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Preclinical Rheumatoid Arthritis and Rheumatoid Arthritis Prevention

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Abstract

Purpose of review: This review is to provide an update on the current understanding of rheumatoid arthritis (RA) development related to disease development prior to the onset clinically-apparent synovitis (i.e. Pre-RA), and opportunities for disease prevention.

Recent findings: A growing number of studies have demonstrated that serum elevations of autoantibodies rheumatoid factor (RF), antibodies to citrullinated protein/peptide antigens (ACPA) and antibodies to other post-translationally modified proteins (e.g. carbamylated proteins) are highly predictive of future development of IA/RA during a period that can be termed Pre-RA. Other factors including genetic, environmental, symptoms and imaging findings can also enhance prediction. Moreover, several novel biomarkers and changes in autoantibodies (e.g. glycosylation of variable domains) have been identified in Pre-RA. There has also been growing evidence that initiation and propagation of RA-related autoimmunity during the Pre-RA phase may be related to mucosal processes. The discovery of Pre-RA has also underpinned the development of several clinical prevention trials in RA; specifically, the PRAIRI study demonstrate that a single dose of rituximab can delay the onset of clinically-apparent IA in at-risk individuals. Additional studies are evaluating the ability of drugs including abatacept, hydroxychloroquine and methotrexate to prevent or delay future RA.

Summary: The results from ongoing natural history and prevention trials in RA should further inform several critical issues in RA prevention including identification and enrollment of individuals at high-risk of imminent RA, the efficacy, safety and cost-effectiveness of prevention, and potentially the identification of new targets for prevention.

Keywords

Rheumatoid arthritis; preclinical; autoantibodies; antibodies to citrullinated protein antigens (ACPA); rheumatoid factor; rheumatoid arthritis prevention

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Introduction

Advances in therapies, early treatment, and treat-to-target strategies have improved outcomes for many individuals with rheumatoid arthritis (RA). However, despite these advances, once the first onset of clinically-apparent inflammatory arthritis occurs in RA, even with therapy, most individuals do not return to a pre-disease state of sympotoms[1,2]. Additional barriers in care of individuals with RA include delays in diagnosis, difficulties in access to rheumatology specialists, and rising costs of drugs[3–5]. As such, RA is disease that could be benefitted from preventive interventions.

Supporting the possibility of prevention, multiple studies demonstrate a period of development of RA that is characterized by abnormalities of autoantibodies and other biomarkers in absence of and prior to the appearance of clinically-identifiable inflammatory arthritis (IA) that characterizes RA. This period can be termed “Pre-RA”[6], and its inclusion in an overall model of RA development is presented in Figure 1. Importantly, the discovery of Pre-RA has led to the development of several prevention trials in RA that may soon result in a paradigm shift in RA where preventive interventions are included in the management of this disease.

Herein, we will review several of these key recent findings in Pre-RA and describe a potential research agenda related to prevention.

Overview and advances in understanding of Pre-RA

The major autoantibody systems described in Pre-RA have been rheumatoid factor (RF) and antibodies to citrullinated protein antigens (ACPAs)[7,8], the most common available version of which is the anti-Cyclic Citrullinated Peptide (CCP) assay[9]. Furthermore, there emerging technologies such as multiplex arrays have identified that there are reactivities to multiple citrullinated antigens prior to the first citrullinated peptides and epitope spreading over time[10,11]. Other autoantibody systems are also abnormal in Pre-RA including antibodies to carbamylated proteins as well as other post-translationally modified proteins such as acetylated proteins[12,13]. Of note, other autoantibodies such as antibodies to malondialdehyde-acetaldehyde adducts (anti-MAA) have been described in RA[14], but not yet in the Pre-RA period. Furthermore, while alterations during Pre-RA in the glycosylation of the Fc portion of antibodies have been known[15], newer studies have identified glycosylation changes in the variable portions of autoantibodies[16]. Additional biomarkers and processes have also been identified in Pre-RA including elevations of survivin[17], increases in 14-3-3 eta[18], and alterations of B and T cell subsets[19,20]; low levels of omega-3 fatty acids have also been associated with an increased risk of progression to IA in ACPA positive individuals[21].

