDZ seems to offer superior reduction of intestinal lymphocyte infiltration especially concerning CD8+ and T9 cells.

Disclosure of Interest: S. Zandler: The etrolizumab Surrogate antibody was produced by Genentech, Sanofi is a shareholder (p = 0.002). Sz. The etrolizumab Surrogate antibody was produced by Sanofi, USA. CA, USA.
OP385 VITAMIN D REGULATES DENDRITIC CELL ACTIVITY AND TRAFFICKING IN CROHN’S DISEASE


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Introduction: Dendritic cells (DC) can determine whether the mucosal immune system mounts an inflammatory or regulatory response to antigen and likely contributes to the pathogenesis of Crohn’s disease. Vitamin D down-regulates DC inflammatory responses and could prove beneficial as a treatment adjunct in Crohn’s disease. Vitamin D also modulates DC homing marker expression. This study assessed the effect of high dose parenteral vitamin D treatment on circulating DC phenotype and function in patients with active luminal Crohn’s disease receiving anti-TNFα therapy.

Aims & Methods: Peripheral blood mononuclear cells were isolated from 14 patients with active luminal Crohn’s disease and suboptimal vitamin D levels (<75 nmol/L) prior to and 6 weeks after starting anti-TNFα (infliximab) therapy. Patients with low vitamin D (<50 nmol/L) were also given a single high dose of parenteral vitamin D (300,000 international units 1.25(OH)2-vitamin D3). Flow cytometry was used to identify total DC, (HLA-DR+ cells negative for markers of other cell lineages (CD3, CD14, CD16, CD19 & CD34)). DC were further subtyped as myeloid (mDC, CD11c+CD123) and plasmacytoid (pDC, CD123+CD11c). Expression of phenotypic markers (including maturation and homing markers and pattern recognition receptors) and on-going intracellular DC cytokine production during 4 hours’ culture were assessed.

Results: Production of TNFα by myeloid DC was significantly reduced (p = 0.016) in those patients who received vitamin D alongside anti-TNFα therapy, beyond that of those who received anti-TNFα therapy alone (mean reduction in TNFα = 24.9% v 39.1% respectively). There was a significant correlation between increase in vitamin D level and decrease in TNFα production by myeloid DC (p = 0.02; R2 = 0.76). An increase of serum 25(OH) vitamin D greater than 20 nmol/L was associated with a decrease in myeloid DC TNFα production. Anti-TNFα therapy alone induced a significant upregulation of the skin homing marker cutaneous lymphocyte antigen (CLA) on myeloid DC (p = 0.0055), an effect which was not seen in patients receiving additional vitamin D. A high dose parenteral vitamin D, given as an adjunct to anti-TNFα therapy in Crohn’s, promotes down-regulation of circulating myeloid DC production of TNFα. This may influence the subsequent interaction of DC and T cells. TNFα promotes a Th-17 response characteristic of Crohn’s inflammation; thus the ability of vitamin D to further block TNFα production may promote a more regulatory T cell response and improve outcomes when used as an adjunct to anti-TNFα therapy. The upregulation of the skin homing marker CLA following anti-TNFα therapy may explain the high rates of cutaneous side effects to this drug class. The down-regulation of CLA by vitamin D in this setting may be useful in those patients suffering cutaneous sequelae of anti-TNFα therapy.

Disclosure of Interest: P. Henty: Advisory board: Dr Falk; AbbVie. All other authors have declared no conflicts of interest.

OP386 CIRCULATING DENDRITIC CELL SUBSETS IN CROHN’S DISEASE SHOW ALTERATIONS IN TISSUE HOMING AND CYTOKINE PRODUCTION


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Introduction: Crohn’s disease is characterised by an exaggerated immune response to mucosal antigen. Dendritic cells (DC) within the gut-homing (CLA+) and in extravascular tissues contribute to the pathogenesis of Crohn’s disease and from healthy controls. An altered phenotype and function in patients with active luminal Crohn’s disease receiving anti-TNFα therapy in Crohn’s, promotes down-regulation of circulating myeloid DC pro-inflammatory responses and could prove beneficial as a treatment adjunct in Crohn’s disease. Vitamin D down-regulates DC inflammatory responses and could prove beneficial as a treatment adjunct in Crohn’s disease. Vitamin D also modulates DC homing marker expression. This study assessed the effect of high dose parenteral vitamin D treatment on circulating DC phenotype and function in patients with active luminal Crohn’s disease receiving anti-TNFα therapy.

Aims & Methods: Peripheral blood mononuclear cells were isolated from 14 patients with active luminal Crohn’s disease and suboptimal vitamin D levels (<75 nmol/L) prior to and 6 weeks after starting anti-TNFα (infliximab) therapy. Patients with low vitamin D (<50 nmol/L) were also given a single high dose of parenteral vitamin D (300,000 international units 1.25(OH)2-vitamin D3). Flow cytometry was used to identify total DC, (HLA-DR+ cells negative for markers of other cell lineages (CD3, CD14, CD16, CD19 & CD34)). DC were further subtyped as myeloid (mDC, CD11c+CD123) and plasmacytoid (pDC, CD123+CD11c). Expression of phenotypic markers (including maturation and homing markers and pattern recognition receptors) and on-going intracellular DC cytokine production during 4 hours’ culture were assessed.

