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Emerging therapies for pre-RA

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Abstract (150 words)

The field of rheumatology has made major contributions to medicine through the identification of cellular and molecular targets, and the development of therapies for the treatment of an impressive range of immune mediated inflammatory diseases. In recent years new milestones have been achieved. These include the recognition of an at risk state, characterized by disease specific autoantibodies in serum and inflammatory joint pain, and the initiation of studies seeking to prevent high risk individuals from progressing to a state of clinically apparent arthritis. Here, the current state of the art of RA prevention is described, highlighting the importance of risk stratification and reporting on a growing portfolio of therapeutic interventions targetting different stages of the preclinical syndrome.

Key words: at risk, risk stratification, RA prevention, arthralgia, ACPA

Goal setting in pre-RA

We are familiar with concepts of goal setting in clinical medicine [1]. As rheumatologists we are committed to adopting best practice, based on the available evidence, while at the same time addressing the concerns and expectations of patients presenting for the first time with signs and symptoms of inflammatory arthritis.

Patients with newly diagnosed rheumatoid arthritis (RA) want to know about likely outcomes of their disease so as to help them manage their work, their social lives, and domestic commitments. By applying concepts of intensive therapy according to local and national guidelines [2], physicians can have some confidence in communicating the likelihood of a good clinical response to disease modifying drugs, and the longer term prospects of disease remission. Such outcomes have been considered as realistic goals for some years [3].

The natural history of the complex and heterogeneous disease entity that we call RA encompasses milestones which, arising over time in ways that may be difficult to define with any precision, include exposure to environmental agents (dietary factors, toxins and pathogens), triggering of immune reactions and the development of joint symptoms [4, 5]. In addition to genetic risk [6], these events are considered critical factors that render an individual to be “at risk”. Goal setting in the context of the pre-clinical phase of RA is much less advanced as it is for established disease. This has as much to do with the variable duration of this pre-clinical phase as it has to do with our understanding of risk, and its stratification. Any therapy that targets the pre-clinical phase of RA, could therefore be viewed as a prevention strategy.

Theoretically, prevention is a rational goal, and becomes a realistic one if we can better understand the immunobiology that underpins the “at risk” state.

What might be the realistic goals for RA prevention given the current state of knowledge? The answer to this question lies in the definitions of prevention [7].

Primary prevention seeks to avoid a disease from developing. For individuals targeted for primary prevention strategies it is implied that features of the disease are absent. Good examples include vaccination to protect against foreign pathogens, or smoking cessation strategies. Secondary prevention applies methods to detect and address an existing disease before the onset of symptoms, and before the disease fully develops. The treatment of hypertension or hyperlipidaemia is a good example.

Tertiary prevention aims to return the patient with established disease to full physical, mental and social health, reducing the harm of active, symptomatic disease, by treatment and rehabilitation. This strategy is central to our approach to managing patients with established RA [2]. As rheumatologists we also recognize the concept of quaternary prevention in which strategies are actively applied to mitigate against the effects of unnecessary or excessive interventions.

With these definitions in mind, what are the options for RA prevention? Primary prevention would necessitate intervention (lifestyle modifications, drug therapy or otherwise) during the asymptomatic phase prior to detection of RA-associated autoantibodies. Here, risk would be attributable to genetic, demographic and lifestyle factors, as well as family history. Defining an optimal duration for intervention, including changes in lifestyle behaviours, would be challenging, and the risks of therapeutic intervention would need to be weighed against the relatively modest risk of developing disease over an extended period of time. Secondary prevention strategies would aim to target the higher risk individual who, in addition to the above

risk factors, has joint symptoms and carries serum autoantibodies associated with RA; higher risk is linked to the combination of rheumatoid factor and ACPA, or high titre ACPA, and to sub-clinical evidence of synovitis or osteitis defined by imaging modalities. While tertiary prevention is less relevant to the current discussion, concepts of quaternary prevention that address issues around risk and benefit of intervention are highly relevant. These are discussed below. Thus, based on our current knowledge and understanding of RA risk, a realistic goal for treating individuals during the pre-clinical phase of RA most closely aligns with concepts of secondary prevention. With this in mind, the remaining discussion focuses on emerging therapies that aim to prevent (or delay) the onset of established disease in symptomatic individuals deemed to be at high risk.

