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Citation

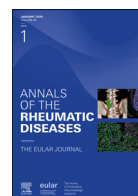
Deane, K. D., Holers, V. M., Emery, P., Mankia, K., Gabalawy, H. el, Sparks, J. A., ... Cope, A. P. (2024). Therapeutic interception in individuals at risk of rheumatoid arthritis to prevent clinically impactful disease. *Annals Of The Rheumatic Diseases*, 84(1), 14-28. doi:10.1136/ard-2023-224211

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).



Review

Therapeutic interception in individuals at risk of rheumatoid arthritis to prevent clinically impactful disease

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ARTICLE INFO

Article history:

Received 16 May 2024

Accepted 19 August 2024

Keywords:

Arthritis

Rheumatoid

Autoantibodies

Risk Factors

Anti-Citrullinated Protein Antibodies

Antirheumatic Agents

ABSTRACT

Multiple clinical trials for rheumatoid arthritis (RA) prevention have been completed. Here, we set out to report on the lessons learnt from these studies. Researchers who conducted RA prevention trials shared the background, rationale, approach and outcomes and evaluated the lessons learnt to inform the next generation of RA prevention trials. Individuals at risk of RA can be identified through population screening, referrals to musculoskeletal programmes and by recognition of arthralgia suspicious for RA. Clinical trials in individuals at risk for future clinical RA have demonstrated that limited courses of corticosteroids, atorvastatin and hydroxychloroquine do not alter incidence rates of clinical RA; however, rituximab delays clinical RA onset, and methotrexate has transient effects in individuals who are anticitrullinated protein antibody-positive with subclinical joint inflammation identified by imaging. Abatacept delays clinical RA onset but does not fully prevent onset of RA after treatment cessation. Additionally, subclinical joint inflammation and symptoms appear responsive to interventions such as methotrexate and abatacept. To advance prevention, next steps include building networks of individuals at risk for RA, to improve risk stratification for future RA and to understand the biological mechanisms of

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Handling editor Josef S. Smolen

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<https://doi.org/10.1136/ard-2023-224211>

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RA development, including potential endotypes of disease, which can be targeted for prevention, thus adopting a more precision-based approach. Future trials should focus on interceptions aimed at preventing clinical RA onset and which treat existing symptoms and imaging-defined subclinical inflammation. These trials may include advanced designs (eg, adaptive) and should be combined with mechanistic studies to further define pathophysiological drivers of disease development.

INTRODUCTION

The term ‘risk’ suggests that an action or event might happen. Importantly, it implies the event is associated with harm. In medicine, risk is related to factors (ie, risk or protective factors) that influence the likelihood of disease onset, or worsening of an existing disease, in individuals who have inherited or acquired those risk factors. While an ‘at-risk state’ can be silent or symptomatic, it can be detected through population-based screening programmes or more targeted approaches in individuals who are already known to be at higher risk for disease [1–3]. At-risk states can be further evaluated through ‘risk stratification’ approaches where higher or lower-risk states can be determined. As an example, the Fracture Risk Assessment Tool (FRAX) can risk stratify an individual’s risk for osteoporotic-related fracture [4].

Importantly, the concept of risk is closely linked to prevention. The WHO defines prevention as ‘approaches and activities aimed at reducing the likelihood that a disease or disorder will affect an individual, interrupting or slowing the progress of the disorder or reducing disability’ [5]. The WHO has also defined the different types of prevention. Primordial prevention is defined as prevention of exposures of populations to risk factors in the first place [6,7]. Primary prevention refers to actions aimed at avoiding or ameliorating the first apparent clinical manifestation of a disease (eg, vaccination against infectious pathogens), and secondary prevention focuses on early detection of a disease during a period in which it has not yet resulted in critical and permanent damage. Secondary prevention improves the chances of positive health outcomes when coupling early identification programmes with preventive drug therapies or other interventions of proven efficacy when administered at the appropriate stage of the disease, such as adopting lifestyle changes. Tertiary prevention includes actions taken to reduce the impact of an existing disease.

Notably, not all prevention strategies have as their primary goal the avoidance of a clinical or ‘symptomatic’ manifestation of a disease. Indeed, for cardiovascular disease (CVD), interventions are still considered beneficial if they can delay an event, or even lead to a less severe event if it does occur. With vaccines, it is also still considered beneficial if a less severe illness develops even if there was not a complete avoidance of infection (eg, SARS-CoV-2 vaccines reducing clinical severity of COVID-19 [8]). Furthermore, interventions in an at-risk stage of a disease may be considered ‘secondary prevention’; however, that term can be challenging to apply in many diseases, especially as understanding evolves of when disease starts, and also because there have been advances in technologies for identifying tissue injury that does not manifest itself through clinical signs and/or symptoms.

Rheumatologists often practice ‘secondary’ and ‘tertiary’ prevention by working to diagnose conditions early and then treating the diseases over time to improve well-being and prevent worse outcomes; rheumatologists also engage in ‘primary’ prevention such as administering vaccines. Importantly, however, a large portion of care for rheumatic diseases to date is based on the established paradigm of diagnosis and initiation of

therapy when an individual is identified as having an ‘illness’, typically characterised by symptom burden combined with physical findings of target organ damage (eg, arthritis, rash). In rheumatoid arthritis (RA) specifically, the approach has been to identify an individual that has clinical evidence of inflammatory arthritis (eg, a swollen joint consistent with synovitis) that can further be diagnosed as RA based on historical and examination features, blood tests and imaging [4,5]. However, considerations for the prevention of these first clinically defined manifestations of RA have generated substantial interest in recent years, arising in part through an increased understanding of the molecular and cellular features of the at-risk state, and, critically, the ability to identify and some extent stratify those who are at risk.

Furthermore, the identification of an at-risk state has underpinned the execution of clinical trials designed to prevent or delay the first onset of clinical and classifiable RA. Experience from these trials has defined key areas (box 1) that include improving risk stratification for RA and identifying key biological pathways to target for effective prevention, among others, that need to be addressed to further advance the field and make prevention an integral part of care not only for RA but also potentially for other rheumatic and autoimmune diseases. To address these areas, in this review rheumatologists who have led and/or extensively participated in these clinical studies share their collective experience in RA prevention, acquired over several decades through design and execution of observational studies and clinical trials.

Box 1 Key factors to develop effective rheumatoid arthritis (RA) prevention

- Identify, define and accurately risk stratify individuals who are at risk for RA.
- Develop infrastructure to identify individuals who are at risk for RA (eg, clinical networks, potentially public health screening campaigns).
- Understand stage-specific biology of disease development that can be exploited to improve risk stratification/prediction as well as define stage-specific pathways (or risk endotypes) that can be targeted in a precision-medicine approach in interventional studies.
- Design clinical trials with outcome measures appropriate for the at-risk state that effectively evaluate potential therapeutic targets for prevention as well as treat symptom complexes that may be present in the at-risk period; trials should include input from appropriate stakeholders (trial participants, investigators, sponsor and regulatory agencies).

Early insights into the at-risk state of RA and terminology

Our current understanding of the RA at-risk state, defined as the state that precedes the first appearance of a swollen joint, is described in figure 1. Notably, we define the state of a swollen joint detected on physical examination as ‘clinical RA’ which may or may not also meet established classification criteria for RA. This term is used in part because that is a standard that many clinicians adopt to diagnose and then recommend disease-