Results: Production of TNFα by myeloid DC was significantly reduced (p = 0.016) in those patients who received vitamin D alongside anti-TNFα therapy, beyond that of those who received anti-TNFα therapy alone (mean reduction in TNFα = 24.9% v 39.1% respectively). There was a significant correlation between increase in vitamin D level and decrease in TNFα production by myeloid DC (p = 0.02; R2 = 0.76). An increase of serum 25(OH) vitamin D greater than 20 nmol/L was associated with a decrease in myeloid DC TNFα production. Anti-TNFα therapy alone induced a significant upregulation of the skin homing marker cutaneous lymphocyte antigen (CLA) on myeloid DC (p = 0.0055), an effect which was not seen in patients receiving additional vitamin D. A high dose parenteral vitamin D, given as an adjunct to anti-TNFα therapy in Crohn’s, promotes down-regulation of circulating myeloid DC production of TNFα. This may influence the subsequent interaction of DC and T cells. TNFα promotes a Th-17 response characteristic of Crohn’s inflammation; thus the ability of vitamin D to further block TNFα production may promote a more regulatory T cell response and improve outcomes when used as an adjunct to anti-TNFα therapy. The upregulation of the skin homing marker CLA following anti-TNFα therapy may explain the high rates of cutaneous side effects to this drug class. The down-regulation of CLA by vitamin D in this setting may be useful in those patients suffering cutaneous sequelae of anti-TNFα therapy.

Disclosure of Interest: P. Henty: Advisory board: Dr Falk; AbbVie. All other authors have declared no conflicts of interest.

OP387 A PROTEOMIC APPROACH TO EXPLAIN THE PROTECTIVE ROLE OF INULIN IN PREVENTING LPS-INDUCED HUMAN COLONIC SMOOTH MUSCLE IMPAIRMENT

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Introduction: Fructans, such as inulin, are dietary fibers which stimulate gastro-intestinal function acting as probiotics. We recently demonstrated the protective effect of inulin on LPS-induced damage of colonic smooth muscle in an ex vivo experimental model, which seems to be related to presence of oxidative stress. The aim of this study was to identify the proteomic pattern with the protective effect of inulin in an LPS-induced oxidative stress was evaluated on colonic mucosa using a proteomic approach. Human colonic mucosa and submucosa, obtained from disease-free margins of resected segments for cancer, were sealed between two chambers containing Krebs solution, with or without the mucosa overlaid with 5 mL of Krebs, or 100 μg/mL LPS solution, or 100 μg/mL LPS + 100 mg/mL inulin Fructafit IQ (LPS + INU). The biological system was kept oxygenated for 30 min at 37°C. The solutions on the submucosal side were collected following mucosal exposure to Krebs in the absence (N-undernatant) or presence of LPS (LPS-undernatant) or inulin + LPS (INU-undernatant). Undernatants were tested for the effects on human colonic smooth muscle strips contractility using an organ bath system. Proteomic analysis (iTRAQ based analysis) was used to identify and compare the soluble proteome of human colonic mucosa and submucosa treated. Each sample was labelled by one of four reagents of the iTRAQ 4-plex and then combined into one aliquote. Triplicate labelling was performed, which showed a high level of reproducibility.

Conclusion: Inulin exposure was able to restore, in human colonic mucosa, the LPS-dependent alteration of some proteins involved in the host response and in the intestinal smooth muscle contraction (ZG16, CALM1/MLCK/MYL signaling pathway) and to reduce the upregulation of two proteins involved in the radi-cal oxidative stress induced by LPS (APEL, GSTK1). Moreover, the administration of inulin entails a higher level of some detoxification enzymes (MT2A, GSTK1, and UGT2B4) with respect to LPS treatment. Following exposure to the LPS-undernatant, a significant decrease in maximal Ach-induced contraction was observed with respect to the controls. In controls, the contractile muscle strips incubated with the N-undernatant (49 ± 5% vs 10 ± 1% respectively, P < 0.05) and this was completely prevented by pre-incubation of the LPS with Inulin (12 ± 2%, P = ns versus N-undernatant).

Disclosure: Our data suggest that the exposure of colonic mucosa to inulin is able to prevent LPS-dependent altered expression of some key proteins which promote intestinal motility and the host response, reducing the radical-mediated oxidative stress.
Disclosure of Interest: All authors have declared no conflicts of interest.

Reference

OP388 TLR4 IS STILL ACTIVE IN GP96-DEFICIENT MACROPHAGES
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Introduction: Gp96 is a chaperone for multiple protein substrates which plays an important role in innate and adaptive immunity. Lack of this protein in intestinal macrophages (iMACs) of Crohn’s Disease (CD) patients is correlated with a loss of tolerance against the host gut flora, triggering a chronic and persistent inflammation. iMACs are crucial for pathogen recognition at the mucosal surface of the gastrointestinal tract and Toll-like receptors (TLR), one of the best investigated family of pattern recognition receptors, lead to the phosphorylation of NFkB after their activation. Previous studies of our group revealed a strong expression of TLR2 and 4 on inflammatory iMACs leading to a higher susceptibility of CD patients to LPS, in parallel with a specific loss of gp96.

Aims & Methods: We aim to study the impact of the gp96-knockdown on TLR-function in the human monocytic cell line MM6 and in a conditional gp96-LysMcre knock-out mice. MM6 cells were stably transduced with lentiviral gp96-knockdown vector. The lentiviral vector particles were produced by co-transfection of HEK293T cells with transfer, packaging and envelope plasmids using Fugene HD Transfection Kit. After transduction, cells were treated with LPS (100 ng/ml) for 2 hours. Furthermore, in order to analyze the relevance in vivo, conditional LysMcre-gp96 knock-out (KO) mice were also generated after crossing gp96lox/lox-mice with LysM-Cre mice. Peritoneal macrophages were isolated from both, wild-type (WT) and KO mice, and treated with LPS (100 ng/ml) for 2 hours. In transduced MM6 cells and peritoneal macrophages, TLR2 and TLR4 expression was analyzed by flow cytometry and the expression of NFkB, IL-1B, IL-6, IL-8, and TNFα was analyzed by Western blot, PCR and ELISA. Results are expressed as percentage or fold induction ± SEM. All experiments were performed with an n ≥ 3.

