Published in final edited form as:

Best Pract Res Clin Rheumatol. 2013 August ; 27(4): 467–485. doi:10.1016/j.berh.2013.09.002.

Can Rheumatoid Arthritis Be Prevented?

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Abstract

The discovery of elevations of rheumatoid arthritis (RA)-related biomarkers prior to the onset of clinically apparent RA raises hopes that individuals who are at risk for future RA can be identified in a preclinical phase of disease that is defined as abnormalities of RA-related immune activity prior to the clinically apparent onset of joint disease. Additionally, there is a growing understanding of the immunologic processes that are occurring in preclinical RA, as well as a growing understanding of risk factors that may be mechanistically related to RA development. Furthermore, there are data supporting that treatment of early RA can lead to drug free remission. Taken as a whole, these findings suggest that it may be possible to use biomarkers and other factors to accurately identify the likelihood and timing of onset of future RA, and intervene with immunomodulatory therapies and/or risk factor modification to prevent the future onset of RA in at-risk individuals. Importantly, several clinical prevention trials for RA have already been tried, and one is underway. However, while our understanding of the growing understanding of the mechanisms and natural history of RA development may be leading us to the implementation of prevention strategies for RA, there are still several challenges to be met. These include developing sufficiently accurate methods of predicting those at high risk for future RA so that clinical trials can be developed based on accurate rates of development of arthritis and subjects can be adequately informed of their risk for disease, identifying the appropriate interventions and biologic targets for optimal prevention, and addressing the psychosocial and economic aspects that are crucial to developing broadly applicable prevention measures for RA. These issues notwithstanding, prevention of RA may be within reach in the near future.

Keywords

Rheumatoid arthritis; Preclinical disease; Pathophysiology; Prediction; Prevention

Introduction

Rheumatoid arthritis (RA) is a systemic, autoimmune inflammatory disease that primarily affects the joints. While the exact prevalence rate across the entire population is unknown, available data suggests that affects ~1% of the population, making it one of the most common autoimmune rheumatic diseases(1, 2). Furthermore it leads to >30 \$billion dollars

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Disclosures

Dr. Deane has filed for a patent regarding the use of biomarkers to predict actionable outcomes in rheumatoid arthritis

in health-related costs annually in the United States alone(3). While as discussed below there are emerging data that early treatment of RA can lead to increased rates of drug-free remission(4), for the vast majority of patients with RA who are managed in routine clinical practices, once it becomes clinically apparent it is a disease that requires prolonged if not lifelong therapy(5). Based on these figures, means to prevent RA could lead to substantial improvements in public health.

Patients with RA typically present to health-care once the signs and symptoms of arthritis (joint pain, stiffness and swelling) develop; however, established and emerging data from multiple studies support that the initial immune dysregulation of RA, as measured by RA-related autoantibodies (e.g. rheumatoid factor [RF] and antibodies to citrullinated protein antigens [ACPAs]) and other inflammatory markers, occurs long prior to the first joint symptoms. While the terminology to describe the autoimmunity of RA prior to the onset of clinically apparent synovitis is still being established(6) (and how to classify clinically apparent disease is also difficult, evidenced by 2 classification criteria(7, 8)), currently, a workable label to describe the period of detectable RA-related autoimmunity prior the onset of the clinically apparent signs and symptoms of joint disease of RA is the '**preclinical**' phase of RA development (Figure 1).

Importantly, abnormalities of RA-related biomarkers during preclinical RA are highly predictive of future onset of clinically apparent RA. In addition, a growing number of studies of preclinical RA are identifying mechanisms of RA development as well as risk factors that are likely truly related to disease pathogenesis. When these factors are taken as a whole, they suggest that RA may be preventable, and there is hope that we may soon be able to approach the management of RA much like the medical community approaches cardiovascular disease today where risk factors are identified and modified to prevent the future occurrence of clinically apparent disease.

Herein will be reviewed some of the current understanding of the natural history, risk factors and mechanisms of RA development, with discussion on these issues focused on potential strategies that could be employed to prevent disease as well as some challenges to be addressed in order to make the prevention of RA a reality in the near future.