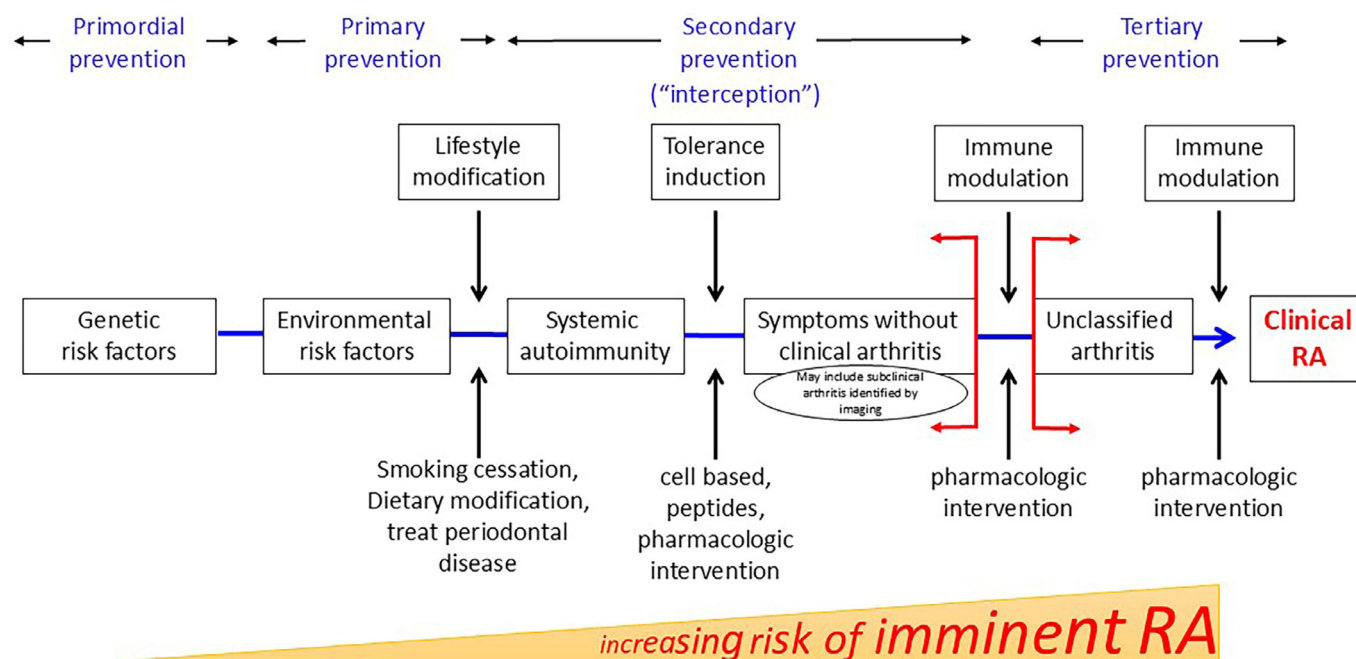


Figure 1. Disease prevention in the RA at-risk state. The different stages of the at-risk state are illustrated, aligned with potential interception check-points, with the choice of intervention reflecting the risk:benefit ratio. Although increasing risk of imminent RA is illustrated going left to right, progression through each stage is not inevitable for all at-risk individuals. It remains to be determined whether immune modulation could be considered for those at lower risk who have yet to develop evidence of autoimmunity. RA, rheumatoid arthritis.

modifying antirheumatic drug (DMARD) treatment for RA; furthermore, the presence of a swollen joint is a requirement to fulfil the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2010 RA classification criteria [9]. However, we acknowledge that imaging is increasingly being used to identify joint inflammation—and may be used to make a clinical diagnosis of RA in some cases, even if a swollen joint is not detectable on physical examination. As discussed in more detail below, the use of imaging to identify joint inflammation as a risk factor for future clinical RA, or used to define that clinical RA is present, is both an opportunity as well as a challenge that needs to be addressed.

Furthermore, at this time, we have favoured the term for the stage of RA that precedes the first swollen joint and where risk factors for RA are present as ‘at risk of RA’ or an ‘at-risk state’, rather than pre-RA. This is because pre-RA, a term not currently favoured by patient research partners unless used retrospectively in individuals who have developed clinical RA, implies a disease trajectory that is inevitable [10], while findings from cohort studies as well as the clinical prevention trials clearly demonstrate that not all individuals who have risk factors for RA (and may be considered in an at-risk state) progress to clinical RA (although it is acknowledged that some conditions commonly use ‘pre’ to define certain stages of disease for example, pre-diabetes [11]). Notably, the at-risk state can be further clarified through ‘risk stratification’, where there may be an overall increased risk based on the presence of some risk factors, but there are also varying levels of risk within that—we discuss this important point in more detail below. In addition, we adopt the term ‘imminent disease risk state’ for those individuals in whom risk stratification suggests that development of clinical RA is highly likely to occur within 12 months, although we acknowledge that accurately identifying individuals within this imminent state of developing clinical RA is a challenge that remains to be met, and we additionally discuss this in more detail below. We also wish to highlight that the constellation of symptoms

(eg, joint pain, stiffness, swelling and fatigue) that can be identified in part using patient-reported outcomes may constitute an illness that requires intervention, even if clinical RA is not present. Moreover, here, we use the term ‘interception’ to describe an intervention that is used to effect prevention of clinical RA and may use the terms ‘intervention’ and ‘interception’ interchangeably.

Defining, identifying and stratifying risk in individuals who are at risk for RA

Retrospective studies exploiting biobank samples have allowed the identification of biomarkers associated with the at-risk state, including autoantibodies and inflammatory markers such as cytokines and chemokines (figure 1 and table 1) [12–16]. While these studies have provided important insights into aspects of the natural history and biology of RA, some have limitations in that participants typically were not evaluated in real-time during the ‘at-risk’ period to determine the precise relationships between the evolution of autoantibodies and other markers and signs and symptoms of clinical RA. The case–control nature of many of the studies also limits the ability to develop robust prediction models for future RA. Fortunately, however, prospective studies of individuals at risk for future RA have been especially informative regarding these key points.

There are multiple approaches for prospective studies of the ‘at-risk’ state in RA (table 2, figure 2). These can include identification and study of individuals with genetic/racial or familial risk factors for RA. For example, individuals from populations who have high prevalence rates (eg, some North American indigenous groups) may be considered ‘at risk’ for RA [17]. Furthermore, relatives of an individual with established RA may be considered ‘at risk’ due to the known increased prevalence of RA in families [18]. Indeed, prospective studies of North American indigenous populations and family members of patients

Table 1
Biobanking and nested case–control studies demonstrating that autoantibodies and other biomarkers precede the diagnosis of seropositive clinical RA

Aho <i>et al</i> (1991 [82] and 2000 [83])	Finnish health-survey/biobank studies that identified RF and antibodies to filaggrin precede onset of clinical RA.
Rantapää-Dahlqvist <i>et al</i> [12] and Kokkonen <i>et al</i> [16]	Swedish biobank study demonstrating that RF isotypes and ACPA (by anti-CCP2 assay) as well as numerous cytokines and chemokines were elevated prior to RA diagnosis.
Nielen <i>et al</i> [13]	Dutch biobank study demonstrating that RF and ACPA (by anti-CCP first generation assay) were elevated prior to RA diagnosis.
Majka <i>et al</i> [14] and Deane <i>et al</i> [15]	USA Department of Defense biobank study demonstrating that RF and ACPA (by anti-CCP2 assay) were elevated prior to RA diagnosis and levels of cytokines/chemokines increase as diagnosis approaches.
Arkema <i>et al</i> [84]	USA Nurses' Health Study cohort reporting ACPA reactivity up to 10 years before RA onset. Those with high ACPA levels carrying the HLA-DRB1 shared epitope were at highest risk.

ACPA, anticitrullinated protein antibody; anti-CCP, anti-cyclic citrullinated peptide antibody; RA, rheumatoid arthritis; RF, rheumatoid factor.

with RA have yielded important insights into the natural history and risk factors of RA development [19–23].

Much of the prospective data relative to the at-risk period has come from approaches which have focused on determining an at-risk status that is based on the presence of musculoskeletal (MSK) symptoms such as arthralgia in combination with biomarkers of autoimmunity (table 2, figure 2). This approach has yielded critically important findings related to symptom complexes, immunobiology and natural history of clinical RA development and has supported the development of models for risk stratification for the development of RA (see below). This is also a method by which most clinical rheumatologists encounter individuals in the at-risk period and therefore provides ‘real-world’ information on the natural history of RA that may be applicable to clinical care settings. Furthermore, individuals at risk for RA can be identified in ‘real time’ by this approach and can be enrolled in observational studies that can be used as at-risk cohorts for recruitment into prevention trials (see below). To generate a definition that can distinguish symptomatic at-risk patients from a broader population with MSK symptoms, an EULAR task force defined the clinical characteristics of patients with arthralgia who are considered at risk of RA by experts, based on their clinical experience. This resulted in the EULAR definition of arthralgia suspicious for progression to RA, which was developed primarily to identify a more homogeneous group of symptomatic individuals for future scientific investigation [24].

Other methods of identifying individuals at risk of RA include population-based testing for RA-related biomarkers through activities such as health fairs or population surveys, with testing done through the interest of participants regardless of the a priori presence of symptoms or other risk factors. Since broad-scale biomarker testing to evaluate risk for future RA is not yet standard of care, these approaches are best considered as ‘research only’. However, such approaches may help to identify larger numbers of at-risk individuals in the very earliest stage of risk (figure 1) at a time when the impact of interventions targeting reversible risk factors could be significant. Moreover, future biomarker-based prevention strategies, if approved, could be

similar to strategies used now in assessing CVD risk through cholesterol testing, or diabetes risk through autoantibody and glucose testing.

As discussed above, once an individual has been defined as being ‘at risk’ for RA because of the presence of one or more risk factor, the next important challenge is to quantify that level of risk, because within broad definitions of risk discussed above (eg, family history and MSK symptoms), there is still high variability in progression to clinical RA. This approach can be termed ‘prediction’, although the concept of ‘risk stratification’ is perhaps more applicable if a goal is to use a variety of factors to identify an individual’s (or groups of individuals) specific level of risk for developing future RA [25,26]. As an example, osteoporotic-related fracture risk can be stratified using approaches such as the ‘FRAX’ score, and preventive treatment for potential fractures started when a certain risk state for a fracture is reached [4]. Notably, there is also a potential to include individuals at risk for future clinical RA who have a current clinical syndrome (eg, arthralgia) that warrants a diagnosis and treatment now; that concept will be discussed below in more detail.