Results: After checking that the efficiency of lentiviral knockdown was more than 90% by flow cytometry experiments we observed that the expression of TLR4 and TLR2+gp96-shRNA transduced cells were slightly decreased, 81% and 77% respectively, compared with mock-transduced MM6 cells, 92% and 97% respectively. In line with this, the analysis of the expression of TLR4 and TLR2 receptors in peritoneal macrophages showed a similar slight decrease in KO mice (74.4% and 77.0% respectively) compared with WT mice (78.2% and 90.5% respectively). The functionality of TLR4 receptor was also analyzed and treatment with LPS induced a significant increase in the ratio pIκBα/ικBα in gp96-shRNA cells (1.6 fold induction) and in KO peritoneal macrophages (5.1±1.5). In protein expression of pNFkB in both gp96-shRNA (1.7) and in KO peritoneal macrophages (1.5±0.6) compared with non-treated mock-transduced cells and WT peritoneal macrophages. Furthermore, LPS induced a significant increase in the mRNA expression of IL-1β, TNFα and IL-6 in gp96-shRNA cells (1.9 fold induction) and in KO peritoneal macrophages (1.6±0.9). IL-1β, IL-6, IL-8 and TNFα were analyzed by Western blot, PCR and ELISA. Results are expressed as percentage or fold induction ± SEM. All experiments were performed with an n ≥ 3.

Conclusion: TLR4 receptor is still active and functional even in the absence of gp96.

Disclosure of Interest: All authors have declared no conflicts of interest.

Wednesday, October 19, 2016 10:30-12:00
GASTRIC AND JUNCTIONAL Cancers - ROOM 1.86

OP389 A NEW, BIOLOGICALLY RELEVANT CLASSIFICATION FOR ADENOCARCINOMAS AT THE GASTRO-OESOPHAGEAL JUNCTION
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Introduction: SRGAP1, a co-target of miR-340 and miR-124, functions as a potential oncogene with an amplification and recurrent mutation in gastric tumorigenesis.

Aims & Methods: We aim to investigate the biological functions of SRGAP1 and comprehensively review its regulation by deregulated miRNAs in gastric carcino- genesis. The mRNA and protein expression of SRGAP1 was analyzed by qRT-PCR and Western blot. The biological role of SRGAP1 in GC was demonstrated by MTT proliferation, monolayer colony formation, cell invasion and migration assays through siRNA-mediated knockdown. The prediction of miRNAs which potentially target SRGAP1 was performed by TargetScan (http://www.targetscan.org/) and miRDB (http://mirdb.org). miR-340 and miR-124 were screened out for further validation. The regulation of SRGAP1 by miRNAs was confirmed by qRT-PCR, Western blot and dual luciferase activity assays by ectopic expression in vitro.

Results: SRGAP1 is over-expressed in 9 out of 12 (75.0%) GC cell lines both from the mRNA and protein level. In clinical samples form TCGA cohort, SRGAP1 shows gene amplification in 5/288 (1.9%) cases and its mRNA upregulation shows positive correlation with the copy number change. The mutation rate of SRGAP1 in primary GC is 8/288 (3.1%) Knockdown of SRGAP1 in MKN28, MGC-803 and SGC-7901 cells showed significant anti-oncogenic effect in vitro. SRGAP1 downregulation suppressed cell proliferation, reduced monolayer colony formation, and inhibited tumor growth over 50% of the tumorigenesis and migration ability. Moreover, luciferase activity experiments revealed SRGAP1 knockdown significantly inhibited Wnt/β-catenin pathway, which was further confirmed by the inactivation of β-catenin and downregulation of CCND1 and c-Myc. Conclusion: SRGAP1 is an important target of GF288 and miR-124 in GC. These two miRNAs showed decreased expression compared with adjacent normal epithelium cells and the downregulation of miR-340 and miR-124 were associated with poor survival. Enforced overexpression of miR-340 and miR-124 in GC cells alleviated tumor-suppressive function by inhibiting cell proliferation and inducing G1 phase cell cycle arrest. In paired GC samples, the expression of SRGAP1 protein showed negative correlation with the expression of miR-340 and miR-124.

Conclusion: SRGAP1 is over-expressed and plays an oncogenic role in GC through activating Wnt/β-catenin pathway. Apart from gene amplification and mutation, the activation of SRGAP1 in GC is partly due to the downregulation of miR-340 and miR-124. These findings provided unclear whether this also reflects the molecular phenotype and hence how this stratification might influence therapy and prognosis in an era of personalised medicine.

Aims & Methods: The aim of this study was to determine the molecular phenotypes of GOJ tumours and to relate this to the Siewert classification. The gene expression profile of 107 tumours from gastro-oesophageal junction (GOJ) was assessed by the Illumina HTv4.0 beadchip array (GOJ1: 35, GOJ2: 31, GOJ3: 18, true gastric comparators: gastric fundus/proximal body: 6, distal body: 9, antrum: 8). Only tumours of intestinal Lauren type were included. Different gene expression subtypes were defined using limma in R, unbiased sub-
clinical implications that targeting SRGAP1 might have therapeutic potential for GC.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP392 HOXB7 PROMOTES EPITHELIAL-MESenchYmal TRANSITION AND METASTASIS IN GASTRIC CANCER

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Introduction: In the previous study we observed that HOXB7 is highly expressed in gastric cancer and promote migration or invasion, and inhibit apoptosis in gastric cancer cells.

