Biologic Prescribing Decisions Following Serious Infection; Results from the British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA)

Authors:
Sujith Subesinghe 1,2 MBBS BSc MSc MRCP, ssubesinghe@nhs.net
Andrew Ian Rutherford 1,3 MBBS BSc MSc MRCP, arutherford1@nhs.net
Rachel Byng-Maddick 4 MBBS MRCP PhD, rachel.byng-maddick@nhs.net
Kimme Leanne Hyrich 5,6 MD PhD FRCP, kimme.hyrich@manchester.ac.uk
James Benjamin Galloway 1,3 MBChB, MSc, CHP, FRCP, PhD, FAcadMedEd, james.galloway@kcl.ac.uk

1. Academic Department of Rheumatology, Weston Education Centre, King’s College London, Cutcombe Road, London, SE5 9RJ
2. Department of Rheumatology, Guy’s and St. Thomas’ NHS Foundation Trust, Guy’s Hospital, Great Maze Pond, London, SE1 9RT
3. Department of Rheumatology, King’s College Hospital NHS Foundation Trust, Denmark Hill, London, SE5 9RS
4. Department of Rheumatology, Homerton Hospital, Homerton Row, Hackney, London, E9 6SR
5. Arthritis Research UK Centre for Epidemiology, Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK
6. NIHR Manchester Musculoskeletal Biomedical Research Centre, Central Manchester University Hospitals NHS Foundation Trust and University of Manchester Partnership, Manchester, UK
Abstract:

Objectives: To establish whether the decision to stop, continue or switch tumour necrosis factor inhibitor therapy (TNFi) to a biologic drug with an alternative mode of action following a serious infection (SI) impacts upon the risk of recurrent SI in patients with RA.

Methods: Patients recruited to the BSRBR-RA with at least one episode of SI whilst on TNFi were included. The biologic treatment decision following SI was considered. A multivariable adjusted Cox proportional hazards model was used to identify predictors of recurrent SI and whether biologic treatment choices influenced future SI risk.

Results: In total, 1,583 patients suffered at least 1 SI whilst on TNFi. Most patients (73%) were recorded as continuing TNFi 60 days after an index SI. The rate of recurrent SI was 25.6% per annum (95%CI 22.5-29.2). The rate of recurrent SI was highest in patients who stopped their TNFi; 42.6% per annum (95%CI 32.5-55.7) and lowest in those who switched biologic drug class (12.1% per annum, 95%CI 3.9-37.4). Compared to patients stopping biologic therapy, patients who continued or switched...
drug class had significantly lower risk of recurrent SI (drug continuation HR 0.54, 95%CI 0.40-0.74, drug switch HR 0.29, 95%CI 0.09-0.95).

Conclusions: Patients who continued or switched their TNFi post index SI had a lower risk of recurrent SI infection compared to those who stopped the drug. This may be explained by better control of disease activity with reintroduction of biologic therapy, a driving factor for SI or alternatively channelling fitter patients to restart biologic therapy.

Introduction

Biologic drugs have revolutionised RA management however the risk of serious infection (SI) associated with the disease and its therapies are concerning for clinicians and patients [1]. SI is a frequent cause of drug cessation [2]. The British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA) reported a small but statistically significant increased risk of SI associated with tumour necrosis factor inhibitor therapy (TNFi) compared to non-biologic therapy (TNFi SI rate 4.2/100 patient-years follow-up (95%CI 4.0-4.4) versus non-biologic therapy 3.2/100 patient-years of follow-up (95%CI 2.8-3.6) [3]. Similar findings have been reported from other national biologic registries [4-6]. A prior history of SI is a predictor of recurrent SI in RA [7, 8].

British Society for Rheumatology guidelines advise caution in using TNFi in patients at high risk of infection [9]. Discontinuing TNFi during a SI is recommended, restarting only when infection has completely resolved [9]. The decision to stop, continue or switch to an alternative biologic drug class after SI remains at the discretion of the prescriber in collaboration with the patient.
This study investigated the pattern of and association with biologic prescribing choices (i.e. drug cessation, continuation or switch to a drug with an alternative mode of action) following a SI and future SI risk.