A pragmatic approach to recognising the “high risk” individual

The contributions of specific factors that confer risk of developing RA have been described in previous chapters in this series, and so require no further in depth discussion here. Guidelines have been published that describe the essential features of the different phases of the at risk state, with the intention of harmonizing research studies and clinical trials [8]. Nonetheless, in the clinical setting a systematic assessment of such factors is required to allow the supervising physician to make an objective assessment about the phase of RA (“pre-clinical phase” versus “onset imminent” versus “very early established”), and the level of risk. Assuming the ACR/EULAR 2010 criteria for the diagnosis are not met (9), and there is no evidence of clinically apparent synovitis, then these two factors will best determine whether therapeutic intervention as part of a secondary prevention strategy is indicated, whether additional investigations are required or whether a judicious period of

monitoring is more appropriate. These key assessments, which can be acquired through structured questionnaires and clinical examination are summarized in *Practice Points*, and have been informed by recent published guidelines [10]. To further refine this assessment additional information can be included, depending on local resources, focused around imaging (high resolution ultrasonography – HRUS [11-13], and magnetic resonance imaging - MRI [14]), serology (maturation of the immune response through epitope spreading and isotype usage [15]) and tissue biopsies (lymph node and synovium [16-18]). Algorithms and risk scores, and how they can impact the outcome of interventional studies, have been reported that allow stratification of risk based on the likely outcomes over time [19-23]. These can inform discussions with patients, with the caveat that risk strata are based on populations, and that more precise risk predictions are likely to be forthcoming when the immunobiology of the preclinical phase and its transition to established disease is better understood.

While application of many of these tools are at an experimental stage and are yet to be validated in large pre-RA cohorts before translation to the routine clinical setting, they can provide fundamental information that will allow the supervising rheumatologist to discriminate between an individual with clinically suspect arthralgia and evidence of autoimmunity (“at risk” but time of onset is unpredictable; monitoring maybe appropriate with no intervention), and an individual with joint symptoms, a maturing autoimmune response, combined with osteitis by MRI and subclinical synovitis and tenosynovitis by HRUS, who has a significant likelihood of developing RA within 2-3 years [14]. These high-risk subjects, in whom it is reasonable to conclude that “*the disease has started*” should be considered for

therapeutic intervention. In the absence of evidence based guidelines, the options are either empirical or, preferably, enrollment in a clinical trial. Either way, decisions are likely to be influenced by patient and public perception of risk. In the context of rheumatic disease, this is an area of great interest, and of importance if progress is going to be made.

How do we identify at risk subjects?

A growing appreciation and recognition of the “at risk” phenotype then prompts two questions. Firstly, have the rheumatology community reached a stage at which active screening to identify at risk subjects in the community has become priority?

Secondly, what pathways would allow rheumatologists to capture at risk individuals in a cost effective way? These questions are of particular relevance to the clinical trial setting in which the recruitment of at risk individuals to RA prevention studies is already a major challenge. For purposes of discussion, I focus here on the at risk subject defined simply as an ACPA positive individual with inflammatory joint pain.

In addressing the first question one is minded of the World Health Organisation’s guidelines for screening or “Wilson’s Criteria”, where strategies focus on identifying the possible presence of an as yet undefined disease [24]. While a screening approach may be “universal” (targeting all subjects in a certain category) or “case finding” (involving a smaller group of individuals deemed to be at risk), the principles and practice of screening for disease, published by the WHO in 1968, remain the same. These principles were revised in 2008 with advanced molecular and genomic technologies in mind (Table 1) [25].

These guidelines highlight some of the challenges faced by establishing such a screening programme, not least being the cost, the potential stress and anxiety associated with risk, or by a false positive result. Perhaps the most important, highlighted in Table 1, are that there should be a treatment for the condition, and an agreed policy on whom to treat. These are two areas for which there is no consensus for the preclinical phase of RA, and so for these reasons alone, it would seem premature to consider population based screening policies.