The '**preclinical**' phase of RA development

Multiple studies now demonstrate that there is a '**preclinical**' phase of RA development during which there are abnormalities of autoantibodies and inflammatory markers prior to the onset of appearance of the signs and symptoms of joint disease that characterize clinically apparent RA (Figure 1)(9–21). Some of these studies have been prospectively conducted; however, most have utilized biospecimens fortuitously collected prior to the onset of RA. As such, the exact timing of appearance of biomarkers prior to the onset of signs and symptoms of RA has been difficult to identify, but overall RA-related biomarkers, and especially autoantibodies, seem to appear in the circulation on average 3–5 years prior to the onset of clinically apparent RA.

Initial studies of preclinical RA focused largely on the autoantibodies RF as well as ACPAs, the most commonly tested version of which is the anti-cyclic citrullinated peptide (anti-CCP) antibody, and a range of inflammatory markers including C-reactive protein and a variety of cytokines and chemokines (10–14, 16, 21–26). More recent studies have evaluated a wider range of immunologic factors in preclinical RA that include factors such as additional ACPA tests (27), autoantibodies to peptidyl arginine deiminase (PAD, the human enzyme that is responsible for tissue citrullination)(28, 29), alterations of glycosylation of antibodies (30), an increasing array of cytokines and chemokines as well as gene expression

profiles(18–20, 31), immunoglobulin isotypes and avidity (32, 33), and autoantibodies to specific citrullinated peptides and proteins (34–36). Furthermore, multiple studies have shown that the levels of autoantibodies increase in preclinical RA as the time of clinically apparent disease approaches(12, 13, 19, 27).

In particular, the studies detailing autoantibodies to specific citrullinated peptides and proteins in preclinical RA have provided important insights into the pathophysiology of RA development. As background, while the antigen structure for the first commercially available anti-CCP is publically available (37, 38) the later generation anti-CCP assays test for autoantibodies to proprietary citrullinated antigens; therefore, it is unclear if the test is positive what specific citrullinated protein is being recognized by a particular patient. Several research groups have developed autoantibody assays for specific citrullinated peptides and proteins, and applied these tests to preclinical RA. Using a bead-based array to test autoantibodies to multiple individual citrullinated proteins/peptides in preclinical RA samples from subjects from the United States military, Sokolove and colleagues demonstrated that there is epitope spreading to citrullinated targets in the preclinical RA period, and the numbers of autoantibodies to citrullinated proteins increased in preclinical RA as the time to diagnosis approached (34). Interestingly, they also identified that the expansion of autoantibodies to citrullinated targets appeared to stop after the diagnosis of RA, suggesting that once clinically apparent RA developed there epitope spreading halted although the reasons for this finding, such as medication effect or other factors, are not known. Brink and colleagues used a Swedish cohort to also evaluate individual ACPAs in preclinical RA samples, and demonstrated that an increased number of positive ACPAs had a higher specificity for future RA (39). Similar to what was seen in the Sokolove study, Brink and colleagues also found that systemic autoimmunity in RA was initially restricted to a small number of ACPAs that expanded as time to RA diagnosis approached. Of interest, the ACPAs detected earliest in the preclinical period were found to often disappear over time suggesting that early in the development of RA autoimmunity may be initiated by a break in tolerance to certain citrullinated proteins, and over time the development of autoantibodies to other citrullinated proteins may be important in the propagation of autoimmunity and transition to clinically apparent disease.

Of note, the prolonged period of preclinical autoimmunity in RA has raised the hypothesis that RA does not start in the joint but rather at some extra-articular site, with this hypothesis supported by several joint examination and imaging studies, as well as a synovial biopsy study, that have found that the majority of subjects with circulating RA-related autoantibodies do not have clear evidence of synovitis (40–44). The finding of IgA-related autoantibodies in preclinical RA (12, 19), associations between preclinical RA autoantibody positivity and lung disease(41, 45, 46), as well as associations between RA and organisms that cause periodontal disease, gut disease or genitourinary disease (47–51) suggest that the site of initiation of RA may be a mucosal surface. Investigations into these aspects of RA development are rapidly expanding but, as will be discussed below, they raise an important issue regarding RA prevention: should extra-articular sites be targets for preventive interventions?