While Pre-RA can be characterized by initiation and then expansion of autoimmunity inflammation prior to the onset of clinically-apparent IA, to date the specific initiating and propagating factors in disease development are unknown. However, of particular interest to understanding the initiation and propagation of RA-related autoimmunity in the Pre-RA stage, a transition to clinically-apparent IA, as well as potentially to identify novel targets for

treatment and prevention, is understanding the anatomic site of initiation of RA-related autoimmunity in Pre-RA. Importantly, while RA-related autoantibodies may be generated in the joints in individuals with established disease[22], several imaging studies, and one biopsy study, suggest that in most individuals who exhibit circulating RA-related autoantibodies, the joints do not have detectable synovitis[23–25]. If the joints are indeed without inflammation in Pre-RA, two questions can be raised: where are the RA-related autoantibodies being generated and what factors drive propagation and transition to clinically-apparent IA?

To address those questions, emerging data suggests that mucosal sites within the lung, oral cavity, and gut may contribute to the evolution of RA from Pre-RA to clinically-apparent IA (reviewed in[26]). Supporting this, there have been findings that ACPA generation in the lung in individuals at-risk for future RA is related to mucosal inflammation and neutrophil extracellular trap formation[27]. Other data suggest that the periodontal region and oral mucosa may play an important role with periodontal inflammation and local citrullination in the initiation of RA autoimmune response [28–30]. ACPA generation with peptidylarginine deiminase types-2 and -4 detection has been shown in the gingival tissue associated with inflammation in individuals without RA[31]. In particular, while data is somewhat conflicting, the periodontal pathogens *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have been suggested to be associated with the ACPA in patients with RA or in animal models[32,33]. Furthermore, an increased prevalence and severity of periodontal inflammation has been associated with serum ACPA elevations in first-degree relatives of patients with RA[34,35]. In addition, a recent study demonstrated increased prevalence of periodontitis and *Porphyromonas gingivalis* in ACPA positive individuals without IA[36].

Gut mucosa plays an important role on development and maintenance of an individual's immune system as much as the lung and oral cavity. Although the gut mucosa could have a role in disease pathogenesis of RA, the data supporting an association between the gut and autoimmunity in Pre-RA pathogenesis are limited[37]. However, some studies have suggested that gut microbiota may play some role in the early evolution of RA including findings that gut microbiome was altered in RA with early patients compared to controls[38–40]. In particular, *Prevotella copri* was reported to be enriched in untreated early RA patients and an at-risk group[37,41].

Importantly, several recent studies raise the point that mucosal processes may play a role in the transition from Pre-RA to clinically-apparent RA. Specifically, Kelmenson and colleagues demonstrated that IgG ACPA was elevated the earliest in Pre-RA while IgA ACPA increased around the time of transition to clinically-apparent RA[42]. Furthermore Arleevskaya and colleagues identified that the incidence of upper respiratory tract infections was higher in those who developed RA compared to contorls[43]. Finally, Jubair and colleagues noted in a collage-induced murine model of collagen-induced arthritis that antibiotics given after initial triggering of immunity with collagen injection abrogated future arthritis to a greater extent than when antibiotics were given before collagen injection[44].

In aggregate, these studies suggest that mucosal processes may act as co-factors or propagating factors in the development of RA perhaps once systemic autoimmunity has

already developed. However, more studies are needed in order understand the exact role that these processes play in RA development, and how ultimately these processes could be identified and targeted for prevention.

Prediction of future RA

There have been multiple retrospective case-control as well as prospective longitudinal studies in which biomarker markers and other factors have been evaluated for their ability to predict the likelihood and timing of future clinically-apparent IA/RA[7,8,45,46] and reviewed in[47]).

In general, in case-control studies, seropositivity for ACPA and/or RF strongly predicts future development of clinical RA, with positive predictive values (PPVs) typically >80%. Furthermore, several prospective studies of ACPA-positive individuals, identified variously through family studies, cohorts of symptomatic outpatients, and population screenings, have demonstrated PPVs for development of RA ranging from ~20 to >70% over 2-5 years of follow-up[21,45,46,48,49]. In these studies, the presence of ACPA, especially in high levels and accompanied by RF positivity are the most powerful predictors of future RA. However, other features also can improve prediction. These include self-reported joint pain and tenderness on examination, ongoing smoking, obesity, and genetic factors such as the shared epitope[21,45–49].