The second question addresses pathways to capture individuals for assessment of risk. This can be achieved in a number of ways, without the need for a formal screening process. Given that the task of identifying at risk subjects and their subsequent assessment should be undertaken by experts in the diagnosis and treatment of patients with inflammatory arthritis, it is logical that Early Arthritis Clinics would operate as the coordinating unit for such activity in most centres. The flow of at risk subjects would likely arise through, or be influenced by, one or more of the following routes:

- (1) Early Arthritis Clinics: this route is deemed opportunistic. Referrals from general practitioners in primary care would be enriched for subjects with inflammatory joint pain. Some will have tested positive for rheumatoid factor (RF), some for anti-CCP and some will have tested positive in both assays.
- (2) Active engagement with primary care: an increased awareness of the concept of the preclinical phase of RA, and the phenotypes of “at risk” individuals, influences the threshold for RF and/or anti-CCP testing in the community.
- (3) Primary care database searches: databases in primary care provide ideal platforms to screen for subjects with joint pains. Search strategies can be

stratified by gender, age and, if already available, positive testing for RA associated autoantibodies. At the same time concurrent medications will identify those who have already been given a diagnosis of RA or other form of inflammatory arthritis.

- (4) Screening of clinical laboratory results: autoantibody tests are provided by the majority of NHS Trusts in the UK. Some of the larger and more specialised clinical immunology laboratories, often those affiliated with a clinical immunology service, may serve multiple hospitals. Depending on the unit, laboratories may run many thousands of tests per year, including but not confined to requests from local rheumatology services. Experience suggests that positive results may slip through the net. These may include testing initiated outside the rheumatology setting, such as from the emergency room or from other medical specialties.
- (5) Education and public engagement: concepts of screening and prevention for cardiac disease and cancer are better appreciated than those emerging for rheumatic disease. Campaigns aimed at educating the public about rheumatic symptoms increase awareness of risk, and will prompt assessments in primary and secondary care. RheumaBus provides one good example, specifically focused on screening for subjects with inflammatory sounding joint pains “on the high street” [26].

These examples highlight the notion that success in identifying subjects at risk of developing RA depends not only on awareness of primary and secondary care physicians, but on at risk individuals themselves.

What are the logical treatment options for pre-RA?

A systematic approach to exploring appropriate therapy choices for pre-RA must necessarily be underpinned by the disease's natural history (Figure 1) [8]. Using this schematic as a framework, at least two factors are likely to determine, ultimately, the treatment options, the time frame, and the level of risk. During Stages A and B, the risk may be modest, while the timeline to disease onset could be measured in terms of many years, even decades. Subjects with a family history of RA carrying heritable factors but who are yet to demonstrate any serological evidence of autoimmunity may fit in this category. Given that there exists evidence for such environmental factors [27-31], and assuming these epidemiological factors associated with established disease are also linked to disease initiation, such subjects would be ideally suited to modifiable lifestyle changes such as weight loss, dietary manipulation, cessation of smoking and possibly aggressive treatment of periodontal disease. While application and monitoring of such an intervention is a challenge, the risks are negligible (and indeed are likely to be highly beneficial to general health status), and likely to have impact over extended periods of time if such lifestyle modifications are strictly adhered to.

Stage C, still in the asymptomatic phase, heralds the onset of autoimmunity, manifest by the presence of autoantibodies. The autoantigenic specificities provide unique clues as to the antigenic targets of the pathogenic autoimmune response in that particular individual. In this group of individuals a precision medicine approach might take the form of targeted immune modulation, along the lines of cell-based immunotherapy – systemic or localised or a peptide based vaccination strategy [32, 33], or an immunodulatory approach adopted for treating the early phase of

autoimmune diseases such as type 1 diabetes [34]. Ideally, the period of treatment or frequency of dosing would be dictated almost exclusively by evidence of immune modulation, for example seroconversion. The application of biological therapies during stage C is a biologically plausible option, but might favour therapeutic agents that target adaptive immune responses.