There are several published studies in which formal risk stratification models for future clinical RA have been presented (table 3). These approaches have used a variety of risk factors including family history of RA, symptoms, autoantibodies, inflammatory markers (eg, erythrocyte sedimentation rate), genetic tests and imaging findings of ‘subclinical inflammatory arthritis’ (which can be defined as imaging findings of joint/tendon inflammation without a swollen joint on physical examination). In general, for anticitrullinated protein antibody (ACPA) (+) individuals who were found on clinical evaluation to have MSK symptoms, rates of development of clinical RA within 1–5 years range between 20% and 40%; however, with additional factors, such as subclinical inflammation defined by imaging, positive predictive values (PPVs) can be in the region of 70%–80% (table 3). Nonetheless, the strongest risk factors for RA are the presence of autoantibodies, and, not unexpectedly, dual positivity of ACPA and rheumatoid factor is the strongest autoantibody predictor [27–29]. Detection of high levels of glycosylation of the ACPA IgG variable domain adds to risk when evaluated over time, is quantifiable and may be reversible [30,31].

Risk stratification criteria for use in research are being developed by an EULAR/ACR task force, taking advantage of data from 10 arthralgia at-risk cohorts and the expertise from a group of rheumatology experts, patient partners and health professionals from Europe and North America. After a data-driven approach, consensus was obtained. This initiative resulted in criteria that incorporated clinical, serological and imaging variables which could be adapted for use in the presence or absence of imaging to detect subclinical joint inflammation (AUCs (area under the curve) of 0.80 and 0.87, respectively). Endorsement of these criteria by EULAR and ACR and a formal publication are underway; furthermore, an additional task force that will explore risk stratification in individuals identified in population-based approaches (eg, ACPA testing of FDR or at health fairs) is also underway.

These risk stratification models are highly informative and indeed have underpinned the design of clinical prevention trials described below. However, there are some caveats. First, these models have largely been developed in individuals who initially presented to clinical care providers with MSK symptoms. As such, we know less about prediction in individuals who may be found to be at risk through population-based approaches and

Table 2
Selected prospective studies of individuals at risk of RA

Genetic and/or familial risk factors defining the at-risk state	
del Puente <i>et al</i> 1988 [19]	Longitudinal study (~19 years) in the USA of ~2700 Akimel-O'odham (Pima) people; study participants did not have clinical RA at baseline but are from a population that has high prevalence of RA; 70 individuals (~3%) developed incident IA/RA; RF was associated with increased risk for IA/RA.
Silman <i>et al</i> 1992 [21]	Longitudinal study (~5 years) in the UK of ~370 FDR from families in the UK with multiple cases of RA; 14 individuals (~8 per 1000 p-y) developed incident IA/RA; RF was associated with increased risk for IA/RA.
Ramos-Remus <i>et al</i> 2015 [23]	Longitudinal study (~5 years) in Mexico of ~1800 FDR; 17 individuals (~1%) developed incident clinical IA; RF and ACPA (anti-CCP2) were associated with increased risk for IA/RA, with highest risk in dual-positive individuals (PPV~64%).
Tanner <i>et al</i> 2019 [20]	Longitudinal study (~12 years) in Canada of 374 FDR of probands with RA from an Indigenous North American population that has a high background prevalence rate of RA; 18 individuals developed incident clinical IA/RA (~9.2 per 1000 p-y). RF and ACPA positivity were associated with higher risk; however, a subset of individuals reverted to autoantibody negative states and did not develop IA/RA.
Bemis <i>et al</i> 2021 [22]	Longitudinal study in the USA of 131 FDR found to be positive for RF or ACPA (anti-CCP2, 3 or 3.1) in testing of a larger FDR population (n~1780); 20 (~15%) individuals developed incident IA/RA after a median of ~4 years; anti-CCP positivity at levels ≥2 times the upper limit of normal were associated with increased risk for development of IA.
Gilbert <i>et al</i> 2021 [85]	Longitudinal study (~12 years) of ~1450 FDR; 16 individuals (~1%) developed incident IA/RA after a mean follow-up of ~5 years; RF and ACPA positivity were associated with increased risk for development of IA.
MSK symptoms/arthritis with or without autoantibody positivity defining the at-risk state	
van de Stadt <i>et al</i> 2013 [27]	Longitudinal study in The Netherlands (Amsterdam) of 374 individuals who were referred to rheumatology clinics with MSK symptoms and were positive for RF and/or ACPA; 131 (~35%) individuals developed IA/RA after a median of ~12 months; dual positivity for RF and ACPA were associated with the highest risk for development of IA/RA (additional details of risk stratification/prediction from this cohort is presented in table 3).
Rakieh <i>et al</i> 2015 [86]; Duquenne <i>et al</i> 2023 [28]	Longitudinal study in the UK (Leeds) of ACPA positive individuals identified with new MSK symptoms from regional primary care and secondary care referrals; evolving rates of incident IA/RA, with a variety of risk factors identified (additional details of risk stratification/prediction from this cohort is presented in table 3).
van Steenberghe <i>et al</i> 2016 [87]; Rogier <i>et al</i> 2022 [64]; Heutz <i>et al</i> 2024 [61]	Longitudinal study in The Netherlands (Leiden) of individuals who presented to outpatient rheumatology clinics with arthralgia; evolving rates of incident IA/RA, with a variety of risk factors for progression to IA/RA identified (additional details of risk stratification/prediction from this cohort is presented in table 3).
van der Ven <i>et al</i> 2017 [88]	A multicentre at-risk cohort (Rotterdam) of 196 individuals with arthralgia with or without ACPA IgG, followed up for 12 months and 31 (~16%) developed IA/RA. The focus was to evaluate baseline ultrasonography as a predictor of developing IA. Ultrasound power doppler signal, morning stiffness and age were associated with higher risk of developing IA/RA.
Prajzlerová <i>et al</i> 2021 [89]	The ARRA cohort (Prague) of individuals was assembled to identify risk factors for the development of IA/RA in individuals with arthralgia, with or without ACPA, incorporating analysis of circulating lymphocyte and monocyte populations phenotypes; 41 of 207 (~20%) of individuals developed IA/RA. Details of prediction models from follow-up of this cohort are presented in table 3.
Other population-based studies	
Westra <i>et al</i> 2021 [90]	Longitudinal follow-up study in The Netherlands (Lifelines) of 308 individuals identified as ACPA positive (anti-CCP2) through testing done as part of a large-scale (n~40 000) population study; at 2-year follow-up 75 of 308 individuals had clinically suspect arthralgia (CSA) based on interpretation of answers to the Connective Tissue Disease Screening Questionnaire although formal joint examinations were not performed; CSA was associated with additional positivity for RF and higher levels of auto-antibodies.
Bergstedt <i>et al</i> 2022 [29]	Longitudinal study in the USA of 90 individuals who were found to be positive for ACPA through testing offered for research purposes at a health fair; 26 (29%) of participants developed incident IA/RA; dual positivity of RF and ACPA, and the presence of the shared epitope were associated with higher risk of incident IA/RA.
O'Neil <i>et al</i> 2022 [91]	Longitudinal study in a Canadian cohort of indigenous North Americans who were also first-degree relatives of patients with RA. A subset of 42 participants were ACPA positive, 12 of whom developed IA. A 48-plex proteomic array was evaluated, and proteins associated with the JAK-STAT pathway appeared to be enriched in those at highest risk to develop future IA/RA.

ACPA, anti-citrullinated protein antibodies; CCP, cyclic citrullinated peptide; IA, inflammatory arthritis; MSK, musculoskeletal; PPV, positive predictive value; p-y, person-years; RA, rheumatoid arthritis; RF, rheumatoid factor.

not initially identified as being at risk for RA because they presented to healthcare programmes because of MSK symptoms/arthritis. To this point, emerging data suggest that ACPA positivity, even if identified through population-based approaches that include ACPA testing at health fairs or of FDR is still associated with PPVs of developing RA over longer periods of time of ~20%–50% [22,23,29]. This finding suggests that population-based approaches may identify individuals earlier in the at-risk period; furthermore, these approaches may achieve a higher priority if clearly effective treatment were available for people at risk. Second, these models do not include estimates of severity or persistence of clinical arthritis that may develop. This is important because individuals with MSK symptoms, or those found through population-based approaches may have a milder form of RA than those who are identified with clinical RA through referral to specialist centres (which could represent time length bias). Furthermore, given the growing understanding of ‘palindromic rheumatism’, it is possible that these

approaches identify individuals who will not develop persistent arthritis. Indeed, it is emerging that findings such as imaging evidence of ‘subclinical inflammation’ may resolve over time without DMARD therapy, even in autoantibody-positive individuals deemed to be at risk [32,33]. Importantly, some clinicians may use subclinical inflammation to diagnose clinical RA and initiate treatment [34] which based on these findings may result in potential overtreatment [35,36] (and a concept to reduce overmedicalisation is termed ‘quaternary prevention’ [7]). To address this point, going forward the field will need to develop clear guidelines on how to incorporate imaging into clinical trials as inclusion factors and outcomes, as well as how to use imaging in clinical care to establish a diagnosis of clinical RA. Third, risk stratification/prediction models do not clearly define specific biological states that may represent an individual’s unique ‘endotype’ for developing RA—and, in particular, specific biological pathways to target. This is key because ideally risk stratification should both identify an individual’s risk for