Risk factors for RA development

Preventive strategies that target risk factor modification would ideally be based on a sound understanding of the modifiable exposures that influence the development of RA. There are numerous factors that have been associated with increased risk for RA. Some of these risk factors are presented in Table 2. Several of the strongest risk factors are certain genetic factors including the presence of HLA alleles containing the ‘shared epitope’, female sex, family history of RA, and exposure to cigarette smoke (52–56). In particular, smoking is the

strongest known environmental risk factor, especially for ACPA positive RA, and is thought to explain up to 35% of ACPA positive RA(57). There are also emerging understanding of other factors that may influence RA risk including the protective effect of factors such as alcohol use and intake of certain fatty acids (58, 59). Furthermore, as mentioned above, there is growing evidence suggesting that certain infections and/or inflammatory processes such as periodontal disease and infections with *Porphyromonas gingivalis* may be triggers for RA(47).

However, a caveat to these risk factors and their association with RA is that most of these associations were identified in subjects who had established RA, and there may be many biases associated with such findings including recall bias, or effects of immunomodulatory therapy on a variety of biomarkers of risk (e.g. associations of infections may be influenced by immunosuppression). It is also not clear in the majority of studies if the risk factors for RA that have been identified are related to the initiation of RA, which likely occurred years prior to the clinically apparent onset of their disease. Furthermore, even if a risk factor is truly associated with RA, the reasons behind why they are related to RA is not wholly clear, although there is emerging data to explain how certain risk factors may influence RA. For example, smoking can lead to citrullination of human tissue likely through a variety of means including upregulation of PAD enzymes(60, 61). Also, HLA molecules that contain the shared epitope may preferentially present citrullinated peptides to the immune system(62). Smoking and the shared epitope may therefore act in concert to drive the development of ACPAs and ultimately RA (63). In addition, *Porphyromonas gingivalis* produces an enzyme that can citrullinate human enolase, and autoantibodies to citrullinated enolase are found in strong association with RA(47, 64); therefore, this organism may drive some aspects of autoimmunity in RA.

An overall model of RA development

Based on available data it is likely that RA develops as described in Figure 1 where initially genetic, environmental and perhaps stochastic factors combine to initiate autoimmunity. Once an initial break in tolerance has occurred, over time, and influenced by ongoing factors that include the same or perhaps additional genetic and environmental factors, autoimmunity evolves to a more pathogenic stage. This state is manifested by expansion of autoreactive T and B cells, epitope spreading, increases in inflammation, up-regulation of signaling molecules, increases in autoantibody levels, and alterations of autoantibodies pathogenicity such as changes in glycosylation rendering them more capable of inducing disease. Ultimately, tissue injury occurs to a sufficient degree that the clinical symptoms and signs of RA develop.

Notably, while most studies suggest that abnormalities of RA-related autoantibodies are highly specific for future RA, some individuals with elevations of these autoantibodies may never progress to RA. However, such individuals may still be valuable to study to learn mechanisms of development of RA-related autoimmunity, and perhaps identify key factors that are responsible for the initiation as well as propagation of autoimmunity. Furthermore, emerging data suggest that asymptomatic autoimmunity is not as benign as once thought. In particular, studies demonstrating that the presence of autoantibodies including antinuclear antibodies (ANAs) and RF are associated with cardiovascular disease even in absence of a classifiable rheumatic disease may lead to a shift in our understanding of the pathogenic role of autoimmunity in a broad range of illnesses(65–67), and we may soon classify autoimmunity as a pathogenic condition that requires intervention even in absence of a classifiable disease.

How accurate are prediction models for future RA (and how accurate do they need to be)?

An important step in ultimately preventing RA is accurate identification of subjects who are at future risk of disease (i.e. to prevent, we must first accurately predict). Importantly, prediction includes identifying the likelihood of ever developing disease, as well as identifying the time period in which clinically apparent disease will appear. This is because if clinical trials are developed for RA prevention, they will need to be designed around a clear understanding of the number of subjects expected to develop RA within the temporal confines of the clinical trial.