**Patients and Methods:**

The BSRBR-R A is a large prospective observational cohort established to evaluate the safety and efficacy of biologic drugs (including adalimumab, etanercept, infliximab, certolizumab-pegol, anakinra, rituximab and tocilizumab) [10]. Abatacept is not included in the BSRBR-RA. The study achieved ethics approval from the Multicentre Research Ethics Committee for North West England in December 2000 (MREC00/8/053, Integrated Research Application System 64202). All participants give written informed consent. The register's methodology has been previously described [10].

**Baseline assessment:** Data captured at baseline (defined as the date of the first registered drug with the BSRBR-RA), included patient demographics, disease duration, disease activity score in 28 joints (DAS28), health assessment questionnaire score (HAQ), smoking status, oral steroid use and comorbidity. Current and previous drug exposures were also recorded.

**Patient follow up:** Questionnaires were sent to supervising rheumatologists and patients biannually for 3 years (annually to rheumatologists thereafter) to gather information on drug exposures and adverse events. The BSRBR-RA was notified of any deaths of recruited patients by NHS Digital.

**Case definition:** Participants were included if they suffered at least one SI episode whilst on their first TNFi (or within 5 half-lives of stopping TNFi) and survived at least 60 days after the index SI. SI events after 1st June 2008 were considered. This date was when the first patients in the BSRBR-RA rituximab cohort were recruited (thus
allowing a drug switch to an alternative biologic class from TNFi). The data cut-date was 30th June 2016.

SIs were defined as episodes requiring intra-venous antibiotics, hospitalisation or resulting in death. Cases of SI were identified through all three methods of patient follow-up. Patient reported SIs required verification by their treating rheumatologist. Only SI occurring with first biologic drug exposures on TNFi were included. SIs were coded using ‘Medical Dictionary for Regulatory Activities’ terminology and classified into seven categories (‘sepsis’, ‘lower respiratory’, musculoskeletal’, ‘skin and soft tissue’, ‘gastrointestinal’, ‘genitourinary’ and ‘other’, see supplementary data).

Patient follow up began 60 days after the index SI. This ensured only new episodes of SI were considered and allow adequate time for SI resolution. The biologic drug decision following an index SI was based upon an intention to treat analysis. If a patient was recorded as receiving TNFi at day 60 post index SI date, they were considered as having continued biologic. If a patient was recorded as receiving either rituximab or tocilizumab 60 days after an index SI, they were considered to have switched drug. Follow up continued for 12 months, ending in the event of patient death, recurrent SI or reaching the end of follow up. Individual patient record review was performed to manually code treatment decisions. A decision tree is shown in supplementary material. This analysis did not consider what happened to biologic exposure in the immediate period around the infectious episode.

**Statistical Methods:** Characteristics of biologic treated patients with SI during follow-up were tabulated. Incidence rates were calculated, and a multivariable Cox proportional hazards model was used to identify whether biologic treatment decisions were associated with future SI risk. Adjustments were made for age, gender, baseline DAS28, HAQ, disease duration, polypharmacy (a surrogate measure of comorbidity).
Polypharmacy has been associated with an increased risk of unplanned hospitalisations and was used as a surrogate measure for comorbidity [11]. Individuals were divided into three categories (0–5, 6–10, ≥11) based on the number of medications they were taking (excluding RA therapies). Multiple imputation of missing baseline covariates was performed with 20 cycles using the ICE package in Stata 14 (Statacorp LLC, Texas, USA).

Results:
In total, 21,943 with 115,423 patient-years follow-up were registered in the BSRBR-RA; 1583 patients suffered at least 1 SI whilst receiving their first TNFi during the follow-up period. The 30-day mortality following SI was 10.4% (95% CI 9.2-11.6%). The baseline demographics are presented in Table 1. Lower respiratory tract infections were the most frequently observed SI (42% of all events), followed by skin (19.5%), gastrointestinal (10.6%) and genitourinary infections (10.1%). Sixty days after an index SI, most patients (72.5%) were recorded as continuing TNFi, 21.3% had stopped drug and 6.2% had switched to an alternative drug class (rituximab or tocilizumab). Comparing baseline characteristics, patients who switched drug class were younger, more likely to be male, smokers, steroid users, have higher DAS28 and lower HAQ compared to patients who continued or stopped TNFi following SI. Irrespective of the index SI organ class, most patients had continued TNFi 60 days post index SI. Patients who suffered musculoskeletal infections had the highest percentage of patients still ‘off drug’ at 60 days (31%) however, most patients (69%) had restarted biologic therapy.