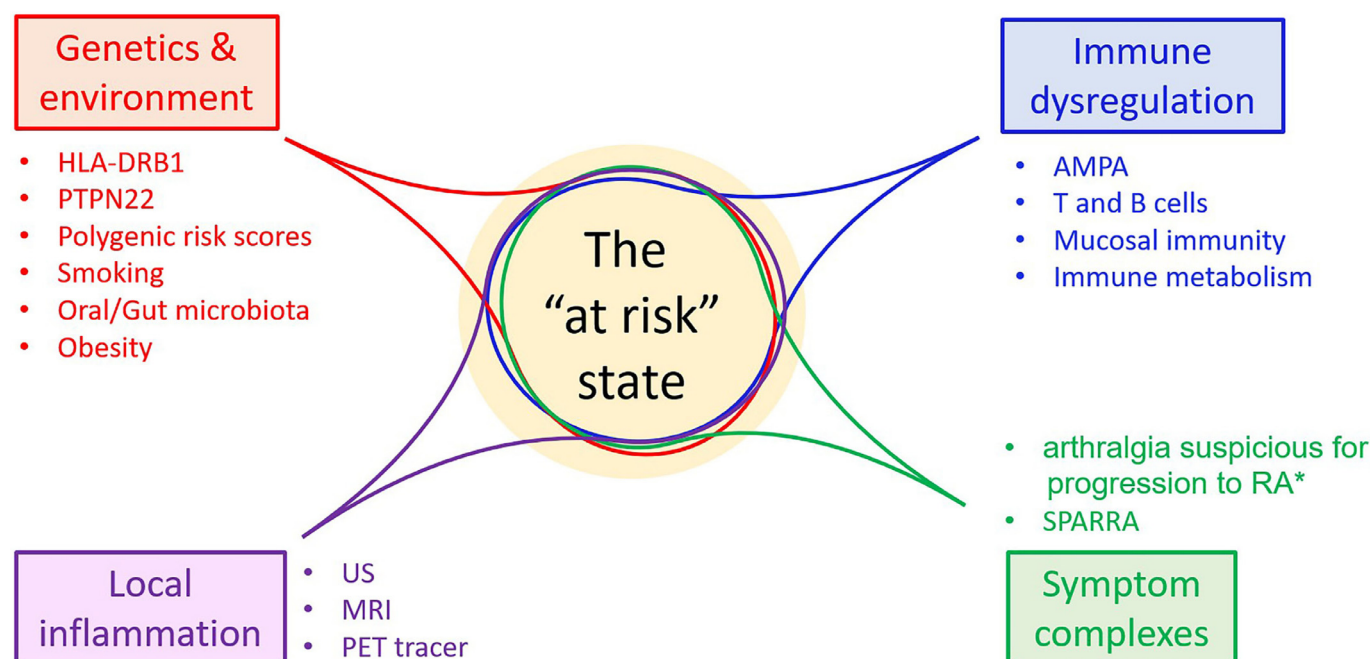


Figure 2. Emerging features of the at-risk state. The core determinants of risk are highlighted, with emphasis on genes and environmental exposures, identification of immune signatures, symptom complexes and the use of imaging modalities to detect subclinical inflammation. Importantly, we need to understand the interplay between genetic and other host factors, the environment and the initiation and propagation of immune dysregulation and the development of clinical RA so that these processes can be targeted for effective prevention. *EULAR definition. AMPA, antibodies to modified protein antigens; EULAR, European Alliance of Associations for Rheumatology; MRI, magnetic resonance imaging; PET, positron emission tomography; RA, rheumatoid arthritis; SPARRA, the Symptoms in Persons At Risk of Rheumatoid Arthritis; US, ultrasound.

future clinical RA but also provide insights into what factors should be targeted to reduce that risk—in essence, more personalised prevention akin to individually treating cholesterol or blood pressure abnormalities in CVD prevention. This becomes especially important in at-risk individuals in whom synovitis is absent. Finally, as discussed below, clinical prevention trials have enrolled individuals in part based on the risk stratification models presented in [table 3](#). In some of the clinical trials, the rates of progression to RA within the placebo arms are lower than would be expected using the published models that were developed in observational studies. This may be because individuals who participate in clinical trials are somehow ‘healthier’, perhaps due to lifestyle factors, than the at-risk populations included in the observational studies. Clearly, prediction models need refinement, and as mentioned above there are efforts underway sponsored by EULAR and the ACR to develop risk stratification models in both arthralgia-based and population-based approaches, and these projects should yield important results that will address many of the challenges in risk stratification that are discussed above.

Summary of RA interception trials

The ability to identify individuals who are at risk for RA, as well as estimate the rates of progression to RA, have underpinned the execution of published clinical trials. The chronology of these studies is depicted in [figure 3](#), with details summarised in [table 4](#). Importantly, in the design of these trials, the inclusion criteria were developed to identify individuals with a range of PPVs for future clinical RA of 30%–50%. This is not a 100% ‘risk’ of developing clinical RA; however, ethical review boards and regulatory agencies have considered that these PPVs are sufficient, given the known potential risks and benefits, to approve the conduct of these trials.

In terms of interception, corticosteroids alone [37], a single dose of rituximab (with corticosteroids) [38], atorvastatin [39], methotrexate (with single-dose corticosteroids and noting 23% ACPA positivity) [40] and hydroxychloroquine [41] did not reduce overall rates of progression to clinical RA within the study periods. However, in these trials, rituximab delayed the onset of clinical RA, and methotrexate was associated with both improved function and diminished evidence of inflammation seen on MRI of the joints. In addition, in two trials, compared with placebo, abatacept-treated participants had reduced rates of progression to clinical RA within the trial period (although within both arms a proportion of participants did not develop clinical RA) [42,43]. Moreover, in APIPPRA (Abatacept in individuals at high risk of rheumatoid arthritis, ultrasound detected synovitis and power Doppler scores were reduced by abatacept [42]. In ARIAA (Abatacept inhibits inflammation and onset of rheumatoid arthritis in individuals at high risk), abatacept reduced MRI inflammation [43], findings consistent with the imaging outcomes reported in the ADJUST study which trialled abatacept in individuals with undifferentiated IA at baseline [44]. Interestingly, while not specifically designed for RA prevention, VITAL (Vitamin D and omega 3 trial) tested the effects of 5 years of supplementation with vitamin D, omega-3 fatty acids, both, or neither in men over 50 and women over 55 years of age at enrolment on the prevention of several prespecified outcomes, including a composite of all incident autoimmune diseases. Vitamin D, with or without omega-3 supplementation, significantly reduced rates of development of overall autoimmune disease, with signals for reduction of several individual autoimmune diseases, including RA [45]. Furthermore, in additional follow-up 2 years beyond the initial 5 years of randomised intervention in the VITAL trial, omega-3 fatty acid supplementation was shown to have significantly lowered the rate of autoimmune disease development, while that for RA remained low but

Table 3
Risk stratification and prediction models for RA

Study	Design and primary outcome	Findings
van de Stadt <i>et al</i> 2013 [27]	Prospective evaluation of 374 individuals who presented to several Dutch rheumatology clinics with arthralgia and ACPA and/or RF positivity and without IA at baseline. 131 (35%) participants developed IA after a median of 12 months.	Nine features were included in the model: 1. First degree relative with RA (1 point). 2. Drinking alcohol (1 point if no). 3. Symptoms start <12 months prior (1 point). 4. Intermittent symptoms (1 point). 5. Symptoms in upper and lower extremities (1 point). 6. Pain scale ≥50 on Visual Analogue Scale (2 points). 7. Morning stiffness ≥1 hour (1 point); 8. Self-reported swelling in any joint (1 point). 9. Autoantibodies: – RF-IgM pos/ACPA neg (0 points). – RF-IgM negative and ACPA positive <3×cut-off (2 points); – RF-IgM negative and ACPA positive ≥3×cut-off (3 points). – RF-IgM and ACPA positive (4 points). All features if present (or positive) indicate point(s) with the exception of alcohol intake which if negative = 1 point. Scores of 7–13 were associated with rates of development of IA of ~74% by 3 years, and ~81% at 5 years.
Karlson <i>et al</i> 2012 [92]	Evaluation of the interactions between environmental factors, genetic risk scores and gene–environment interactions for the development of RA in the Nurses’ Health Study (NHS: 317 cases, 551 controls), and the Swedish Epidemiologic Investigation of RA cohort (EIRA: 987 cases and 958 controls).	Primary models produced an AUC of 0.72 in NHS, 0.73 in EIRA women and 0.76 in EIRA men. A full environmental, genetic and gene–environment interaction model provided optimal predictive ability.
Sparks <i>et al</i> 2015 [93]	Evaluation of epidemiological and genetic risk models incorporating autoantibody profiles, family history, genetics, smoking and body mass index (BMI) among women in the Nurses’ Health Study (NHS, 381 RA cases and 410 controls) and the Swedish Epidemiological Investigation of RA (EIRA, 1244 RA cases and 971 controls).	Models demonstrated AUCs of 0.74 for seropositive RA in the NHS and 0.77 for ACPA + RA in EIRA. Discrimination was improved for women with a family history in the NHS (AUC 0.82) and in EIRA (AUC 0.83). When combining positive family history, high genetic susceptibility, smoking and increased BMI had an OR of 21.73 for ACPA-positive RA.
Matthijssen <i>et al</i> 2019 and 2020 [94,95]	580 individuals with CSA were followed for the development of IA; 18% progressed to IA within 2 years.	The model contained 4 variables: ACPA-positivity, RF-positivity, >2 locations of subclinical inflammation on MRI and presence of MCP-extensor peritendinitis on MRI. PPVs were up to 86%. This model yielded an AUC of 0.79.
Duquenne <i>et al</i> 2023 [28]	A single centre (Leeds, UK) prospective evaluation of 455 ACPA(+) individuals who initially presented to primary care with musculoskeletal complaints; 148 (32.5%) participants developed IA after a median of 255 weeks of follow-up.	A ‘simple’ score method was recommended to be applied in primary care and included: Morning stiffness 30 minutes or more (9 points) Levels of ACPA (8 points if ≥3 to <10×ULN; 17 points if ≥10×ULN) Positivity of RF (11 points) An elevated ESR (6 points) A ‘simple’ score ≥18 of was associated with a PPV of ~27% of developing clinical RA within 1 year. A ‘comprehensive’ categorical scoring method was recommended to be applied in rheumatological practice and included ~13 variables (including ultrasound findings), and a certain score was associated with a PPV of ~70% of developing IA within 5 years.
Prajzlerová <i>et al</i> , 2021 and 2024 [89,96]	The ARRA cohort (Prague) at-risk individuals is defined as having arthralgia without arthritis and being either ACPA or meeting the clinical EULAR CSA definition. Immune phenotyping of PBMC was undertaken by flow cytometry.	An initial report identified a shift from classical (CD14 ⁺⁺ CD16 [–]) to non-classical peripheral blood monocytes (CD14 ^{+/–} CD16 ⁺⁺) in ACPA ⁺ at-risk individuals. A follow-up predictive model identified risk factors associated with progression to arthritis including high ACPA IgG, higher % of B cells and lower % of NK cells (AUC 0.78). This was not the case in ACPA negative individuals.