Stage D is defined by the presence of symptoms and a substantial increased risk in developing RA. At some early phase of stage D, which may be difficult to define with precision, evidence of subclinical inflammation either in bone marrow, tenosynovium or the synovium itself, or combination of these would manifest itself. Arguably, the disease has started and so therapies proven to be efficacious in slowing the progression of undifferentiated arthritis to RA [35, 36], or in treating very early RA would be plausible candidates. This might include synthetic DMARDs, biological DMARDs or a combination of these agents. Whether it is already too late for a tolerogenic immunomodulatory approach is not known, but agents likely to have an immunomodulatory as well as anti-inflammatory mechanism of action might be preferred. Interventional approaches to intervene at each stage of the natural history of RA are summarised in Figure 2.

This staged approach raises a number of questions. How does one balance the risk versus benefit of each intervention? What is the optimal duration of “preventive therapy”? How should each intervention be evaluated, and what are the realistic clinical and laboratory endpoints? Further experience in treating RA in its preclinical phase is required before the answers to these questions emerge. We can predict with some confidence, however, that traditional assessments of disease activity applied to

established disease may not be sensitive enough for evaluating subjects with pre-RA, or even relevant under circumstances where symptoms are modest or absent. This points to the need for a set of laboratory tools that define, or are at least surrogate markers of, immune function – specifically adaptive and innate immune reactions linked to disease specific autoimmune responses. These and related molecular tools may also be applied to stratify the disease in its earliest phase, according to transcriptomic signatures in whole blood, as has been done for more established disease [37]. Whether such signatures would stratify the disease more or less cleanly remains to be determined.

Therapies for pre-RA; what is the current evidence?

Whilst there is considerable ongoing effort aimed at understanding the immunobiology of pre-RA there are currently no recommendations or guidelines for treating subjects at high risk of developing the disease. At this time, clinical trial data are limited, having until very recently focused on exploring the effects of interventions on the transition from undifferentiated arthritis to RA. These studies are relevant to the discussion and so are summarized briefly below.

The PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment (PROMPT) study was a randomized, placebo controlled clinical trial that recruited 110 subjects with probably RA, according to ACR 1958 criteria, of symptom duration less than 2 years [35]. Subjects were randomized to receive methotrexate or placebo and followed up for 30 months. The primary endpoint was the development of the ACR 1987 classification criteria for RA. While progression occurred in both groups at rates of 40% (methotrexate) and 53% (placebo), subjects randomized to the

methotrexate group developed RA significantly later. Sub-group analysis demonstrated striking differences between placebo and methotrexate groups in anti-CCP positive patients, with 14/15 patients progressing earlier in the placebo group (93%) compared to 8/12 in the methotrexate group (67%); no differences were observed in anti-CCP negative patients. Lower radiographic progression was documented in the anti-CCP positive methotrexate group. The study concluded that methotrexate delays the onset of anti-CCP positive RA, prolonging the period of undifferentiated arthritis without altering remission rates. Spontaneous remission rates in the placebo group, as well as reduced efficacy in the anti-CCP negative group suggests that the potential for over-treatment with methotrexate is a significant issue in patients with UA. A follow up study from the PROMPT investigators, confirmed the importance of stratification to uncover therapeutic effects [23].

In 2009, investigators in the UK reported the benefits of corticosteroids in patients with very early inflammatory arthritis [38]. In the STIVEA trial, 268 subjects were randomized to receive either three weekly injections of placebo or 80 mg intramuscular methylprednisolone. Criteria for enrollment included a requirement for tenderness and soft tissue swelling of two or more joints, at least one of which had to involve small joints of the hand or wrist, and symptom duration of between 4 and 10 weeks. The primary endpoint was the need to start DMARDs at the 6 month visit. Patients in the placebo group received more DMARD therapy by 6 months than those in the corticosteroid group (76% versus 61%; adjusted Odds Ratio 2.11), with median DMARD-free survival of 2.8 months in the placebo group and 8.3 months in the corticosteroid group. For those subjects who had progressed to RA (60.4% for placebo and 48.6% for corticosteroid treated patients), disease activity scores by 12

months were similar. However, by 12 months signs and symptoms of arthritis had resolved in more subjects treated with corticosteroid compared to placebo (22/111 versus 11/111). Overall the treatment was well tolerated. These data indicate that very early use of corticosteroids delays the onset of inflammatory arthritis and may prevent progression to RA in up to 10% of patients presenting with very early inflammatory arthritis.