Aims & Methods: We aimed in this study to demonstrate the roles of HOXB7 in development of epithelial-mesenchymal transition (EMT) and metastasis in gastric cancer using in vitro and in vivo model. We established HOXB7-expression stable cell lines (MKN45-B7) and mock cells (MKN45-mock). Western blot was performed to validate EMT markers and phospho-Akt/PTEN activity. By injection of stable cell lines, xenograft tumors were produced on the 8-week old male Balb/C nude mice (nu/nu). 4 weeks after injection, we extracted xenograft tumors, and implanted fragment of tumors on the stomach of another 8-week old nude mice. 6 weeks after implantation, mice were sacrificed and their peritoneal metastasis, perigastric lymph node and volume of gastric tumor were compared between both groups.

Results: MKN45-B7 cells frequently showed fibroblast-like mesenchymal phenotype, whereas most of MKN45-mock cells showed epithelial phenotype. Mesenchymal markers (snail, vimentin) were up-regulated and epithelial marker (E-cadherin) was down-regulated in MKN45-B7 cells, as well as phospho-Akt level was increased and PTEN expression was decreased compared by MKN45-mock cells. The volume of xenograft tumor was significantly increased in MKN45-B7 cell-injected mice than MKN-mock cell injected mice. Mean number of peritoneal metastasis/perigastric lymph node and volume of gastric tumor with MKN45-B7 tumor-implanted mice. When transiently transfect siAkt on MKN45-B7 cells, snail and vimentin expression were down-regulated, whereas E-cadherin expression was up-regulated, compared by siControl-transfected MKN45-B7 cells.

Conclusion: Our findings suggest that HOXB7 may play crucial role in inducing EMT and promoting metastasis in gastric cancer via modulating Akt/PTEN axis.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP393 SIGNIFICANCE OF COLONOSCOPY IN PATIENTS WITH GASTRIC HIGH GRADE DysPLASIA OR EARLY GASTRIC CANCER

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Introduction: Relationship of gastric cancer and colon cancer, it is not yet clearly identified. But usually there is high risk of colorectal cancer known as gastric cancer patients.

Aims & Methods: The purpose of this study was to discuss the development risk of colorectal neoplasms in gastric cancer patients with gastric cancer category 4 lesion (high-grade dysplasia, HGD and early gastric cancer, EGC) who underwent endoscopic submucosal dissection (ESD) compared to healthy controls. We also investigated the associated risk factors for colorectal neoplasm and colon cancer. The study group included a total of 209 patients with gastric cancer category 4 lesion (95 HGD and 114 EGC) who underwent ESD, and 610 healthy controls were included. All of the patients underwent concurrent screening colonoscopy between January 2009 and May 2014. High risk colorectal neoplasm was defined as > 1 cm, adenoma with villous component, adenoma with HGD, or more polyys or adenocarcinoma.

Results: High-risk colorectal neoplasm was found in 50/209 patients (23.9%) in patient group and 47/610 (7.7%) in controls (p < 0.05). Colon cancer was diagnosed in 16/209 patients (7.6%) in patient group and 18/610 (2.9%) in controls (p < 0.05). The incidence of high-risk colorectal neoplasm were associated with age, DM, colon cancer family history, and presence of gastric cancer 4 lesion. The risk factors of colon cancer were associated age, and colon cancer family history, and presence of gastric cancer 4 lesion. The incidence of high-risk colorectal neoplasm and colon cancer in patient group who underwent gastric ESD was higher than that in the control group. Therefore, patients undergoing ESD with category 4 lesions may need screening colonoscopy.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP394 PALLIATIVE CHEMOTHERAPY AND TARGETED THERAPIES FOR ESOPHAGEAL AND GASTRO-ESOPHAGEAL JUNCTION CANCER

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Introduction: More than 50% of patients with esophageal (EC) or gastro-esophageal junction cancer (GEJC) have metastatic disease at the time of diagnosis. Chemotherapy and targeted therapies are increasingly used for palliative treatment with the intent to control tumor growth, improve quality of life, and prolong survival. To date, scientific proof is lacking.

Aims & Methods: Therefore, the aim of this study was to systematically review and compare the effectiveness of chemotherapy and targeted therapy to best supportive care (BSC) and, to compare the addition of a cytostatic or targeted therapeutic to a control arm in patients with EC/GEJC. This abstract is based on a pre-peer review of a formal Cochrane Review. Upon completion and approval, the final version is expected to be published in the forthcoming Systematic Reviews. We searched the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE, and searched reference lists of studies. The search was not restricted to English language publications only. Randomized controlled trials of chemotherapy and/or targeted BSC versus a control arm, in patients with esophageal or gastro-esophageal junction cancer were included. Two authors independently extracted data.

Results: For the comparison of palliative chemotherapy or targeted therapy versus BSC, five trials with a total of 751 patients were included in the meta-analysis for overall survival (OS). This analysis demonstrated a significant benefit in OS in favor of the group receiving palliative chemotherapy and/or targeted therapy compared to BSC (hazard ratio (HR) 0.81 (0.71 to 0.92)). A similar trend was observed for progression free survival (PFS), including two trials and 542 participants, with a HR of 0.58 (95%CI 0.28 to 1.18). For the comparison of adding a cytostatic and/or targeted agent to a control arm, ten trials, with 1288 patients in total were included for the meta-analysis of OS. This analysis demonstrated a significant benefit in OS in favor of the arm with the addition of cytostatic or targeted therapeutic with a HR of 0.77 (95% CI 0.70 to 0.85). The median increased survival time was limited, one month for adding an additional cytostatic or targeted therapeutic to the control arm. Subanalysis with second line therapies showed a similar benefit as first line therapies. Ramucirumab was the only agent, investigated more than once, that significantly improved both OS and PFS. Palliative chemotherapy and/or targeted therapy increased the frequency of treatment related toxicity at least grade 3. However, treatment related deaths did not occur more frequently. Quality of life was better in the arm that reported this outcome, often improved in the arm with an additional agent.