During the 12-month follow up period, there were 223 recurrent SI events. The rate of recurrent SI in the whole cohort was 25.6% per annum (95%CI 22.5-29.2). The rate of recurrent SI was highest in patients who at day 60 were still off their TNFi;
42.6% per annum (95%CI 32.5-55.7). Amongst this cohort, 8% had restarted a biologic prior to having a second event whilst 92% had not received any further biologic therapy prior to their recurrent infection. The rate of recurrent SI was 23.2% per annum (95%CI 19.9-26.9) in patients who continued TNFi following SI and lowest in patients who switched TNFi to a biologic with an alternative mode of action (12.1% per annum, 95%CI 3.9-37.4).

In an adjusted multivariate Cox model, compared to patients stopping biologic therapy, patients who continued or switched drug class had a significantly lower risk of recurrent SI (drug continuation Hazard Ratio (HR) 0.54, 95%CI 0.40-0.74, drug switch HR 0.29, 95%CI 0.09-0.95). Other predictors of recurrent SI included female gender, increasing age and baseline steroid use (Table 2).

Discussion:

Sixty days after an index SI, most patients were recorded as continuing TNFi. The recurrent SI rate was lower in patients who continued TNFi or switched drug class following a SI compared to patients who had not restarted TNFi at 60 days. Either there is a clinical advantage of continuing biologic immunosuppression following a SI or this reflects a channelling bias.

Higher DAS28 is an independent predictor of SI [12]. Earlier re-introduction of biologic therapies may have provided better disease control and therefore lower the risk of recurrent SI. In those who stopped their biologic following SI, there may have been higher corticosteroid exposure to manage their RA. This strategy may convey a higher infection risk than biologic treatment. Alternatively, patients at the highest SI risk could have been channelled away from continuing biologic therapy.

The risk of suffering a recurrent SI was lowest in patients who switched biologic therapy class to either tocilizumab or rituximab. This group were younger, with higher
DAS28, lower HAQ and lesser polypharmacy burden compared to the other groups. These patients may represent the ‘fittest’ in the cohort with a lower baseline SI risk hence the significantly lower hazard of suffering a recurrent SI. Caution should be exercised in interpreting this result as the number of patients who switched biologic was low and HR 95%CI were wide. Infection incidence rates are similar across biologic drug classes [13, 14]. A recent study comparing the risk of SI in patients who had failed a TNFi and switched to either rituximab or a second TNFi found no significant difference in SI risk between drugs [15]. It is difficult to explain the lower risk of SI in biologic switch patients by the different infection risk profiles of rituximab or tocilizumab.

The traditional predictors of SI (disease duration, smoking, seropositivity, DAS28, HAQ) were not significantly associated with an increased risk of recurrent SI in the adjusted Cox model. The lack of association is likely to be spurious and may be explained by selection bias.

There is limited data in the literature regarding biologic prescribing decisions following SI and the risk of recurrent SI. Using American Medicare data, Yun et al. [16] reported similar proportions of patients continuing, stopping and switching biologic therapies following SI. Compared to our results, a higher rate of recurrent SI (34.6 per 100 patient-years) was reported in patients continuing TNFi following SI. This is likely explained by an older, more steroid dependent cohort and by differences in study methodology. Accort et al. [17] considered the incidence of recurrent SI in patients treated with either a TNF inhibitor, other biologic and non-biologic anti-rheumatic drug across a variety of inflammatory rheumatological indications. Patients treated with a TNFi in combination with a non-biologic DMARD had a lower risk of recurrent SI compared with patients treated with a non-biologic DMARD alone. This may be
explained by either better disease activity control supporting our results or channelling bias.