ACPA, anticitrullinated protein antibody; ARRA, At-Risk of RA cohort; AUC, area under the curve; CSA, clinically suspect arthralgia; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; PBMC, peripheral blood mononuclear cells; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor; ULN, upper limit of normal.

not significantly so, suggesting a longer-term effect of this agent [46].

There are several important considerations when evaluating the results of these trials, and in particular, when contemplating the development of future prevention studies in RA. First, most of these studies recruited individuals who had first presented to healthcare providers with MSK symptoms; exceptions are StopRA (Strategy to prevent the onset of clinically-apparent rheumatoid arthritis) where one-third of participants were identified through population-screening approaches (eg, ACPA testing at health fairs) (unpublished data), and the VITAL trial which enrolled participants from the general population. This MSK symptom-driven approach allowed recruitment activities to

leverage existing clinical ‘pipelines’ where individuals with MSK symptoms are evaluated for additional risks for RA. It also likely enriches for a subset of at-risk individuals with a prolonged prodrome of symptoms sufficiently severe to warrant seeking medical care, and excluding those with disease that is more subtle, or in contrast, explosive in onset, or that has waxing and waning or palindromic symptoms. Second, most of the studies used medications that have already been approved for use in clinical RA. This was based on assumptions that since these medications have proven efficacy in clinical RA they may offer benefit during the ‘at-risk’ stage. It is conceivable that the use of treatments approved for RA facilitated both approval by ethics committees as well as the willingness of at-risk

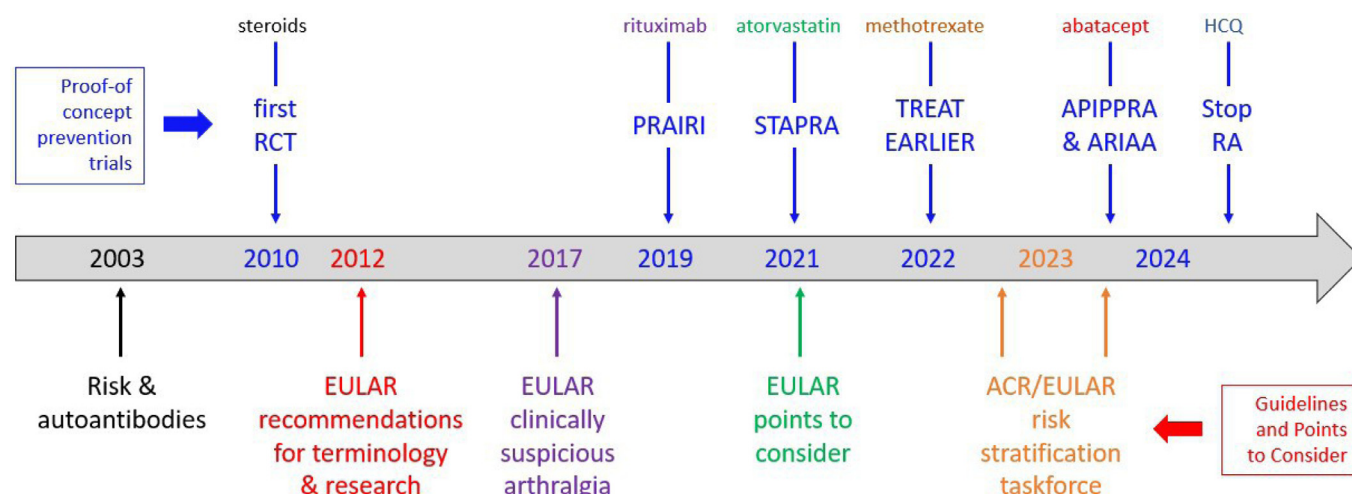


Figure 3. Milestones in the history of the RA at-risk state. Clinical trials in individuals at-risk of RA are illustrated, underpinned by consensus guidelines and points to consider led by task forces of EULAR and the ACR. ACR, American College of Rheumatology; APIPPRA, abatacept in individuals at high risk of rheumatoid arthritis; ARIAA, abatacept inhibits inflammation and onset of rheumatoid arthritis in individuals at high risk; EULAR, European Alliance of Associations for Rheumatology; HCQ, hydroxychloroquine; PRAIRI, prevention of clinically manifest rheumatoid arthritis by B-cell directed therapy in the earliest phase of the disease; RA, rheumatoid arthritis; RCT, randomised clinical trial; STAPRA, statins to prevent rheumatoid arthritis; StopRA, strategy to prevent the onset of clinically-apparent rheumatoid arthritis; TREAT EARLIER, intervention with methotrexate in patients with arthralgia at risk of rheumatoid arthritis to reduce the development of persistent arthritis and its disease burden.

individuals to enroll. Third, most of the clinical trials adopted fixed period dosing of the Investigational Medicinal Product under investigation (and in the case of rituximab, a single infusion), with a drug-free follow-up period to evaluate durability of any response. This design has the advantage of improving drug adherence, safety and costs while addressing the notion head-on that interception may have durable effects even after cessation of therapy. However, future studies may need to consider longer duration of therapy, intermittent dosing regimens or combinations of agents to suppress inflammation and restore immune tolerance. Fourth, these studies had differing inclusion criteria. For example, several studies required the presence of ‘arthralgia’ for inclusion; however, while there are formal EULAR-approved criteria for arthralgia that are suspicious for progression to RA [47], these criteria were not available at the inception of many studies that predated them. As such, the type of MSK symptoms leading to inclusion are likely to differ and may have influenced rates of progression. In addition, the primary endpoints differed between studies, although the majority were based on the development of, or time to developing clinical arthritis or RA detected by physical examination. Finally, as discussed above, the overall rates of progression to clinical RA within the placebo arms of these studies varied from as low as 14% to as high as 57%. This demonstrates, unambiguously, that risk over time varies between studies and highlights the need for more robust risk stratification tools and application of interventions that more closely align with that level of risk.

Are we equipped for the next phase of RA interception trials?

It is exciting that the field has advanced to the point when several randomised clinical trials in RA prevention have been completed. In particular, while TREAT EARLIER did not reduce rates of progression to RA, it is encouraging that sustainable improvement in subclinical joint inflammation, physical function, work productivity and symptoms in methotrexate-treated individuals highlights a clinical trajectory of RA modulated by interventions in the at-risk period [40]; it is also encouraging that a limited course of abatacept reduced rates of progression to clinical RA

within the trial period, reduced multiple aspects of the symptom burden and reduced subclinical joint inflammation (APIPPRA and ARIAA) [42,43]. Nonetheless, time-limited interventions were not sufficient to conclusively ‘prevent’ RA, indicating that challenges remain to further advance prevention in RA. These are summarised in box 1 and addressed in more detail below. Importantly, these challenges have been, or are being, addressed by a number of EULAR/ACR task forces, building on the existing framework for studies in the at-risk period summarised in figure 3.