In addition, imaging may also improve prediction of the development of future RA. In particular, Rakieh and colleges found in a study of 100 ACPA positive individuals, 50 of whom developed IA/RA, that the presence of a positive power doppler ultrasound (US) finding, even in absence of a joint thought to have synovitis based on physical examination, improved prediction of future RA[45]. These findings raise an important issue about the role of imaging in defining IA, especially in individuals who may not have clear joint inflammation based a physical examination which has long been the gold standard of diagnosis and management in RA. Indeed, a general consensus that is based on studies demonstrating that in some individuals who exhibit circulating RA-related autoantibodies, that IA may not be present. However, these findings of a power doppler signal suggest that a subset of individuals with systemic autoimmunity may indeed have inflamed joints; in addition, other studies have suggested that structures adjacent to the joints such as tendons may be inflamed in ACPA positive individuals in absence clear articular synovitis[50]. But, given that there is growing understanding that imaging, including US and magnetic resonance imaging (MRI) may identify synovitis even in individuals considered healthy [51–53], and that there may be high variability in interpretation of images, there will need to be more research done before imaging alone could be used routinely to identify a form of arthritis that warrants treatment, even in absence of traditional clinically-apparent IA by examination.

Importantly, in a study of first-degree relatives of patients with RA from an indigenous population in Canada, Tanner and colleagues found that while some individuals with autoantibody positivity (ACPA and/or RF) progressed to RA, a number of individuals with elevated RA-related autoantibodies did not develop RA during follow-up, and in some cases

lost positivity over time[54]. These findings highlight how factors besides autoantibody positivity contribute to the pathogenesis and prediction of RA. However, Kelmenson and colleagues have demonstrated that clinical RA may still develop in patients how lose autoantibody positivity during Pre-RA[42]. Furthermore, Barra and colleagues have demonstrated that ~10% of individuals will be seronegative at the time of initial identification of clinically-apparent IA, and then later develop ACPA and/or RF positivity [55,56]. As such, further studies are needed to understand the biology and predictive value of fluctuating autoantibodies in RA development.

Importantly, history and examination findings alone can may also identify individuals at high risk of developing IA/RA. Specifically, a 2016 EULAR task force defined a set of high-risk characteristics in individuals with arthralgias but without arthritis, a phenotype termed Clinically Suspect Arthralgia (CSA)[57]. CSA can be assessed by the following: recent onset of symptoms, MCP joint symptoms, symptoms worst in the early morning, morning stiffness >60 minutes, first-degree relative with RA, and on examination, difficulty making a fist and positive MCP “squeeze test; if 3 or more of these factors are present, there is ~90% sensitivity and 74% specificity that an individual will develop IA by physical examination. CSA has been validated to some extent in additional work[58]; however, its broad use in identifying individuals at-risk for future IA needs additional study.

Strong predictive models for future RA have led to the development of prevention studies

Building on the predictive ability of autoantibodies, and in particular ACPA, for future RA, over the past several years, multiple trials have been developed to evaluate the potential for pharmacologic intervention to prevent or delay the future onset of RA. Of these, the PRAIRI study (Prevention of clinically manifest rheumatoid arthritis by B cell directed therapy in the earliest phase of the disease) has recently been published[59]. In PRAIRI, 81 individuals who were ACPA and RF positive as well as had an elevated C-reactive protein were randomized to receive either a single infusion of either rituximab 1000 mg or placebo (and all subjects received intravenous corticosteroids). At a median follow-up time of 29 months, the rate of development of IA/RA was not significantly different between groups (34% in treated group vs. 40% in the placebo group). However, the time to development of IA/RA in 25% of subjects was delayed by ~12 months in the rituximab group. More overall adverse events were observed in the rituximab group, but these were deemed not to be treatment-related.

There are several other prevention trials in RA currently underway with estimated completions in the early 2020’s. A U.S. placebo-controlled study entitled StopRA (Strategy for the Prevention of Onset of Clinically-Apparent RA), is enrolling individuals with anti-CCP3 positivity at a level >=2 times the upper limit of normal, regardless of whether arthralgia is present[60]. The enrollment is planned for 200 subjects, and the intervention is hydroxychloroquine for 1 year. Another placebo-controlled study is entitled APIPPRA (Arthritis Prevention in the Pre-Clinical Phase of RA with Abatacept) and is being conducted in the United Kingdom and The Netherlands[61]. Subjects with arthralgia plus either an ACPA level >= 3 times the upper limit of normal or ACPA and RF positivity will

be randomized to receive abatacept or a placebo for one year, with follow-up for an additional year after completion of the study drug. Additional studies to prevent or delay future RA are testing statins[62] in autoantibody positive individuals without IA, and methotrexate in individuals with arthralgia and 'subclinical' IA based on imaging[63].

The results from these studies should be highly informative to the field on several fronts including 1) the feasibility and methodology of identifying autoantibody subjects without IA through clinics, population-based screening or otherwise, 2) identifying 'true' rates of progression to IA/RA in order to refine predictive models and study inclusion criteria, and 3) the efficacy and safety of pharmacologic interventions. In particular, the PRAIRI study noted a delay but not a complete halt to the development of RA, suggesting that longer durations of therapy are needed to adequately prevent the onset of clinically-apparent IA in at-risk individuals. Although a permanent "reset" of the immune system from a limited intervention would be ideal, even starting continuous therapy earlier may have overall benefit. Such an approach could afford improved quality of life and protection against joint damage.