A strength of the BSRBR-RA is robust coding of adverse events and prospective data capture. However, the 6-monthly data capture schedule may have affected the accuracy of infections recorded, timing and the treatment decisions made. We manually reviewed the dataset and validated the patients in whom the subsequent biologic treatment decision post SI wasn’t apparent to maximise data accuracy.

Although we adjusted for steroid exposure at baseline, the BSRBR-RA lacks detailed longitudinal data regarding steroid use. It was not possible to determine whether the steroid exposure, and particularly the dose, was higher in subjects who stopped biologic after SI compared to those who continued or switched therapy. Similarly, we accept that DAS28 and HAQ score at the time of infection was not adjusted for. This relates to the schedule of data capture.

It is likely that the fittest patients who were at the lowest baseline risk of experiencing recurrent SI were preferentially channelled to restart biologic post SI. Frailer patients may have been channelled towards stopping biologic drug due to the risk of recurrent SI associated with restarting biologic being too high.

It was not possible to adjust for the heterogeneity or severity of SI. It is plausible that the patients who suffered the most serious infections remained off drug. Using length of hospital stay as a surrogate marker for SI severity was not a robust method as there are many confounding factors that could increase length of hospitalisation aside from infection. By using polypharmacy as a comorbidity surrogate, we avoided the need to use multiple categorical variables in to regression models. Sensitivity analyses adjusting for comorbidities individually made no meaningful difference to our results.
Patients selected to continue or switch immunosuppression after their index SI had a lower recurrent SI rate compared to those who stopped immunosuppression. We advise exercising caution when interpreting our results. It would be wrong to assume a directly causal explanation as channelling bias is inevitable. We acknowledge unmeasured confounders for which we cannot adjust. We are unable to answer merits of choosing to switch or continue biologic class after SI. The risks and benefits of restarting immunosuppression following a SI need to be carefully considered on an individual patient basis.

**Key messages:**

1. Most patients who experience SI on TNFi re-start biologic within 60 days.
2. Recurrent SI are common; 26% annual risk of recurrent SI following an index event.
3. Channelling fitter patients to restart biologics after SI may explain lower recurrent SI rates.

**Disclosures:**

The BSRBR-RA is a UK-wide national project to investigate the safety of biologic agents in routine medical practice. This work was supported by the British Society of Rheumatology, which receives restricted income from UK pharmaceutical companies, presently Abbvie, Celltrion, Hospira, Pfizer, Union Chimique Belge and Roche, and in the past Swedish Orphan Biovitrum and Merck.

**Acknowledgements:**

The authors acknowledge support from the National Institute of Health Research (NIHR) Biomedical Research Centre based at Guy’s and St. thomas’ NHS Foundation Trust and King’s College London.
References:
1 Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: A population-based study. Arthritis and Rheumatism 2002;46(9):2287-93.
6 Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: What drives the time-dependent decrease in serious infection rates under


14 Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for

15 Silva-Fernandez L, De Cock D, Lunt M, et al. Serious infection risk after 1 year between patients with rheumatoid arthritis treated with rituximab or with a second TNFi after initial TNFi failure: results from The British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology 2017:16.