Further considerations for study design and interventions

The points highlighted above underscore the premise that RA interception should be commensurate with the at-risk state, taking into account the risks and benefits of any particular intervention. Another factor influencing the choice of intervention relates to what at-risk individuals would find acceptable and how this relates to perception of risk, familiarity with RA as well as the drug safety profile [48–50]. Lifestyle modifications, such as cessation of smoking, might be considered more acceptable for asymptomatic individuals with genetic and environmental risk factors (figure 1), especially if it could be demonstrated that those interventions are appropriate for the biological stage of disease [51]; for example, if we know that tobacco smoke is key to propagating RA-related autoimmunity at a certain stage, then smoking cessation for an individual who is a smoker may be a ‘precision-medicine’ preventive approach. Furthermore, qualitative studies have demonstrated that some lifestyle interventions would be acceptable to individuals who are at risk for RA [52,53]. Notably, lifestyle and dietary factors such as exercise and healthy diets are associated with decreased risk of RA in observational studies [54], and specific interventions including whole-food plant-based diet, physical activity and stress management have demonstrated benefits in improving disease activity in clinical RA [55,56]. As such, these types of approaches may be primary interventions for prevention; however, they can be challenging to implement in clinical trials as isolated interventions in part due to adherence as well as potentially long

Table 4
Summary of published prevention trials in rheumatoid arthritis

Study	Bos <i>et al</i> [37]	PRAIRI	STAPRA	TREAT EARLIER	APIPPRA	ARIAA	StopRA*	VITAL
Screened (n)	227	109	189	901	280	13P6	Pending	25 871
Randomised and received IMP (ITT, n)	83	81	62	236	213	98	142	
Baseline at-risk state:								
Symptoms	Arthralgia	Arthralgia	Arthralgia	CSA	Arthralgia	Arthralgia	Not mandated	Not applicable as at-risk state not assessed for inclusion
ACPA (+)	73%	100%	100%	23%	100%	100%	100%	
RF (+)	63%	99%	55%	29%	86%	68%	59%	
Imaging	Not done	46/48 neg	Not done	All MRI +	154/212 neg	All MRI +	Not done	
Shared epitope (+)	100%	56%	Not done	Not tested	NR	Not tested	Pending	
Smoking	NR	73% (ever)	39% (current)	55% (ever)	62% (ever)	58% (ever)	25% (ever)	
Active intervention versus placebo	Dexamethasone 100 mg IM 0 and 6 weeks	Rituximab 1000 mg IV once; methylprednisolone 100 mg once	Atorvastatin 40 mg daily	Methotrexate 25 mg orally weekly; methylprednisolone IM 120 mg once	Abatacept 125 mg SC weekly	Abatacept 125 mg SC. weekly	Hydroxychloroquine 200–400 mg daily	Vitamin D 2000 IU daily; Marine omega-3 fatty acids 2 g daily; Both; Neither; (double placebo)
Treatment period	N/A	N/A	3 years	12 months	12 months	6 months	12 months	5.3 years
Follow-up period after intervention	26 months (21–37) median (IQR)	29 months (14–40) median (IQR)	14 months (6–35) median (IQR)	12 months	12 months	12 months	24 months	2 years
Primary endpoint	50% reduction in autoantibody levels at 6 months	Clinical arthritis	Clinical arthritis	Time to clinical arthritis persisting for ≥ 2 weeks and meeting 2010 criteria or present in $> = 2$ joints	Time to clinical arthritis in ≥ 3 joints or RA by 2010 criteria	Improvement in synovial inflammation by MRI	RA by 2010 criteria or IA and ≥ 1 erosion by radiography	All medical record confirmed or probable incident autoimmune disease including RA, PMR, psoriasis and others
Progression to arthritis end of treatment period	N/A	N/A	N/A	13/119 (11%) methotrexate 14/117 (12%) placebo	7/100 (6%) abatacept 30/103 (29%) placebo	4/49 (8%) abatacept 17/49 (35%) placebo	Trial halted early due to futility of drug to impact progression to RA; pending final analyses	Initial 5 years for confirmed RA: Vitamin D: 15 vs 24 (placebo) HR 0.58 (CI 0.13 to 1.13) Omega-3: 15 vs 24 (placebo) HR 0.58 (CI 0.3 to 1.13)
Progression to arthritis end of study	9/42 (21%) dexamethasone 8/41 (20%) placebo	14/41 (34%) rituximab 16/40 (40%) placebo	9/31 (29%) atorvastatin 6/31 (19%) placebo	23/119 (19%) methotrexate 21/117 (18%) placebo	27/100 (25%) abatacept 38/103 (37%) placebo	17/49 (35%) abatacept 28/49 (57%) placebo	Pending final analyses	7 year follow-up for confirmed RA: Vitamin D: 29 vs 35 (placebo) HR 0.83 (CI 0.51 to 1.35) Omega-3: 25 vs 39 (placebo) HR 0.64 (CI 0.39 to 1.06)
Endpoints meeting-classification criteria for RA	6/17 1987 criteria	24/30 2010 criteria	14/15 2010 criteria	30/44 2010 criteria	65/65 2010 criteria	45/45 2010 criteria	Pending final analyses	Overall 128 RA confirmed cases, and 30 probable cases
Subclinical synovitis	Not tested	Not tested	Not tested	Improvement in MRI scores	Improvement in US scores	Improvement in MRI scores	Not tested	Not tested
Symptoms	Not reported	Not reported	Not reported	Pain, stiffness reduced	Pain, fatigue reduced	Pain, stiffness reduced	Pending final analyses	Not tested
Function	Not reported	Not reported	Not reported	HAQ improved	HAQ and EQ5D improved	HAQ and SF-36 improved	Pending final analyses	Not tested
Other assessments or PROMS	N/A	Reduced B cells; reduced serum IgM and IgA RF, but not IgG RF or anti-CCP in rituximab arm	N/A	Reduced work instability; improved outcomes with MTX in ACPA(+) subset	Reduced work instability, physical and mental well-being, anxiety	Improved quality of life	Pending final analyses	Not tested

*Results from StopRA are only available in abstract form and are based on interim analyses.

ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; APIPPRA, abatacept in individuals at high risk of rheumatoid arthritis; ARIA, abatacept inhibits inflammation and onset of rheumatoid arthritis in individuals at high risk; CSA, clinically suspect arthralgia; EQ5D, EuroQual 5 Dimension; EULAR, European Alliance of Associations for Rheumatology; HAQ, Health Assessment Questionnaire; IA, inflammatory arthritis; IM, intramuscular; IMP, investigational medicinal product; ITT, intention to treat; IV, intravenous; NR, not reported; PMR, polymyalgia rheumatica; PRAIRI, prevention of clinically manifest rheumatoid arthritis by B-cell directed therapy in the earliest phase of the disease; PROMS, patient-reported outcome measures; RA, rheumatoid arthritis; RF, rheumatoid factor; SF-36, Short Form Health Survey; STAPRA, statins to prevent rheumatoid arthritis; TREAT EARLIER, intervention with methotrexate in patients with arthralgia at risk of rheumatoid arthritis to reduce the development of persistent arthritis and its disease burden; US, ultrasound; VITAL, vitamin D and omega 3 trial.

periods of time required to see biological effect (eg, observational studies suggest smoking cessation may be associated with RA risk reduction in 10 or more years [57]). As such, lifestyle/dietary interventions may need to be included in trials as additions to other preventive interventions. In addition, the presence of disease-specific serum autoantibodies or other markers of autoimmunity (ie, autoantigen-specific T cell reactivity) could justify interventions such as antigen-specific immune tolerance adopting cell and/or peptide-based approaches [58]. Furthermore, novel approaches may be instituted that mitigate mucosal-associated processes in gums, gut, respiratory or reproductive tracts that, over time, drive initiation and propagation of immune dysregulation, with candidates for specific interventions being identified through mucosal testing. Notably, while some interventions may be biologically appropriate and acceptable to individuals who are in an ‘asymptomatic’ stage of RA development, the presence of autoimmunity and immuno-inflammatory responses, combined with symptoms and signs of joint inflammation, is a stage where there would be more justification for therapies that target the immune dysregulation suspected of driving these early events. For example, a biological agent that inhibits the expression and function of inflammatory mediators such as TNF (tumor necrosis factor) or IL-6 (interleukin-6) may suppress but not truly modulate the early, asymptomatic at-risk phase but would be more likely to be of benefit at a point when subclinical joint inflammation is detectable by imaging modalities such as MRI or ultrasonography. In contrast, therapies that target the earliest phase of adaptive immune responses may be more plausible options as soon as evidence of adaptive immunity becomes manifest, and these pathways are active. These concepts, supported in part by animal models [59], highlight the need for further interrogation of the molecular and cellular pathways that underpin each phase of the at-risk state.

Regardless of the specific intervention, each approach needs to be not only clinically impactful but also have a favourable risk-to-benefit ratio. Given that in the at-risk state the requirements for assessing ‘activity’ will be quite distinct from those adopted for the assessment of established RA, the ability to monitor cellular and molecular signatures of a therapeutic response will become a priority, aligned with evidence of restoring immune homeostasis, such as seroconversion. In this case, the risk, such as ACPA, and the state of immunoglobulin variable domain glycosylation might be deemed targetable therapeutically. Notwithstanding issues around monotherapy and immunogenicity, the success of any clinically impactful intervention will require adequate adherence to the intervention, and that in turn will be determined by pragmatic routes of administration and dosing schedule deemed acceptable to an at-risk population. Linked to this are the uncertainties surrounding the choice of dosing period, and ongoing risk monitoring to determine the need for retreatment. While treatment with hypertensive agents and lipid-lowering drugs may be lifelong, the possibilities of fixed period dosing, or intermittent dosing (eg, based on the APPIPPRA and ARIAA trials perhaps intermittent dosing of abatacept, especially if there are biomarkers to identify individuals who may respond to additional therapy), remain appealing, not least because of the positive impact in terms of safety. In such scenarios, monitoring the perturbations of host immunity or durability of immune tolerance becomes all the more important.