In terms of identifying the likelihood of developing future RA, elevations of combinations of ACPAs alone and in combination with RF have been shown to be highly predictive of future disease, with some estimates of 100% positive predictive values (PPV) for future RA in case-control studies (12–14), although these PPVs are lower when the prevalence rates of disease in the general population are considered. For example, in the groundbreaking work by Rantapaa-Dahlqvist and colleagues that identified elevations of anti-CCP and RF prior to the onset of RA using samples available from a Swedish cohort study, within the case-control confines of the study, the PPV of anti-CCP and RF-IgM positivity for future RA was 100%; however, when the same sensitivity and specificity derived from this case-control study was applied to a general population where an expected prevalence of RA is ~1%, the PPV of these autoantibodies fell to 16% (12). Based on this, even seemingly robust prediction models developed in case-control studies may have lesser predictive capabilities when applied to more general populations.

However, a prospective study of individuals with positivity for ACPAs and/or RF suggests that elevations of these autoantibodies are truly highly predictive of the future onset of RA. Specifically, a long-running Dutch study has used an extensive health-care network to identify and recruit ACPA and/or RF positive individuals with arthralgia but no clinically detectable synovitis, and then followed these subjects to investigate the natural history and mechanisms of RA development. An early publication from this project demonstrated that risk for RA is associated with being positive for both ACPA and RF, showing that up to 40% of these individuals will have developed RA within approximately two years, with higher rates of progression and quicker onset of disease in subjects with high-titer ACPA positivity (68). Furthermore, as of a publication in 2012, this project has followed 374 individuals for several years, and combined other predictors of RA included having RA in a first degree family member, alcohol non-use, duration, severity and location of joint symptoms (including morning stiffness), and a history of swollen joints as reported by the patient (69); in this model, patients with the highest risk scores had the highest incident rates of RA development (80% with RA within 60 months), and furthermore had the quickest onset of RA (60% had developed RA within 24 months). Certainly these individuals were identified through a specific clinical pathway based on medical evaluations for musculoskeletal complaints and therefore this risk prediction model may not be directly applicable to all individuals; however, the findings do suggest that elevations of RA-related autoantibodies are highly predictive of future RA.

The findings from this Dutch 'arthralgia' cohorts address both the likelihood and timing of RA development. Other studies have indirectly assessed this as well, with the findings that elevations of ACPAs and RF appear on average 3–5 years prior to the appearance of clinical RA, although some individuals have been noted to have elevations of autoantibodies >10 years prior to a diagnosis of RA (12–14). Also, multiple studies have noted that higher levels of autoantibodies, and combinations of ACPAs and RFs, are most likely to be present in a 3-year window prior to a diagnosis of RA (12, 13).

Several studies have also addressed the likelihood and timing of future RA more directly. In particular, Deane and colleagues used preclinical samples from military subjects who developed RA to develop a two-step approach to predicting the likelihood and timing of future RA. They initially identified that that elevations of anti-CCP and/or 2 or more RF isotypes was highly specific for future RA (>95%). In the second step, they identified that within individuals that exhibited that autoantibody profile prior to a diagnosis of RA, an increased number of elevated cytokines and chemokines was associated with a shorter time to onset of RA(19). Solokolve and colleagues used the same military sample set further to identify that elevations of a set of specific ACPAs along with elevations of certain cytokines and chemokines had fair sensitivity (58.2%) and specificity (87.0%) for a diagnosis of RA within 2 years(34).

Furthermore, as some studies have suggested that a combination of genetic factors and autoantibody positivity is highly predictive of future RA(70, 71), an approach that combines autoantibody tests with markers of inflammation, as well as potential inclusion of genetic and environmental risk factors, and symptoms, may be reasonable approach to identify individuals at high-risk of development of future RA, and also be able to determine in what time frame they will develop clinically apparent disease. Supporting this, Karlson and colleagues have developed a prediction model for future RA in the Nurses' Health Cohort that incorporates both genetic and environmental factors to develop a predictive model for RA with an area under the curve of ~0.7(72), although it remains to be seen how this approach can identify the timing of development of future RA, and incorporate additional factors such as autoantibodies and symptoms.