<table>
<thead>
<tr>
<th></th>
<th>Overall Cohort</th>
<th>Drug Stopped at Day 60</th>
<th>Drug Continued at Day 60</th>
<th>Drug Switched at Day 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number (n)</td>
<td>1583</td>
<td>337</td>
<td>1148</td>
<td>98</td>
</tr>
<tr>
<td>Mean baseline age, years (SD)</td>
<td>65.4 (11.4)</td>
<td>65.3 (10.7)</td>
<td>65.6 (11.6)</td>
<td>60.9 (11.8)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>1130 (71.4)</td>
<td>236 (70.0)</td>
<td>828 (72.1)</td>
<td>62 (63.3)</td>
</tr>
<tr>
<td>Mean disease duration, years (SD)</td>
<td>12.9 (9.6)</td>
<td>13.3 (9.9)</td>
<td>12.8 (9.6)</td>
<td>12.3 (9.0)</td>
</tr>
<tr>
<td>Baseline DAS28 score (SD)</td>
<td>6.56 (1.04)</td>
<td>6.50 (1.06)</td>
<td>6.56 (1.05)</td>
<td>6.72 (0.98)</td>
</tr>
<tr>
<td>Baseline HAQ score (SD)</td>
<td>2.06 (0.58)</td>
<td>2.05 (0.56)</td>
<td>2.06 (0.58)</td>
<td>1.99 (0.57)</td>
</tr>
<tr>
<td>Baseline oral steroid use, n (%)</td>
<td>745 (47.3)</td>
<td>169 (50.6)</td>
<td>540 (47.0)</td>
<td>53 (54.6)</td>
</tr>
<tr>
<td>Current smokers at baseline, n (%)</td>
<td>348 (22.1)</td>
<td>77 (23)</td>
<td>249 (21.7)</td>
<td>28 (28.6)</td>
</tr>
<tr>
<td>Seropositive (rheumatoid factor or anti-CCP antibody), n (%)</td>
<td>1026 (65.7)</td>
<td>238 (71.5)</td>
<td>743 (64.7)</td>
<td>60 (62.5)</td>
</tr>
<tr>
<td>Polypharmacy at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5 drugs</td>
<td>670 (42.2)</td>
<td>134 (39.8)</td>
<td>490 (42.7)</td>
<td>50 (51.0)</td>
</tr>
<tr>
<td>6-10 drugs</td>
<td>766 (48.4)</td>
<td>169 (50.2)</td>
<td>554 (48.3)</td>
<td>38 (38.8)</td>
</tr>
<tr>
<td>&gt;11 drugs</td>
<td>147 (9.3)</td>
<td>34 (10.1)</td>
<td>104 (9.1)</td>
<td>10 (10.2)</td>
</tr>
</tbody>
</table>

Table 1: Baseline demographics of patients with at least one serious infection whilst on TNFi therapy

Legend: n – number, SD – standard deviation, DAS28 – disease activity score 28 joints, HAQ – health assessment questionnaire, TNFi – tumour necrosis factor inhibitor therapy, anti-CCP = anti-cyclic citrullinated peptide
<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug cessation</td>
<td>REF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Drug continuation*</td>
<td>0.54</td>
<td>0.40 to 0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug switch*</td>
<td>0.29</td>
<td>0.09 to 0.95</td>
<td>0.041</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.49</td>
<td>1.06 to 2.08</td>
<td>0.019</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.02</td>
<td>1.01 to 1.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration</td>
<td>1.00</td>
<td>0.98 to 1.02</td>
<td>0.657</td>
</tr>
<tr>
<td>Current smoking at baseline</td>
<td>1.10</td>
<td>0.75 to 1.62</td>
<td>0.616</td>
</tr>
<tr>
<td>Baseline DAS28 score</td>
<td>0.91</td>
<td>0.79 to 1.04</td>
<td>0.158</td>
</tr>
<tr>
<td>Baseline HAQ score</td>
<td>1.40</td>
<td>1.06 to 1.86</td>
<td>0.019</td>
</tr>
<tr>
<td>Seropositivity (rheumatoid factor or anti-CCP antibody)</td>
<td>0.67</td>
<td>0.51 to 0.88</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline steroid use</td>
<td>1.47</td>
<td>1.12 to 1.93</td>
<td>0.006</td>
</tr>
<tr>
<td>Polypharmacy at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-10 drugs</td>
<td>1.00</td>
<td>0.75 to 1.34</td>
<td>0.988</td>
</tr>
<tr>
<td>&gt;11 drugs</td>
<td>1.39</td>
<td>0.90 to 2.14</td>
<td>0.141</td>
</tr>
</tbody>
</table>

Table 2: Fully adjusted Cox model considering predictors of recurrent serious infection in biologic users with prior serious infection

Legend: 95% CI = 95% Confidence Interval, DAS28 = Disease Activity Score 28, HAQ = Health Assessment Questionnaire Score, * compared to drug cessation, anti-CCP = anti-cyclic citrullinated peptide