Conclusion: Palliative chemotherapy and/or targeted therapy significantly increased OS compared to BSC in patients with esophageal or gastro-esophageal junction carcinoma. Additionally, patients who received chemotherapy, apeutic or targeted therapeutic agents have an increased OS, PFS and improvement of quality of life, on the expense of treatment-associated toxicity of at least grade 3. Based on the meta-analysis, palliative chemotherapy and/or targeted therapy should be considered standard care for esophageal and gastro- esophageal junction carcinoma.

Disclosure of Interest: All authors have declared no conflicts of interest.

WEDNESDAY, OCTOBER 19, 2016
10:30-12:00
ABSTRACTS ON FIRE: NEW APPROACHES TO COLORECTAL DISEASE – HOTSPOT

OP395 ECONOMIC EVALUATION OF ANTIBIOTIC THERAPY VS APPENDECTOMY FOR TREATMENT OF UNCOMPLICATED ACUTE APPENDICITIS: RESULTS OF THE APPAC RANDOMIZED CLINICAL TRIAL

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Disclosure of Interest: All authors have declared no conflicts of interest.
Introduction: Appendectomy has been the standard treatment for acute appendicitis for more than 30 years. Appendectomies are performed annually in the United States. Although appendectomy is generally well tolerated, it is a major surgical intervention and can be associated with postoperative morbidity. Our APPAC trial comparing antibiotic therapy with appendectomy for the treatment of acute appendicitis in our Appendicitis Acuta (APPAC) randomized clinical trial was conducted in Finland from November 2009 until June 2012. A total of 530 adults patients aged 18 to 60 years with CT-scan confirmed uncomplicated acute appendicitis were enrolled in six Finnish hospitals. Patients were randomly assigned to either conservative treatment (n = 273) or antibiotic treatment (n = 257). The cost estimates were based on the cost levels of the final quarter of year 2012. All costs were recorded, whether generated by the initial visit and subsequent treatment or possible recurrent appendicitis during the one-year follow-up period.

Results: In the operative group the overall societal costs were 16 times higher than in the antibiotic group. In both groups productivity losses represented a slightly higher proportion of overall societal costs than all treatment costs together, with diagnostic and medical having a minor role. Patients in the operative group were prescribed significantly more sick leave days (16.96, SD 8.30) compared with the antibiotic group (9.17, SD 6.89) (p < 0.001). When the age and sex of the patient as well as the hospital of care were controlled simultaneously, the operative treatment option generated significantly more costs in all models.

Conclusion: To our knowledge, this is the first randomized study comparing antibiotic therapy and appendectomy in uncomplicated acute appendicitis to reach a conclusion. Avoiding surgery was the most advantageous in the study resulted in major cost savings. Although 27% of the antibiotic group patients underwent surgery, the differences in costs both to the service providers and to the society overall strongly support evaluating antibiotic therapy as the first alternative for uncomplicated acute appendicitis. Further studies evaluating the optimal treatment of uncomplicated acute appendicitis are strongly encouraged also from an economic standpoint.

Disclosure of Interest: P. Salminen: Research grant / a government research grant (EV0) awarded to Turku University hospital. All other authors have declared no conflicts of interest.

References
OP398 SERRATED POLYPOSIS SYNDROME: A SURGICAL PERSPECTIVE
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Introduction: Serrated Polyposis Syndrome (SPS) is associated with an increased risk of colorectal cancer (CRC). Some patients may require colonic surgery but the literature regarding indication, procedure performed, outcomes and surgical decision making is sparse. We aimed to address these issues.

Aims & Methods: 434 patients with SPS, were retrospectively enrolled from 7 centers in the Netherlands and 2 in the UK. Data were retrieved from medical charts, pathology and endoscopy reports and collected in a centralized database. Data relating to surgical resection and surveillance outcomes were assessed.

Results: A total of 164 (38%) patients underwent colorectal surgery; 114 (70%) for CRC, 31 (19%) for high polyp burden and 14 (9%) for unresectable polyps. Surgery for SPS Cancer Twenty seven (25%) SPS cancers were managed with total colectomy and ileorectal anastomosis (IRA), with the remaining 87 (75%) patients having a more limited resection. 90% of those undergoing IRA had a formal diagnosis of SPS at the time of their surgery compared with only 39% of those undergoing more conservative resections. Fifty eight (90%) patients had a resection for cancer before a diagnosis of SPS was made. Total polyp burden (median 40 v 22.5, p = 0.01) and proximal polyp numbers (median 20 v 12, p < 0.019) were significantly higher in those having more extensive surgery. In the limited resection group eight (9%) patients had developed metastatic tumours; of these only three have recorded formal post-operative endoscopic surveillance. None of these patients met SPS criteria at the time of index surgery. Three had total IRA as management of their second tumour. The median interval to development of second CRC was 24 months. In the limited resection group seven (8%) patients required further surgical intervention for endoscopically unmanageable polyp load. All had IRA as their second procedure. Total polyp burden (median 40 v 23.5, p < 0.01), proximal polyp burden (median 25 v 15, p = 0.002) and number of proximal polyps >10 mm (median 10 v 2, p = 0.005) were higher in this group compared with those having surgery for CRC alone.

Surgery for High Polyp Burden All 31 patients had a diagnosis of SPS and underwent IRA. The median total polyp count was 43 (IQR 34-56.5) and median proximal polyp burden was 31 (IQR 26.8–47.5). None have developed CRC to date. Polyp burden in this group was equivalent to proximal polyp burden was 31 (IQR 26.8–47.5).