In a similar, slightly larger investigator-led, multi-centre, randomised placebo controlled trial of corticosteroids in patients with very early arthritis, 383 patients with symptom duration less than 16 weeks were randomized to receive a single intramuscular injection of 120mg methylprednisolone or placebo [39]. Dual primary endpoints were drug free remission at 12 and 52 weeks. By one year almost 50% of subjects were diagnosed with RA, and 30% with undifferentiated arthritis. This “*real-life-like*” study failed to demonstrate significant differences between treatment groups in terms of disease remission or the requirement for DMARD therapy, with transient benefit only being demonstrated in the corticosteroid group at 2 weeks. Otherwise, the study medication was well tolerated. Remission rates across both treatment arms were substantially higher in those reporting symptoms for less than 8 weeks, especially those with oligoarticular symptoms, suggesting an increased tendency towards spontaneous remission in subjects presenting with symptoms of short duration. This raises important issues around benefit versus risk, and once again emphasise the importance of risk stratification.

In 2010, Emery and colleagues examined the impact of abatacept, the first in class co-stimulatory blocker, on clinical and imaging in 56 patients with undifferentiated

arthritis or very early RA in the phase II ADJUST study (Abatacept study to Determine the effectiveness in preventing the development of rheumatoid arthritis in patients with Undifferentiated inflammatory arthritis and to evaluate Safety and Tolerability) [36]. Inclusion criteria mandated testing positive for anti-CCP and clinical evidence of synovitis in two or more joints. Enrolled subjects were randomized to receive either i.v. abatacept (10mg/kg) or placebo for a period of 6 months, after which study medication was stopped; non-steroidal anti-inflammatory drugs or stable doses of low dose prednisolone ($\leq 10\text{mg}$ daily) were permitted. The primary endpoint was fulfillment of the ACR 1987 classification criteria for RA at 12 months. Mean symptom duration was 7.9 months. After one year 12/26 (46.2%) of abatacept and 16/24 (66.7%) of placebo treated patients had met the ACR criteria for RA; thus the primary endpoint was not met. However, DAS28-defined remission rates were superior in the abatacept treated group (71.4% versus 35%). Analysis of anti-CCP levels demonstrated seroconversion to anti-CCP negative status in 2/22 patients at 6 months and 2/15 at 12 months in the abatacept group, while all placebo treated subjects remained anti-CCP positive. This suggests an impact of abatacept on the autoimmune response in a subset of patients. Of the subgroup of patients undergoing MRI, erosion, osteitis and synovitis scores were superior in the abatacept treated group. Adverse events were comparable in the two treatment arms. This small study demonstrated that abatacept treatment for 6 months alters the progression of inflammatory arthritis, but was not adequately powered to demonstrate evidence of prevention or delay.

Taken together these studies highlight the heterogeneity of the syndrome we define as very early RA or undifferentiated arthritis, as well as the variable responses to

therapy. The trial outcomes point to the impact of very early intervention in subjects with clinically apparent arthritis being more aligned with disease modification rather than disease prevention or delay, and further emphasise the need for well designed clinical trials to define optimal approaches for RA prevention in a high risk group. These therapeutic strategies may not necessarily be the same as those that have proven effective at the onset of disease.

Clinical trials in high-risk subjects

Targeting subjects with inflammatory sounding joint pain (“arthralgia”) is particularly attractive because whilst the duration of presymptomatic and early symptomatic phases are variable, they are likely to be protracted for at least a subset of individuals. This offers a therapeutic window during which the autoimmune and very early inflammatory responses are amenable to perturbation in ways that may halt the disease process, or at least delay disease onset. Clinical trials of at risk subjects also provide an ideal platform for conducting experimental medicine studies focused around deep immune phenotyping and imaging. This information would seek to further refine and stratify individuals by cellular and molecular signatures during this at risk phase, and optimise time points for intervention.