Lessons learnt

The growing portfolio of RA interception studies has been underpinned by input from patients and individuals who are at

risk for RA, and combined with experiences of enrolling at-risk individuals into interception studies (key features are illustrated in figure 4). This must continue, with added emphasis on access to care. More consideration should also be given to how physicians communicate risk for developing RA in the clinical setting, learning from other disciplines, such as CVD and clinical genetics, as well as explaining the benefits of enrolling in prevention studies. Our collective experience has highlighted the advantage of at-risk individuals being included in such studies, reducing the burden on clinicians while providing a referral pathway to healthcare systems for prompt treatment when RA develops. Importantly, one of the major challenges in executing the clinical trials for RA prevention was finding at-risk individuals who were further willing to participate in trials. Learning from the success of enrolment for numerous clinical prevention trials for type 1 diabetes mellitus (T1DM) which relies on international networks to identify individuals who are at risk for disease [60], we need networks in the rheumatology community that can identify and follow individuals who are at risk for RA. From such individuals we can learn more about the natural history of RA and the pathophysiology of disease evolution as well as their preferences through research code-sign. These are also important cohorts for recruitment for relevant clinical trials. Several regions including The Netherlands and the UK have established clinical referral networks [27,28,61], but we will need international efforts for representative codesign and to enhance recruitment feasibility for trials.

The development of fit-for-purpose instruments for assessing the symptom burden will become paramount [62]. Several important studies, informed by patients as well as individuals who are at risk for RA, have investigated the wide constellation of symptoms associated with the at-risk state. Besides pain and fatigue, these include physical and emotional well-being, weakness and loss of strength, anxiety and depression, sleep disturbance and work instability, among many others [63–65]. These instruments require further validation in the context of at-risk states and RA prevention studies, not only to better quantify the burden of symptoms on quality of life, but to evaluate reversibility following intervention and hence clinical impact. The development of such clinical disease activity tools (such as a pre-RA-validated disease activity measure akin to the Clinical Disease Activity Index that is used as an outcome in clinical RA [66]) will benefit from the emerging RA prevention trial datasets. Furthermore, while imaging with US and MRI appear sensitive to change in at-risk individuals with subclinical inflammation [40,42,43], experience from the APPIPPRA and TREAT EARLIER (Intervention with methotrexate in patients with arthralgia at risk of rheumatoid arthritis to reduce the development of persistent arthritis and its disease burden) studies suggests that plain radiographs of hands and feet may not be sensitive enough to capture short-term radiographic outcomes [40,42].

Finally, there have been no safety signals of concern reported between the placebo and treatment arms from RA prevention studies to date. This may reflect the relatively small trial cohort sizes, safety of the individual drugs used in these studies, inclusion/exclusion criteria that optimise safety as well as the trial designs that include a shorter duration of dosing than in trials of participants with clinical RA, and ‘monotherapy’ with study drug (or combination with only a short course of corticosteroid). Other factors that influence safety, especially compared with trials including clinical RA, are differences in age, the burden of comorbidities in those at risk, as well as the fact that at-risk individuals have not been exposed to multiple immune-modulating therapies at the time of interception. Nonetheless, evaluating the balance between risk and benefit and minimising unnecessary exposure to immune-modulating drugs remains paramount,

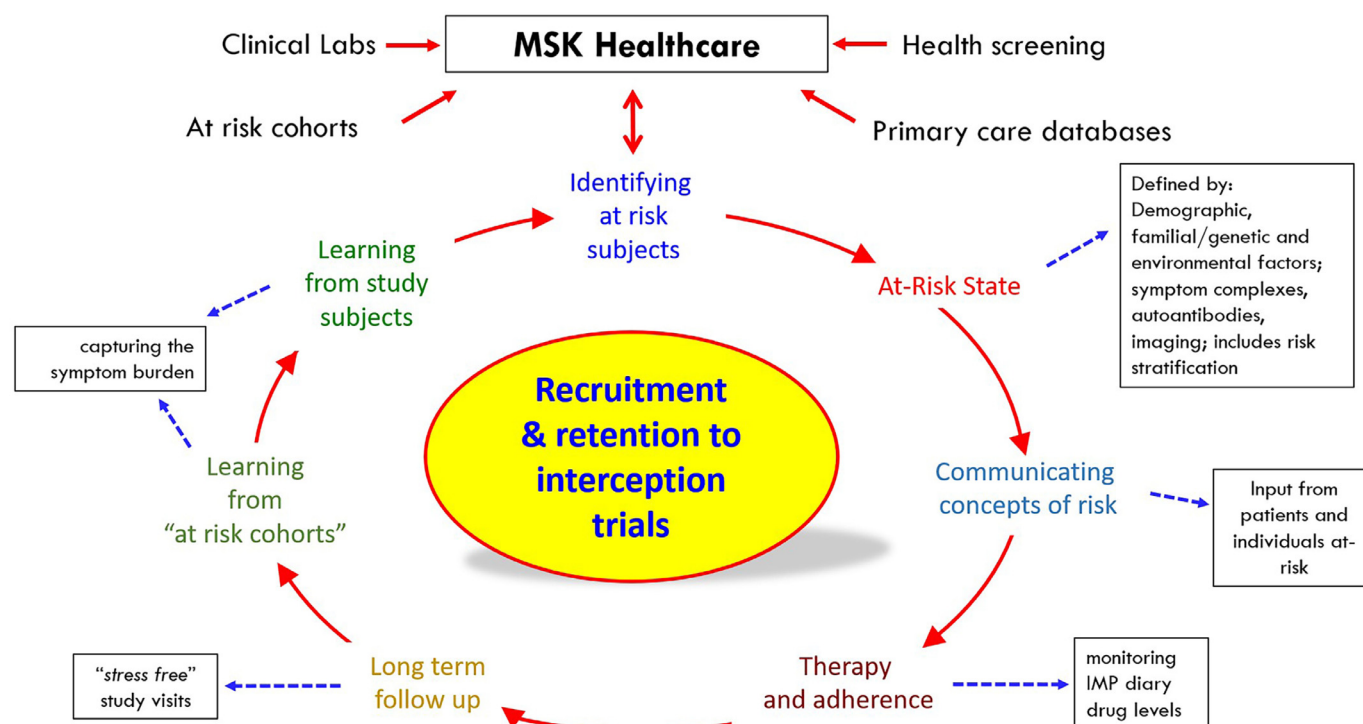


Figure 4. Recruitment and retention in RA interception studies. Core features of study operations are depicted, from screening, participant enrolment through to measures that can be adopted to support retention. The knowledge gained, including input from patient experts, feeds forward into risk screening programmes and refining trial design. IMP, investigational medicinal product; MSK, musculoskeletal; RA, rheumatoid arthritis.

given that often more than 50% of at-risk individuals recruited to the placebo arms of prevention trials to date do not progress to RA within the time frame of the trials.

Importantly, when thinking of the feasibility of making prevention actionable in RA, it is relevant to note that prevention strategies are already undertaken in some autoimmune diseases such as the use of antibiotics to treat streptococcal pharyngitis, which prevents the subsequent development of myocarditis, glomerulonephritis or other autoimmune manifestations [67]. In addition, in T1DM, the presence of multiple autoantibodies to certain antigens (eg, insulin, GAD65, ZnT8A and IA-2A) are highly predictive of future continued loss of insulin production and the onset of symptomatic glucose elevations (a state-designated stage 3 T1DM) [68]. The predictive power of autoantibodies for future stage 3 T1DM has prompted an increasing number of clinical trials (which as mentioned above have leveraged international networks of at-risk individuals for enrolment). Indeed, the immune intervention teplizumab (a humanised anti-CD3 monoclonal antibody immune intervention) is now approved by the Food and Drug Administration in the USA for individuals who have elevations of two or more T1DM-related antibodies and abnormal glucose tolerance testing (a state called ‘stage 2 T1DM’) in order to prevent or delay transition to stage 3 disease [69,70]. Since the approval of teplizumab in stage 2 T1DM, various programmes for islet autoantibody screening have been established for siblings of children with T1DM, and population-based childhood screening is becoming increasingly available. We can envision similar approaches in RA once preventive interventions have been approved.

Looking to the future

Looking ahead, it is apparent that additional therapeutic targets and strategies, as well as improved risk assessment tools, will have to be developed to achieve the desired clinical

outcomes in RA prevention; this will be especially important for seronegative RA. One major limitation is incomplete knowledge of the mechanisms by which the RA disease process is initiated during the at-risk phase and the molecular drivers of the initial break-in tolerance, epitope spreading, IgG V-domain glycosylation and immune targeting of the joint itself [71,72].

To that point, recent studies by a number of groups support a ‘mucosal origins of RA hypothesis’ [73]. This hypothesis posits that the initial systemic break in immune tolerance to self-antigens occurs in association with chronic inflammation and/or dysbiosis at mucosal sites, such as the lungs, the periodontium and the gut. The local drivers are likely to be microbial in origin and to use diverse mechanisms [74–77]. In the absence of resolution, these localised immune processes transition into a systemic process that targets the joints, either by direct effects of microbiota, molecular mimicry and/or immune amplification. This, in turn, leads to inappropriate engagement of a range of effector mechanisms in both synovium and periarticular sites.