In terms of designing an actionable clinical trial that will ultimately have wide-spread applicability, predictive models will need to balance accuracy with feasibility; therefore, models that utilize primarily biomarkers may have the most utility in the design of clinical prevention trials and ultimately to develop readily attained 'personalized medicine' approaches where a specific individual's risk for the likelihood and timing of onset of a future RA can be determined in a manner similar to CVD where individuals are evaluated for risk for a CVD event within a defined period using models such as the Framingham Risk Score (73), and subsequently these risk factors are targeted with lifestyle modifications or pharmacologic therapy to reduce risk for future disease.

Of note, the timing of onset of clinically apparent RA goes beyond biology. It also is affected by psychosocial factors including individuals' perceptions of what abnormal health and joint symptoms are, access to health care, and the ability of initial health care providers to establish a correct diagnosis(74). As such, it may be that within a clinical trial that subjects may be found to develop RA much earlier than would have otherwise been noted. This will need to be taken into account when designing clinical trials. Furthermore, what is considered to be clinically apparent RA is a difficult area. For example, there are now two established classification criteria for RA, the 1987 American College of Rheumatology (ACR) Revised criteria, and the 2010 ACR/European League Against Rheumatism (EULAR) criteria(7, 8). However, while these criteria have use in both clinical and research practices, subjects with a single swollen joint and ACPA positivity may well have RA but fail to meet formal classification criteria of RA. There are other classification criteria for IA such as the Leiden and Norfolk criteria(75, 76), and perhaps these are important outcomes to consider in RA prevention especially as very limited IA may be highly important in natural history studies and clinical prevention trials.

PREVENTION OF RA

Based on the above discussion, there is hope that RA-related biomarkers can be used to identify subjects who are at sufficiently high risk for future RA that they would be candidates to receive interventions to prevent disease while they are still in early phase of disease development prior to substantial joint injury. These interventions could take many forms and include risk factor modification (e.g. smoking cessation, and perhaps increased intake of fish and alcohol). Furthermore, based on numerous studies (see Table 4) that suggest that early pharmacologic treatment in RA leads to improved long-term outcomes, pharmacologic therapy in preclinical RA may lead to abrogation of RA-related autoimmunity and prevention of future RA. In particular, pharmacologic intervention(s) that target specific or more general aspects of the initiation and propagation of RA may halt the progression of RA. For example, if a dominant inflammatory pathway or process (i.e. a certain organism that appears to drive the initiation of RA, or a certain cytokine-driven process) could be clearly identified as important to the initiation and/or propagation of autoimmunity in preclinical RA, it could then be targeted for prevention. Also, given the emerging data that RA may be initiated outside of the joint, perhaps preventive interventions should target the mucosal or other sites where RA may be initiated, or seek to block the transition circulating autoimmunity from initiating joint disease, if indeed that is what occurs in the pathogenesis of RA. Furthermore, prevention may be reached by induction of tolerance to antigens that are important to the initiation and propagation of RA at key time points in the natural history of RA. For example, tolerizing regimens could be introduced to subjects at-risk for future RA who are identified after an initial break in tolerance to citrullinated proteins but prior to substantial expansion of autoimmunity to citrullinated (or other) antigens that are crucial to a transition from preclinical autoimmunity to clinically apparent disease.

As for specific ways to approach RA prevention, as discussed below, broad application of risk factor modification could lead to decreased disease, and such approaches may ultimately be highly important in reducing the societal burden of RA. However, to maximize our understanding of the natural history and mechanisms of RA development as well as ‘prove’ effectiveness of certain interventions, ideally, clinical prevention trials for RA should be done where the specific effects of intervention(s) on RA-related autoimmunity can be measured in a detailed fashion (and preferably in randomized, blinded, controlled trials) in order to optimize the scientific understanding of disease development, as well as to make specific recommendations for wide-spread prevention.

Furthermore, when considering prevention of RA one must consider that the term ‘prevention’ may mean different things to different people. It may mean prevention of progression from a phase of undifferentiated IA to that of classifiable RA (Phases 4 and 5 in Figure 1). It could mean identification of individuals who have developed RA-related autoimmunity in absence of overt IA, and implementation of therapies to prevent the further development of disease. It could also mean modulation of RA-related risk factors to prevent incident autoimmunity. Approaches to each of these types of prevention will be discussed in more detail below.