In spite of our improved understanding of the preclinical phase of RA, there are few trials reported to date that describe therapeutic interventions in anti-CCP positive arthralgia subjects. Two studies are noteworthy. In 2010, the group of van Schaardenburg reported the results of the first pilot RA prevention study, comparing intramuscular injections of dexamethasone (100mg) at baseline and 6 weeks with placebo in 83 at risk subjects with no clinically apparent synovitis [40]. The presence

of the HLA-DRB1 shared epitope was also a requirement. The primary endpoint was at least a 50% reduction in autoantibody levels at 6 months. While dexamethasone significantly reduced median levels of IgM rheumatoid factor and anti-CCP levels with a nadir after one month, it failed to prevent RA. After 26 months of follow up 9/42 in the dexamethasone group and 8/41 in the placebo group had developed clinically detectable synovitis in a median of 4 joints. DAS28 scores were comparable. No detailed imaging was included in the study protocol and so it was not possible to determine whether enrolled subjects had subclinical undifferentiated arthritis. The results indicated that either prolonged therapy was required or that corticosteroid therapy is not sufficient to prevent onset of RA.

Initial results of the first study of a biological agent application to RA prevention led by Tak, Gerlag et al, were presented at the European League Against Rheumatism (EULAR) annual congress in 2016 [41]. Specifically, this study set out to examine the effects B cell depletion in at risk subjects defined by arthralgia, the presence of disease specific autoantibodies (RF and ACPA), a raised CRP or evidence of subclinical arthritis by ultrasonography or MRI. Prevention of clinically manifest rheumatoid arthritis by B cell directed therapy in the earliest phase of the disease – the PRAIRI study –randomized 81 subjects to receive a single 1000mg iv infusion of rituximab or placebo. All study subjects received 100mg methylprednisolone prior to receiving study medication to prevent infusion reactions. During a median follow up of 29 months 30 patients developed arthritis, 16 (40%) in the placebo group and 14 (34%) in the rituximab group, differences that were not statistically significant. However, arthritis-free survival plots indicated that, on average, the arthritis onset in the rituximab treated group was delayed by 12 months. While details of tolerability

and adverse events are yet to be published, this is the first study to demonstrate that immune modulation is feasible and can delay disease onset in at risk subjects.

In both trials, study subjects received parenteral study medication on one or two occasions. This route of administration, and dosing schedules have obvious advantages, but the outcomes point to the possibility that the duration of perturbation is insufficient to halt disease progression, or that the targeting strategy is not the optimal approach for this phase of the disease. In both studies, the inclusion of subjects who already had subclinical evidence of joint inflammation (this is presumed in the dexamethasone study) may well have contributed to the clinical outcomes. If this is indeed the case, then prevention strategies must necessarily target earlier stages in the preclinical phase of RA at a time when inflammatory responses are absent, or explore alternative targeting strategies (Figure 2).

RA prevention studies in progress

In recent years, investigators have become more confident about the clinical and laboratory characteristics of the pre-clinical phase of RA. Recognition of the high-risk individual has facilitated fine tuning of the target population, allowing for rationale and pragmatic design of prevention studies. Ethics committees and Independent Review Boards also recognize that progression of high-risk individuals is sufficient to justify and approve studies that investigate a range of different approaches, and, importantly, a placebo arm. While all studies to date are investigator-led, the private sector is observing this research space with considerable interest. It is relevant to the discussion, therefore, to briefly describe RA prevention studies that are currently in set up or recruiting. While outcome data are yet to be

presented, the study designs are of interest and will surely inform future clinical trials seeking to target this population of at risk individuals. The positioning of these studies is included in Figure 2.