Conclusion: 1. Over one-third of SPS patients required colorectal resection. The vast majority for CRC, of whom only half were known to fulfil criteria for SPS at the time of their cancer resection. 2. Developing metachronous cancer is uncommon. Segmental resection and close endoscopic surveillance may be appropriate for at least some of this patient cohort and more extensive surgery reserved for those whose SPS cancers present concurrently with higher polyp counts. Surgical decision making should be guided by the endoscopic assessment of the SPS.

Disclosure of Interest: All authors have declared no conflicts of interest.

OP399 IMPROVED RISK CLASSIFICATION FOLLOWING COLORECTAL ADENOMA REMOVAL
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Introduction: Current colonoscopy surveillance recommendations after polyp removal are arbitrary and resource demanding. We developed a novel risk classification system for colorectal cancer following adenoma removal.

Aims & Methods: We included 82 colorectal cancers among individuals who underwent polyp removal (0.31%) and 194 in individuals without adenomas (0.15%). The strongest predictors for colorectal cancer risk were adenoma size ≥20 mm in diameter (HR 8.70; 95% CI 5.43–13.95, P < 0.001), high-grade dysplasia (HR 4.15; 95% CI 1.05–16.43, P < 0.001) and adenomas ≥5 mm, with high-grade dysplasia, or with villous histology (≥25%). The initial population comprised 100,000 average-risk individuals aged 40 years. Parameters of transition probabilities, costs, and test accuracy were estimated based on Japanese data.4 Four surveillance

Discussion of Interest: All authors have declared no conflicts of interest.

OP400 COST-EFFECTIVENESS ANALYSIS OF POST-POLYPECTOMY COLORECTOSCOPY SURVEILLANCE USING JAPANESE DATA: RISK-STRATIFIED SURVEILLANCE BASED ON POLYP RESULTS IS MORE COST-EFFECTIVE
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Introduction: To maximize the usefulness of total colonoscopy (CS) in reducing deaths from colorectal cancer (CRC), it is essential that cost-effective post-polypectomy CS surveillance programs are implemented. However, this has not been well examined. European Union and United States guidelines for post-polypectomy surveillance recommend risk-stratified programs based on initial CS results.2,7 Japanese guidelines, however, recommend that post-polypectomy surveillance should be performed within 3 years of polypectomy, regardless of the results of resected polyps.2,7 Given that different surveillance programs are recommended in different settings, it is important to determine the most cost-effective surveillance program.

Aims & Methods: The aim of this study was to determine the most cost-effective post-polypectomy CS surveillance program by performing a Markov model analysis using Japanese data. The model was developed by simulating the clinical course of CRC as a transition from normal epithelium, low-risk adenomatus polyps sized 1–4mm and 5–9mm, high-risk adenomatous polyps, CRC, and finally to death from CRC.4 High-risk polyps included intramucosal cancers and adenomas with a diameter ≥10mm, with high-grade dysplasia, or with villous histology (≥25%). The initial population comprised 100,000 average-risk individuals aged 40 years. Parameters of transition probabilities, costs, and test accuracy were estimated based on Japanese data.4 Four surveillance
strategies were evaluated for costs, gained quality-adjusted life-years (QALYs), and the required number of CS procedures. In strategy 1, post-polypectomy surveillance CSs were performed 1 year after polypectomy regardless of the polyp results. In strategy 2, the interval between surveillance CSs and polypectomy was 3 years regardless of the polyp results. Strategy 3 was a risk-stratified one; surveillance CSs were performed 3 years after the resection of high-risk polyps and 5 years after that of low-risk polyps. In strategies 1, 2, and 3, surveillance CSs were performed 10 years after normal CSs. Strategy 4 was also a risk-stratified one with more intense use of CS than strategy 3; the interval between surveillance CSs and the resection of high-risk polyps, low-risk polyps, and no polyps were 1, 3, and 5 years, respectively. In all strategies, a fecal immunochemical test-based CRC screening program was provided before surveillance, and uptake rates were set at 60% in the base-case analysis. A probabilistic sensitivity analysis (PSA) was also performed for all model parameters.

**Results:** QALYs and costs per person in strategy 1 are as follows: strategy 1, 23,004 QALYs and $1,024.88; strategy 2, 23,000 QALYs and $1,009.02; strategy 3, 23,013 QALYs and $977.40; strategy 4, 23,046 QALYs and $970.31. The required numbers of CS procedures per person in strategy 1, 2, 3, and 4 were 2.143, 1.664, 1.617, and 2.548, respectively. Risk-stratified strategies (strategies 3 and 4) yielded higher QALYs with lower costs than strategies 1 and 2. Comparing strategy 3 with strategy 4, yielded QALYs were higher and required cost was lower in strategy 4. Strategy 4 was most-cost-effective, showing simple dominance over the other strategies, followed by strategy 3; however, strategy 4 required the most CS procedures. The PSA showed that the probability of strategy 1 being chosen as the most cost-effective at the willingness-to-pay value of $50,000 was 67.8%. 

**Conclusion:** After consideration, risk-stratified CS surveillance programs based on the polyp results should be recommended owing to higher expected effectiveness and cost-effectiveness. Furthermore, more intense use of CS procedures in risk-stratified surveillance can heighten the effectiveness and cost-effectiveness in the Japanese setting. However, it does require a larger number of CS procedures; thus, it would be preferable to determine the most appropriate use of CS procedures in risk-stratified surveillance programs depending on the nationwide availability of CS resources.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**References**

**OP401 NEW NBI MAGNIFYING ENDOCOSCOPIC CLASSIFICATION FOR COLORECTAL TUMORS PROPOSED BY THE JAPAN NBI EXPERT TEAM (JNET)**


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**Introduction:** There have been many narrow-band imaging (NBI) magnifying endoscopic classifications advocated (Sano, Hiroshima, Showa, and Jikei classifications) so far in Japan. NBI magnifying endoscopy for qualitative and quantitative diagnosis for colorectal lesions is useful, however, some discussion in Japan has raised issues such as i) the presence of multiple terms for the same or similar findings, ii) the necessity of including surface patterns in magnifying endoscopic classifications, and iii) differences in the NBI findings between polypoid and superficial lesions. To resolve these issues and unify the classifications, the Japan NBI Expert Team (JNET) was set up in 2011. The aim of this study is to scientifically evaluate the NBI scale and determine the NBI findings and diagnostic criteria used in the unified classification (The JNET classification).