Thus, similar to T1DM the at-risk stage of RA could be considered as a continuum, progressing through a number of ‘stages’ during which immune checkpoints that limit progression to autoimmunity fail (figure 5) [72]. Applying this concept, one could envision first identifying the stage at which an individual sits within this at-risk continuum and then applying the most appropriate prevention strategies. It follows from this that such an approach would have to be personalised not only in terms of the magnitude of risk, but also the underlying pathogenic mechanisms at the affected mucosal site, lymphoid organs and synovium.

This staged/checkpoint approach to prevention, therefore, suggests a number of possibilities for prevention [72,78]. With regard to causal microbiome factors, approaches could include probiotics, prebiotics and dietary intervention, treatment of periodontal disease that may drive dysbiosis, specific antibiotic

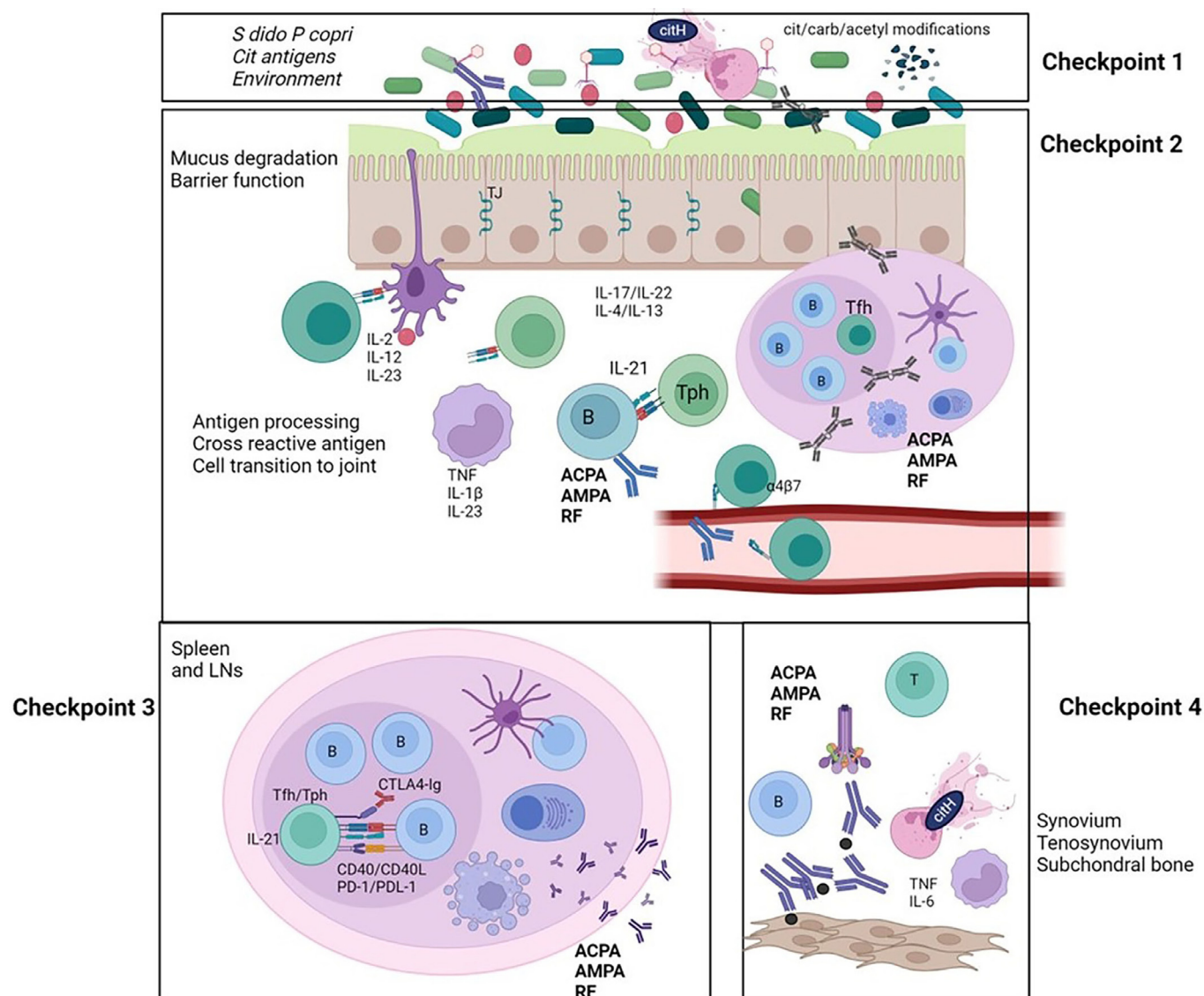


Figure 5. Demonstration of potential checkpoints that fail during the natural history process leading to the development of clinical RA. Considering that the ultimate development of RA follows failed mechanisms that should in principle stop the pre-RA disease process, shown are failed checkpoints that could in principle be therapeutically targeted in at-risk individuals. Some of the mechanisms may also provide benefits for patients with clinical RA. RA, rheumatoid arthritis; RF, rheumatoid factor.

treatment, faecal microbiome transplantation, use of strain-specific bacteriophages, alterations of antibodies active in the gut lumen, modulation of microbial processes such as metabolites/lipids that could affect the host or use of commensal bacterial strains that could abrogate effects of ‘pathogenic’ organisms. With regard to the mucosal barrier and local immune responses, known modulators of inflammation could constitute therapeutic targets, including TNF, IL-12/IL-23, IL-17, sphingosine-1-phosphate (S1P), JAKs (Janus kinases) and lymphocyte homing receptors such as $\alpha 4\beta 7$. Locally delivered therapies are also possible, such as corticosteroids and DNase, as well as pro-resolving modulators such as omega-3 fatty acids. Finally, with regard to modulation of a systemic immune response, an attractive series of drugs are being developed. Beyond utilisation of CTLA4-Ig as in the APIPPRA and ARIAA trials, targeting of the CD40-CD40L pathway, immune modulators of T cells such as teplizumab (which was successful in delaying onset of T1DM [69]) and modulation of T follicular helper (Tfh) and/or T peripheral helper (Tph) differentiation, migration or activity are worth consideration. Likewise, restriction of antigen presentation of citrullinated targets by

peptidyl arginine deiminase inhibitors could provide benefit, as would induction of antigen-specific tolerance.

CONCLUSION

The field of autoimmune rheumatic disease prevention is embarking on a particularly exciting period wherein disease prevention may be achievable. The principles that underpin at-risk states will be just as relevant to the preclinical stages of lupus and ankylosing spondylitis, or understanding the transition from psoriasis to psoriatic arthritis, as it is to RA [79–81]. Indeed, it is now well established that individuals who are in an at-risk state can be identified, and to some extent, risk stratification performed; furthermore, interventional trials can be carried out successfully. While there are substantial challenges ahead, including the development of optimal screening, risk stratification and treatment approaches across healthcare systems, these barriers can be overcome. Importantly, RA prevention also sits in the midst of a broader effort to convert management of autoimmune diseases by healthcare providers from a treatment-only

approach to a more proactive prevention model. In much the same way that CVD prevention has transformed healthcare, the same approach to autoimmune disease can provide substantial population benefits.

Correction notice

This article has been corrected since it published Online First. The author's name, Hani El-Gabalawy, has been updated.

Acknowledgments

The authors thank all the participants in the observational studies and clinical trials related to the natural history of RA and prevention.

Contributors

KDD, VMH and APC co-wrote the initial version of the manuscript and approved the final version. All other coauthors (PE, KM, HEG, JAS, KHC, GS, AvdH-vM, DvS and RT) contributed to the text of the manuscript and reviewed and approved the final version. KDD is the guarantor of this statement.

Funding

KDD and VMH work on this manuscript was supported by the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases grant P30 AR07936 and the University of Colorado Autoimmune Disease Prevention Center.

Competing interests

KDD has received honoraria from BMS, ThermoFisher and Werfen, and in-kind research supplies from Inova Diagnostics; VMH has received equity and funds from Q32 Bio unrelated to this work; PE has received funds for consulting from Anaptysis-Bio, BMS, Boehringer Ingelheim, Galapagos, Gilead, Janssen, MSD, Lilly, Novartis and support for clinical trials from Abbvie, BMS, Lilly, Novartis and Samsung; KM has received honoraria and/or consulting fees from Abbvie, Lilly, Galapagos, Serac Healthcare, Deepcure, UCB, Zura Bio and research grants from Astra Zeneca, Lilly, Gilead, Serac Healthcare and Deepcure. GS has received funds for consulting from BMS, Janssen and Novartis; JAS has received research support from Boehringer Ingelheim and Bristol Myers Squibb unrelated to this work. He has performed consultancy for AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Inova Diagnostics, Janssen, Optum, Pfizer, ReCor, Sobi and UCB unrelated to this work; RT has received funds for consulting from CSL, AbbVie, Nextera, Sandoz, Viela Bio and Janssen-Cilag and received research contracts from CSL and Viela Bio; APC has received consulting and speaker bureau fees from Abbvie, BMS, Galapagos, UCB, Galvani, Janssen, Roche and Arthrogon, and research grant support from BMS, UCB and Janssen, with funds administered by King's College London.

Patient consent for publication

Not applicable.

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