The Personalized Risk Estimator of Rheumatoid Arthritis (PRE-RA) Family Study is a prospective, open label, randomized clinical trial targeting first-degree relatives (FDR) of RA patients who do not have RA themselves. While not a clinical trial of an investigational medicinal product (CT-IMP), the goal is to better understand the willingness of at risk individuals to change lifestyle behaviours, focusing on four behavioural factors linked to RA risk: cigarette smoking, excess body weight, poor oral health, and low fish intake. Such a feasibility study is immensely important for providing a framework for future studies of this type. Consenting individuals are randomized to one of three interventions delivered by on line tool:

- (1) Comparison Arm: subjects will receive standard education about RA;
- (2) PRE-RA Arm: subjects will receive RA education and the PRE-RA tool, adapted from Your Disease Risk, which provides risk estimates for a range of diseases including cancer, heart disease and type 2 diabetes, to include an absolute lifetime risk estimate;
- (3) PRE-RA Plus Arm: subjects will receive the same as those randomized to the PRE-RA Arm plus intensive health education, including input from a trained health counselor. These subjects will also be given advice on how to change and sustain these behaviours. This information will be available to take home.

The primary outcome of the PRE-RA Family Study, measured using a variant of a visual analogue scale – a contemplation ladder, will evaluate the willingness to

change any of these 4 behaviours from baseline to 6 weeks, 6 months and 12 months. The study started in January 2014. Primary completion was in September 2016 and the study is scheduled to complete in June 2018. According to the publicly available data [clinicaltrials.gov], 238 subjects have been enrolled. This intriguing study, whose design was published in 2014 [42], will provide important insights into the challenges associated with making lifestyle changes for subjects informed about their risk of developing RA. The design will also provide important clues as to the optimal approach for changing and sustaining behaviours over time, although whether the same approaches applied to FDR will have similar impact in the general population will require further study. Regardless of these nuances, one anticipates that a very large longitudinal clinical trial would follow, requiring an extensive period of follow up.

Enrolling in the US since March 2016 is the Strategy to Prevent the Onset of Clinically Apparent Rheumatoid Arthritis (Stop-RA) study. This multi-centre, randomized, double-blind, placebo controlled clinical trial seeks to test whether hydroxychloroquine, taken at the 200-400mg dose for 12 months, is both safe and effective for the prevention of RA in 200 subjects who are positive for ACPA (> 2 times the upper limit of normal, equivalent to ≥ 40 units in the anti-CCP3 assay), with or without arthralgia. This approach is based on the observation that up to 50% of such individuals will develop RA over a period of 3 years, regardless of the presence of other risk factors. The primary outcome is the development of RA at 36 months, as defined by the 2010 ACR/EULAR criteria (≥ 6 points), or by a joint examination consistent with inflammatory arthritis with ≥ 1 erosion confirmed by X-

ray imaging of the hands, wrists, and feet. The study is actively recruiting, and the results are expected in the Spring of 2020.

Three RA prevention clinical trials are currently recruiting in Europe as of May 2017. The Arthritis Prevention in the Preclinical Phase of RA with Abatacept (APIPPRA) study recruited its first study subject in December 2014. This multi-centre, randomized, double-blind clinical trial is comparing the effects of 12 months treatment with weekly subcutaneous injections of abatacept (125mg) or placebo on preventing or delaying the onset of clinically apparent arthritis. The primary endpoint is the time to development of 3 or more swollen joints or fulfillment of the 2010 ACR/EULAR criteria for RA, confirmed by ultrasonography. The study is powered to detect a 50% reduction in arthritis development (from 40% to 20%) in the active treatment arm. Study subjects will receive treatment for 12 months and follow up for a further 12 months. The APIPPRA study protocol includes a parallel ultrasound study for all participants, overseen by trained ultrasonographers who are blinded to clinical assessments. Extensive biological sampling every 3 months will permit analysis of immunological signatures associated with the at risk state, progression to arthritis, and with response to intervention. The study is recruiting in the UK and Netherlands, with outcome data expected in Spring 2020.