What are next steps to implement prevention in RA?

The clinical trials mentioned above will provide highly useful data related to prediction, efficacy and safety with the agents tested (Table 1). Furthermore, because finding individuals who are in a Pre-RA phase of RA is difficult as they may not present to clinical care, these trials should also develop infrastructure to identify at-risk individuals that can be utilized in future studies. This infrastructure could be similar to networks such as 'TrialNet' which have been built and utilized to support clinical prevention trials in Type 1 Diabetes[64,65]. Proposed infrastructure would include clinics that can refer individuals with autoantibody positivity and lacking IA to research centers, as well as include screening efforts in higher-risk populations like first-degree relatives of patients with RA, or more general population screens.

Perhaps most importantly, because these trials will represent the largest cohorts of ACPA positive individuals yet studied prospectively, it is also hoped that data from the clinical, genetic and environmental exposure assessments performed during these trials, as well mechanistic studies, will inform the next generation of prevention trials. Of particular interest will be validation of prediction models for future RA. This is important in part because current evidence suggests that not all ACPA positive individuals, even with other high-risk features such as symptoms, will go on to develop IA/RA at least within studied time periods. Therefore, there is a potential for over-treatment if every ACPA positive individual is given a preventive intervention. However, risk-benefit calculations will need to take into account several factors including the risk of the preventive intervention. This is because a because a mild intervention such as lifestyle change or relatively benign drug may be acceptable even if risk for future RA is low. In contrast, individuals with very high risk for future RA may be willing to take more powerful agents, although it may also be that they are so far along in the evolution of RA that prevention may be very difficult to attain with only modest interventions. Furthermore, all the agents used in the above-mentioned prevention trials are known to be effective in clinically classified RA; however, it may be

that there are new biologic targets for prevention that can be identified through more in-depth study of Pre-RA, and these interventions may be stage-specific. For example, an individual who is earlier in Pre-RA may need to focus on lifestyle changes, or certain biology pathways, while others who are at-risk for more imminent RA may need different biologic pathways targeted. Identifying these potentially new targets will require close collaborations between academics and industry.

Another important consideration in prevention is individuals' preferences for preventive interventions – i.e. what will a person be willing to take, and for how long, in order to prevent RA? Several studies have explored this already, and found that much depends on an individual's personal estimation of their risk for RA, their knowledge of RA and what the clinically-apparent disease could mean to them, and the safety and potential efficacy of a therapy[66–68]. To date, these studies have been conducted in largely hypothetical situations, but existing trials will hopefully provide insight into what individuals are willing to do to understand their risk for RA, and what steps they are willing to take to prevent disease.

Future trials may be able to target specific lifestyle or dietary interventions for RA prevention[69–71]. Since many studies have identified that the Pre-RA presence of smoking and obesity are risks for an individual to transition to future clinically-apparent RA, perhaps these factors could be targeted through smoking cessation and weight loss. Incorporating the issue of individuals' preferences for interventions, studies have found that education regarding RA risks may lead to willingness to change[72,73], although the impact of these changes on the long-term development of RA has not yet been studied. A caveat is that lifestyle modifications are difficult to influence; as such, it may be that the dominant studies for RA prevention will be pharmacological, although such studies will need to consider potential additional incorporation of lifestyle measures, especially since individuals may adopt these types of interventions on their own and that could influence trials if done in a non-systematic fashion.

Clinical prevention trials will also provide a basis to evaluate the real-world cost-effectiveness of preventive therapies. This is a critically important part of prevention, especially in regards to gaining the support of large-scale systems (e.g. governmental and health insurance agencies) for prevention, where a goal may be that all individuals get periodic assessment for personal risk for RA, much like lipids are tested and treated in cardiovascular disease prevention.

There is also a growing understanding that a variety of conditions such as lung disease[26], heart disease[74] and mental health disorders[75] may precede a formal diagnosis of RA. This is an intriguing area and could indicate that RA-related autoimmunity has pathogenicity on other organ systems besides the joints in Pre-RA. This area needs further exploration as it could indicate an 'autoimmune-opathy' associated with RA-related autoantibody elevations that may ultimately warrant intervention, even if IA is not present.