**Aims & Methods:** The JNET classification, which is a modification of NICE classification, consists of 4 categories (Types 1, 2A, 2B, and 3) based on vessel and surface patterns without color. We made a hypothesis that each of them are correlated with the histopathological findings of hyperplastic polyp/ sessile serrated polyp (SSP), low grade intramucosal neoplasia, high grade intramucosal neoplasia/shallow submucosal invasive cancer, and deep submucosal invasive cancer, respectively. A web image interpretation study using the modified Delphi (UMIN000010292: Multicenter study for developing universal NBI magnifying endoscopic classification of colorectal tumors in Japan) was conducted. 25 specialists in magnification evaluated NBI findings and histology with 100 NBI still images on the web.

**Results:** Univariate and multivariate analyses and analysis on diagnosability from 5 candidate NBI magnifying findings such as i) loose vessel areas, ii) interruption of thick vessels, iii) scattered vessels, iv) thick, linearized/meandering atypical vessels in the tumor, and v) amorphous areas of surface patterns for Type 3, and i) variable caliber of vessels, ii) thick vessels iii) irregular distribution of vessels, iv) vessel meandering, and v) irregular or obscure surface pattern for Type 2B. Among the five candidate NBI findings, three findings such as 1) loose vessel areas, 2) interruption of thick vessels, and 5) amorphous areas of surface patterns were identified as the diagnosis of type 3. In addition, three findings such as i) variable caliber of vessels, III) irregular distribution of vessels, and V) irregular or obscure surface pattern were selected for the diagnosis of type 2B.

**Conclusion:** Subclassification of NICE Type 2 (2A & 2B) could be performed scientifically with NBI magnifying findings with color using web image interpretation study, which could conduct differential diagnosis between low grade intramusosal neoplasia and high grade intramusosal neoplasia/shallow submucosal invasive cancer.

**Disclosure of Interest:** All authors have declared no conflicts of interest.

**Table (OP401)**

<table>
<thead>
<tr>
<th>JNET</th>
<th>Type 1</th>
<th>Type 2A</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel pattern</td>
<td>Invisible</td>
<td>Regular caliber</td>
<td>Variable caliber</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regular distribution (meshed/spiral pattern)</td>
<td>Irregular distribution</td>
</tr>
<tr>
<td>Surface pattern</td>
<td>Regular dark or white spots</td>
<td>Regular (tubular/branched / papillary</td>
<td>Irregular or obscure</td>
</tr>
<tr>
<td></td>
<td>Similar to surrounding normal mucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most likely histology</td>
<td>Hyperplastic poly/ Sessile serrated poly</td>
<td>Low grade intramucosal neoplasia</td>
<td>High grade intramucosal neoplasia/Shallow submucosal invasive cancer</td>
</tr>
</tbody>
</table>

OP402 SUBCLASSES OF TYPE-II PIT PATTERN REVEAL ALTERNATIVE TUMORIGENIC PATHWAYS OF COLORECTAL SERRATED LESIONS


Aims & Methods: We aimed to identify clinicopathological and molecular features of SLs without Type II-O pits. We analyzed the methylation of CIMP (CIMP-high, -low, and -negative) was determined by using the five methylation markers. Type II pit was subcategorized into classical Type-II pit, Type II-Open (Type II-O) pit, Type II-Long (Type II-L) pit, Type II-Open plus tumor pit and Type II-Long plus tumor pit. These results suggest that lesions with Type II-L pit and those with Type II-L plus tumor pit were the same HP. Our data suggest that Type II-L plus tumor pit is a useful hallmark of the premalignant stage of CRCs with KRAS mutation and CIMP-low.

Disclosure of Interest: All authors have declared no conflicts of interest.

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Introduction: Colorectal serrated lesions (SLs) include hyperplastic polyph (HP), traditional serrated adenoma (TSA) and sessile serrated adenoma/polyp (SSA/P). Emerging evidences suggest that SSA/Ps are precursor lesions of colorectal cancers (CRCs) with BRAF mutation and the CpG island methylator phenotype (CIMP). We have previously reported that Type II-Open (Type II-O) pit pattern, which is highly specific to SSA/P. However, clinicopathological and molecular features of SLs without Type II-O pits remain unclear.

Results: Endoscopic findings were classified as 41 Type II pit, 8 Type II-L pit, 92 Type II-O pit, 21 Type II plus tumor pit, 22 Type II-L plus tumor pit, 50 Type II-O plus tumor pit and 214 tumor pit. We identified Type II-L plus tumor pit, which was specific to TSA with KRAS mutation and CIMP-low (sensitivity, 60%; specificity, 96%). As compared to lesions with only Type II-L pit, KRAS mutation and CIMP-low were more frequent in lesions with Type II-L plus tumor pit. Progression of Type II-L pit lesions to TSA was associated with KRAS mutation and accumulation of moderate DNA methylation. In contrast, BRAF mutation was frequently observed in colonic tumors with Type II plus tumor pit. These results suggest that lesions with Type II-L plus tumor pit are useful hallmark of the premalignant stage of CRCs with KRAS mutation and CIMP-low.