Prevention of progression from undifferentiated IA to classifiable RA

The progression of undifferentiated IA to classifiable RA is highly related to the definitions of disease states that are used. Specifically, it may take months for someone to progress from undifferentiated IA to classifiable RA if classifiable RA is defined by the 1987 ACR criteria(77). However, with the 2010 ACR/EULAR criteria, an individual with IA and high-titer RA-related autoantibody positivity may transition relatively quickly to classifiable RA

because it may be only a matter of having 3 swollen small joints evolve to 4 swollen small joints(8).

With these issues in mind, several studies have evaluated the efficacy of interventions to prevent progression of undifferentiated IA to classifiable RA. In the PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment (PROMPT) study, 110 patients with undifferentiated IA of <2 years duration were randomized to receive MTX versus placebo. They were followed for ~18 months for the primary outcome of fulfillment of the 1987 ACR RA classification criteria(78). In this trial, 40% of the MTX-treated patients developed RA compared to 53% in the placebo group, although importantly the majority of benefit of MTX in delaying or preventing development of classifiable RA was seen in the anti-CCP positive subgroup of patients. Furthermore, the onset of classifiable RA was later in the MTX-treated group, and radiographic joint damage was also less in MTX-treated subjects.

In the Stop Arthritis Very Early (SAVE) trial, patients with IA of <16 weeks duration were given a single intramuscular (IM) dose of 120 mg of methylprednisolone versus placebo, and followed for 12 months for the development of RA by 1987 criteria(79). This intervention did not result in any decrease in progression to RA between the study groups.

In the STIVEA trial, patients with early IA (4–10 weeks duration) were given 3 weekly IM injections of 80 mg of methylprednisolone versus placebo, and followed for 12 months(80). This intervention resulted in the delay of prescription of DMARDs, and per the authors, prevented the development of RA (1987 criteria) in 1 of 10 subjects treated.

In the ADJUST trial, 50 patients with undifferentiated IA (2 or more swollen joints not fulfilling 1987 RA criteria [2010 criteria not assessed]) were randomized to receive abatacept versus placebo for 6 months, with the primary outcome evaluated being the development of RA (1987 criteria) at 12 months. At 12 months, 12/26 (46%) of abatacept-treated patients had progressed to RA compared to 16/24 (67%) of placebo-treated subjects, and there was a decrease in autoantibody titers in those who received abatacept, although no statistical comparison was provided for these results and in the abatacept treated subjects autoantibody levels rose upon cessation of therapy.

In addition, several case studies have shown that hydroxychloroquine (HCQ) use in patients with palindromic rheumatism is associated with a slowing or halting of the progression to persistently active and classifiable RA, supporting that pharmacologic intervention may halt the development of RA (81–86). In particular, in an observational study by Gonzalez-Lopez and colleagues of patients with palindromic rheumatism, use of HCQ (or chloroquine) halted the progression to classifiable RA (1987 criteria) in 44/64 (~69%) of subjects, and in comparison to observational controls, use of antimalarials led to a nearly 3-fold decrease in progression to persistent disease. In addition, in a case-series by Hanonen and colleagues, 7/15 (~47%) of patients with PR treated with HCQ had complete disease remission (86). While these are uncontrolled studies that contained a variety of types of patients, some of whom likely did not truly have a ‘preclinical’ RA phenotype as some later developed lupus or seronegative spondyloarthropathies, the findings have some relevance to RA prevention and suggest that HCQ may have directly applicability to halting progression of RA from early clinically apparent IA to persistent articular disease (84, 87).

Overall, the results of these studies in preventing the progression from undifferentiated IA to classifiable RA are mixed; however, overall, it appears that an intervention sustained for some period of time with an immunomodulatory agent appears to reduce some of the progression of RA, and supports that progression from IA to RA may be prevented. Further discussion regarding choices of specific pharmacologic agents to prevent RA is below.