The rheumatology community needs to buy-in to prevention as well. There has been a tendency for rheumatologists to avoid treatment of individuals with only biomarker abnormalities – in other words 'treat the patient, not the test'. This has been to a large extent

due to the lack of specificity for rheumatic disease of some tests such as RF and anti-nuclear antibodies. However, while avoiding overtreatment is important[76], strong predictive values for future RA using models that include biomarkers and other factors will help overcome barriers to prevention in RA as well as potentially other rheumatic diseases. Indeed, there is a study underway in the United States called SMILE (Study of Anti-Malarials in Incomplete Lupus) to determine if hydroxychloroquine can halt or delay the progression from incomplete lupus to classifiable disease[77]. Findings from the prevention studies in RA and SLE may help change the paradigm of these diseases as well as other rheumatic/autoimmune diseases that follow a similar mode of development.

Conclusions

The understanding of Pre-RA development is growing, and prediction of future RA is improving. Based on strong predictive power of autoantibodies, and in particular ACPA, several prevention trials have been completed or are ongoing in RA. The information from the published PRAIRI is intriguing, and additional information from the ongoing clinical trials for prevention, as well as other natural history studies may soon move the field forward to where prevention is routinely implemented in clinical care of RA.

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Key articles/references

References 2 **and** 5 **(Gul et al, Rosa et al).** These citations describe that the timing of diagnosis and ‘remission’ from the standpoint of individuals with RA are not ideal, supporting that there are needs to improve RA care that may be helped by preventive strategies.

Reference 25 **(Holers et al).** This review describes hypotheses and date regarding potential mucosal role(s) in the development of RA.

Reference 46 **(Van Boheemen et al).** This review presents results from a number of studies on the use of biomarkers and other factors to predict the future onset of RA.

Reference 51 **(Zabotti et al).** This review evaluates the benefits and concerns of imaging in Pre-RA.

Reference 58 **(Gerlag et al).** This citation is the full publication of the PRAIRI study which is a clinical trial of rituximab in individuals at-risk for RA.

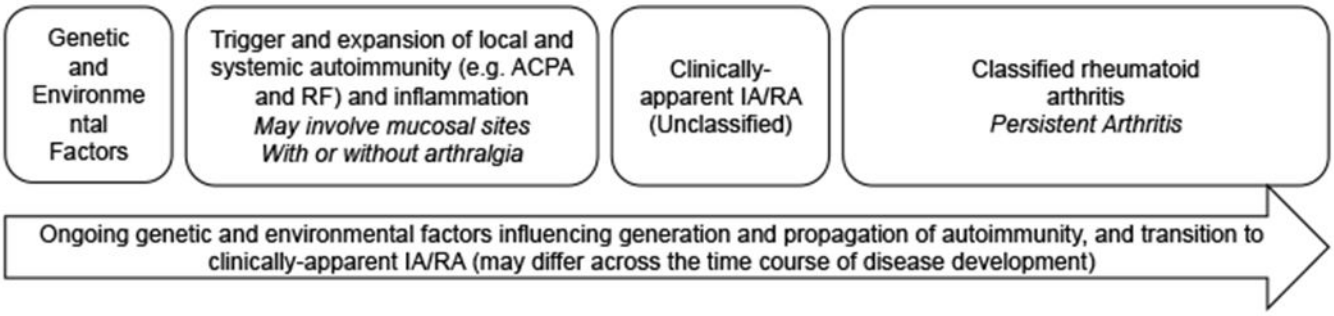

Figure 1.
Model of RA Development

Table 1.

Key steps to implementing rheumatoid arthritis prevention

Deep understanding of existing prevention trials to enhance understanding of prediction of future disease, understand efficacy, and potentially identify new targets for prevention
Identification of appropriate targets for prevention - May include pharmacologic targets, dietary and lifestyle interventions - Will need to take into account the genetic, environmental (including micro-organisms) that initiate and propagate RA
Broad agreement on terminology applicable to the natural history of RA
Understanding of individuals' preferences for participating in screening and prevention for RA
Develop highly accurate prediction models for future RA - These models can use established and emerging biomarkers and other factors. - Will need to estimate overall risk for future RA, as well as timing of future RA so that interventional studies can be designed around specific time intervals and estimates of outcomes of RA
Development of infrastructure to identify individuals at-risk for future RA who are informative in clinical trials that can be leveraged to implement prevention trials in RA (and ultimately other rheumatic diseases)
Engage rheumatology, primary care, health care systems (including governmental), public health agencies and industry to support prevention
Ultimately understanding the overall efficacy and cost-effectiveness of RA prevention so that RA prevention can be broadly implemented and have a positive impact on public health