Conclusion: Our data suggest that Type II-L plus tumor pit is a useful hallmark of the premalignant stage of CRCs with KRAS mutation and CIMP-low.

OP403 ARTIFICIAL INTELLIGENCE (AI) IN ENDOSCOPY–DEEP LEARNING FOR OPTICAL BIOPSY OF COLORECTAL POLYPS IN REAL-TIME ON UNALTERED ENDOSCOPIC VIDEOS

M. F. Byrne1, D. K. Rex2, N. Chapados3, F. Soudani4, C. Oertel5, M. Linares-Petion6, G. Kelly6, N. Iqbal7, F. Chandelier8

Aims & Methods: We investigated a Deep Learning Artificial Intelligence model with a proprietary deep convolutional neural network (DCNN) for the computer-assisted NICE optical biopsy for colon polyps. We used 92 endoscopic videos, for the support of clinically efficient optical biopsy. We used 38 NICE type 1, 52 NICE type 2, using Olympus 190 series colonoscopes. Optical biopsy was done on all polyps by an expert with >95% accuracy (using pathology as the reference standard) prior to removal and histological confirmation.

Introduction: Artificial Intelligence model with a proprietary deep convolutional neural network (DCNN) for the computer-assisted NICE type 1&2 differentiation. We designed a 5-class model representing Types 1, 2, and unsuitable (frames without statistically representative information–blur, bubbles, liquid). The model operated at the individual frame level, without prior segmentation. For model training purposes, each frame was manually tagged. The final dataset was split into training and validation sets, without overlap. Finally, the analysis was performed separately for NBI and WL frames, allowing for reporting of frame processing time and classification performance.

Results: A total of 33,954 training frames were used, split equally across NBI & WL, and type 1, type 2, & unsuitable classes. We performed a 5-fold cross-validation on the tagged frames for quality control. The trained DCNN model was then used to evaluate the unaltered videos in real-time, with an accuracy for polyp classification of 90% for NBI, and 83% for WL. The confusion matrix on whole-video classification of colorectal polyps gives a sensitivity of 93% and specificity of 85% for NBI. Finally, the processing time of our DCNN model ran at between 23 and 30 frames per second (fps) using a decent gamer-grade GPU (NVIDIA Titan-X) on an unaltered video feed of 60 fps, delivering near-realtime computer support.
Conclusion: To our knowledge, this is the first application of deep learning to the optical biopsy challenge for polyp differentiation into NICE types 1&2 using non-magnification colonoscopy and NBI, specifically in a clinically representative workflow where computer support is provided in realtime on unaltered endoscopic video streams. Although the present investigation was carried on a limited datasets of 92 videos, our deep learning model has shown clinically efficient and relevant performance for optical biopsy, well aligned with PIVI guidelines and the performance of experts. Ongoing work will determine if such a computer support solution could aid in the widespread adoption of a “resect and discard” strategy, and reduce the economic burden of pathological evaluation of benign diminutive colon polyps.

Disclosure of Interest: M.F. Byrne: Chairman of Satis Operations Inc D.K. Rex: Olympus consulting and research support N. Chapados: Imagia has commercial interests in artificial intelligence F. Soudan: Imagia has commercial interests in artificial intelligence C. Oertel: Imagia has commercial interests in artificial intelligence M. Linares Perez: research support from Satis Operations Inc R. Kelly: research support from Satis Operations Inc F. Chandelier: Shareholder in Cadens Medical Imaging

All other authors have declared no conflicts of interest.

<table>
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<tr>
<th>Age, mean (SD), y</th>
<th>48 (7)</th>
<th>48 (7)</th>
<th>50 (17)</th>
<th>52 (14)</th>
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<tbody>
<tr>
<td>Women, n (%)</td>
<td>5 (63)</td>
<td>5 (46)</td>
<td>19 (54)</td>
<td>17 (53)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>22.6 (3.6)</td>
<td>23.3 (4.1)</td>
<td>22.2 (3.1)</td>
<td>22.2 (2.8)*</td>
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<tr>
<td>Stoma present, n (%)</td>
<td>7 (88)</td>
<td>11 (100)</td>
<td>10 (29)</td>
<td>10 (32)*</td>
</tr>
<tr>
<td>Colon-in-continuity, n (%)</td>
<td>1 (13)</td>
<td>1 (9)</td>
<td>22 (63)</td>
<td>24 (77)*</td>
</tr>
<tr>
<td>Estimated small bowel length, mean (SD), cm</td>
<td>128 (98)</td>
<td>129 (77)*</td>
<td>54 (43)</td>
<td>73 (56)</td>
</tr>
<tr>
<td>Baseline PS, mean (SD), L/wk</td>
<td>21.6 (8.1)</td>
<td>15.9 (10.4)</td>
<td>11.5 (5.9)</td>
<td>11.2 (6.4)*</td>
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<tr>
<td>Baseline PS duration, mean (SD), y</td>
<td>7.2 (7.4)</td>
<td>8.1 (8.0)</td>
<td>5.6 (5.3)</td>
<td>6.1 (5.7)*</td>
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</table>

*n = 31, 1n = 9, 2n = 32, 3n = 30.

Disclosure of Interest: U. Pape: Has received grant/research support and served as an advisory board member or speaker’s bureau for NPS Pharmaceuticals, Inc., Shire plc, and Fresenius Kabi GmbH; served as a study investigator for NPS Pharmaceuticals, Inc.

P.B. Jeppesen: Has received grant/research support and served as a consultant, advisory board member, and study investigator for NPS Pharmaceuticals, Inc.

H. Lee: Employee and stockholder of Shire plc.

A.A. Grimm: Employee of Shire plc.

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