Prevention of initial onset of IA in subjects who have developed RA-related autoimmunity

Moving even further back into the evolution of RA, subjects who have developed abnormalities of RA-specific autoantibodies in absence of overt IA as defined by physical examination findings of synovitis (Figure 1) may be targeted for disease prevention. This time period of RA development is particularly attractive to target because, as discussed above, abnormalities of these biomarkers are highly predictive of the future onset of RA and therefore in clinical trials they can be used to inform subjects of their specific risks for developing RA, as well as give some indication as to the expected timing of onset of clinically apparent RA – factors which are highly important in designing the duration of a clinical trial, powering the study, and recruiting subjects. In addition, immune modulation during this period of RA development may be particularly amenable to alteration because more ‘permanent’ changes in inflammation such as changes in fibroblasts that render them more persistently activated may not yet have occurred(88, 89).

Bos and colleagues published the results of such a trial in 2010 wherein they treated 83 anti-CCP positive subjects with ‘arthralgias’ but no IA based on examination by 2 rheumatologists with 2 doses (baseline and 6 weeks) of IM 100 mg dexamethasone versus placebo(90). Dexamethasone reduced autoantibody titers (ACPAs and rheumatoid factor); however, it did not delay the progression to clinically apparent IA suggesting that another agent, or more sustained therapy would be necessary to prevent the development of RA.

Along a similar vein, in 2009, Dutch investigators initiated the PRAIRI study (Prevention of clinically manifest rheumatoid arthritis by B cell directed therapy in the earliest phase of the disease), which is a randomized controlled trial to evaluate the efficacy and safety of rituximab to prevent the onset of RA in individuals who are at high risk for future onset of clinically apparent RA. Based on information published on the Dutch clinical trials network (www.trialregister.nl/trialreg/admin/rctview.asp?TC=2442) the inclusion criteria for this trial are subjects with elevations of RF and ACPAs in absence of physical examination evidence of IA, and one or more of the following measures: elevated C-reactive protein, evidence of subclinical synovitis by imaging. Subjects are being treated with a single dose of rituximab 1000 mg, or placebo, with the primary outcome being a decrease in the number of subjects who develop classifiable RA at 4 years (it is unclear from the website which criteria for RA will be used). Secondary outcomes are immunologic changes that may indicate abrogation or permanent improvements in RA-related autoimmunity. The results of this trial should be become available shortly, and while one could argue that since part of the inclusion criteria is that subjects would have imaging evidence of synovitis that this is really a study of prevention IA from progressing to RA, it will be highly informative to the field of preclinical RA, and RA prevention. In particular, the rates of progression to classifiable RA identified in this study can inform future trials; furthermore, a full understanding of the methods of this trial to identify individuals who are at high-risk for future RA will be enlightening as a major part of any preventive effort for RA is identifying those who are at-risk for future disease.

Choosing a pharmacologic agent to prevent RA – which one(s)?

The above described attempts at RA prevention have selected specific pharmacologic agents and duration of therapy that were hoped to abrogate the progression of disease. The duration of therapy is a particular important point because ideally, a pharmacologic intervention would be given for a short and well-defined period of time, and lead to permanent abrogation of autoimmunity, although even starting an immunomodulatory agent that needs to be continued to maintain disease quiescence may still be beneficial if some of the damage from early, clinically apparent RA could be prevented.

As to which pharmacologic agents should be used to prevent progression from undifferentiated IA to RA, or used even earlier in the natural history of RA - that remains open for debate. Should drugs that target relatively specific aspects of immunity (e.g. abatacept and T cell costimulation(91)) be used, or should agents be used that may have broader immunologic effects, such as methotrexate and hydroxychloroquine that likely affect the immune system through several pathways(81, 92–94)? Since many studies of early RA suggest that combination therapy with either methotrexate and anti-TNF agents, or even triple therapy are superior to monotherapy in controlling disease, should a combination of those medications be used to prevent future RA in high-risk individuals?

However, while use of combination therapy may be considered by many as the optimal approach control disease in many patients with established RA, it is not clear if that approach would be necessary or appropriate in preventing RA in high-risk asymptomatic subjects where safety is as much of a concern as efficacy. As such, the specific pharmacologic agents that are used in RA prevention will need careful consideration, and it may be that safer, better tolerated agents may need to 'fail' prior to the use of potentially more effective yet risky therapies. Importantly, a greater understanding of mechanisms of development of RA in general as well as during the preclinical period may yield additional targets for pharmacologic interventions. For example, Deane and colleagues identified that elevations of IP-10 preceded the appearance of anti-CCP in preclinical RA(19); therefore, perhaps targeting these may prevent the development of autoimmunity. Furthermore, perhaps the IL-17 or IL-10 pathways are of critical importance in preclinical RA, and targeting these pathways may therefore result in RA prevention. This will need to be explored in future well-conducted preclinical RA studies that may include animal models of disease development.