A similarly designed RA prevention study is currently enrolling in the Netherlands – the TREAT EARLIER study, in which enrolled subjects who are ACPA positive or negative will be randomized to receive intramuscular steroids and methotrexate or placebo. A combination of clinical, serological and MRI imaging are being used to identify high-risk subjects. The primary outcome will be the frequency of clinically

detectable arthritis fulfilling the 2010 criteria for RA or of unclassified arthritis with a SJC of more than 2 joints, both persisting for at least 4 weeks, obtained after 2 years. Subjects will be treated for one year, and followed up for a further year. The Statins to Prevent RA (STAPRA) study is a double-blind, placebo controlled study that will evaluate whether atorvastatin 40mg or placebo, taken for up to 3 years, can prevent or delay the development of clinically apparent arthritis. The trial seeks to recruit 220 study subjects, deemed to be at risk by virtue of carrying IgM rheumatoid factor and ACPA, or high titre ACPA ($\geq 3 \times$ upper limit of normal), in the absence of clinically apparent arthritis. The primary outcome is the development of clinical arthritis confirmed by a rheumatologist. It is anticipated that the study will be closed to recruitment by July 2020.

These novel interventional studies share a number of key features. Firstly, stratification has been prioritized, with the “at risk” individual being defined by the presence of RA-specific autoantibodies in serum, with or without the presence of symptoms, or stratification by imaging. A successful trial outcome will depend on the number of primary outcome events in the placebo arm, permitting meaningful comparison with the active arm, and this will be determined by an accurate estimate of the progression to disease of the sample population, which in turn will determine sample size. Secondly, to date these prevention studies include placebo arms, which will have distinct advantages around determining the impact of each intervention. Thirdly, the homogeneity of enrolling subjects, is also reflected in the similar sample sizes across studies - being around 200.

Summary and future perspectives

The field of rheumatology has reached a major milestone – namely the successful prosecution of clinical trials aimed at prevention or delaying the onset of RA. Two trials have completed, and several more are actively recruiting. In the coming years evidence will emerge that informs optimal study design. We also hope to learn whether or not therapies licensed for use in patients with established RA have an important place in RA prevention. Our current understanding of the evolution of the disease would suggest that prevention strategies may in fact turn out to be very different depending on the phase of disease, in the same way that primary, secondary and tertiary interventions differ in other conditions. A good example is the evolution and treatment of hypertension, which may range from lifestyle modifications (early), to pharmacological therapy (established), to the management of its complications including ischaemic heart disease and stroke (late).

The data to date point to the importance of risk stratification as an essential component of any prevention study. As evidence emerges, and our efforts to define risk become more refined, we will be able to test a wider range of interventions where the level of risk is far outweighed by the potential benefits.

Practice points: Clinical assessment of risk

History taking:

- Joint symptoms of recent onset (< 12 months)
- Symptoms localised to MCP joints
- Duration of morning stiffness ≥ 60 mins
- More severe symptoms present in the early morning
- First degree relative with RA

Physical examination:

- Difficulty making a fist
- Positive MCP joint squeeze test

Imaging:

- Ultrasound evidence of tenosynovitis
- Evidence of grey scale synovitis with power Doppler signal

Laboratory investigations:

- High titre anti-CCP antibodies (ACPA)
- Evidence of autoantibodies to multiple antigenic epitopes

adapted from van Steenbergen et al [10]

Research agenda

- The refinement of risk stratification algorithms
 - A better understanding of the immunobiology that underpins the preclinical phase of RA
 - The development of strategies to support and maintain adherence to lifestyle modifications for individuals at risk of RA
 - The development of pathways to identify subjects at high risk in the community
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Table 1: WHO guidelines for screening 2008 (adapted from ref 25)

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- The screening programme should respond to a recognized need.
 - The objectives of screening should be defined at the outset.
 - There should be a defined target population.
 - There should be scientific evidence of screening programme effectiveness.
 - The programme should integrate education, testing, clinical services and programme management.
 - There should be quality assurance, with mechanisms to minimize potential risks of screening.
 - The programme should ensure informed choice, confidentiality and respect for autonomy.
 - The programme should promote equity and access to screening for the entire target population.
 - Programme evaluation should be planned from the outset.
 - The overall benefits of screening should outweigh the harm.
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Figure legends

Figure 1: The natural history of RA. The preclinical phase of RA comprises multiple stages characterized by distinct clinical phenotypes. Figure adapted from Gerlag et al [8].

Figure 2: Overview of strategies for RA prevention. Points of intervention are highlighted (arrows). Completed studies are shown below the boxes, and clinical trials and studies in progress are listed above.

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Conflict of interest statement

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