Risk factor modification and RA prevention

As discussed above, multiple environmental and lifestyle-based risk factors for RA have been identified, and modifying these to prevent RA is an attractive approach, especially given the potential toxicities of pharmacologic interventions. For example, exposure to tobacco smoke is strongly associated with RA, with some estimates that it explains ~30% of the risk for seropositive RA(57). Based on this, some have proposed that broadly-implemented programs for smoking cessation would result in a significant reduction of RA(57). In addition, recent attention has focused on the potential role of periodontal inflammation and infection with the organism *Porphyromonas gingivalis* in the pathogenesis of RA(95). If this relationship is truly causal, perhaps treatment of periodontal disease/infection may result in reduced risk for future RA.

However, while some risk factors for RA have been identified, and there are purported mechanisms for some of these associations (e.g. smoking and certain pathogens), it is not at all clear how most of the identify risk factors influence RA-related autoimmunity. In particular, it is not clear when these risk factors are important in the natural history of RA – are some tied to initiation of RA, and other propagation? This is important because smoking cessation in an ACPA positive individual may be too late to abrogate the onset of clinically apparent disease. Furthermore, risk factors may differ between individuals or groups of individuals. For example, some people may develop RA related to periodontal disease, but others may have a different inciting factor. As another example, factors for RA may be very different in women compared to men. Additionally, risk factor modification may take years to affect RA-related autoimmunity and disease progression. For example, Karlson and colleagues found in the Nurses' Health Study that risk for RA returned to baseline >20 years after smoking cessation; such an effect would be very difficult to see in a clinical trial. As such, while risk factor modification is attractive, it may be that more active interventions

such as pharmacologic therapies in high-risk individuals, have the highest likelihood of success to prevent RA, although certainly encouraging healthier lifestyles can have broad benefits beyond RA prevention, and as such factors such smoking cessation and improved diet should be recommended to all. However, more data is needed before more specific environmental risk factor modification and lifestyle changes can be recommended as a broad target for RA prevention.

How to make RA prevention a reality

Certainly a greater understanding of the natural history and mechanisms of RA development as well as well-designed clinical trials are needed to develop and optimize prevention strategies for RA. Several of these issues are discussed in more detail in Table 5. Furthermore, there will likely need to be advances in other aspect of RA such as imaging in early disease, and symptom and outcome assessments as it is not clear that current understanding of these issues is adequate to enable their highly effective use in preclinical RA. For example, while ultrasound may be more sensitive than physical examination to detect synovitis (96, 97), it is not clear the accuracy of those findings, especially in individuals with early synovitis. In addition, development of optimal preventive approaches to RA would benefit from input from experts in public health policy who could inform issues related to preventive approaches to RA including cost-effectiveness and methods to screen populations for subjects in whom targeted preventions for RA would be most beneficial. In particular, do we envision potential screening approaches for risk for RA through approaches like those taken for colon cancer and cardiovascular disease, where all members of the population are screened? Or, will prevention of RA take a more targeted approach, such as focusing on individuals with higher risk for RA, such as first-degree relatives of patients with RA(56)? While focusing on high-risk groups such as relatives of patients with RA is attractive, would that be the best approach, as much of RA occurs in individuals without a clear family history of disease, and therefore focusing on relatives would not affect the majority of those who develop RA? The rheumatology community that is interested in RA prevention may also benefit from direct insight from cardiovascular disease experts who saw their disease undergo a sea-change in approach from management of acute events to disease prevention several decades ago. Notably, given that autoantibody biomarkers in preclinical RA are highly predictive of future disease, prevention efforts will likely focus on seropositive RA; however, additional approaches and new biomarker discovery will be necessary to extend preventive approaches to seronegative RA.

Fortunately, both retrospective and prospective studies of the natural history of RA are being performed by multiple research groups, and their findings should provide valuable data relevant to natural history of RA (98–100); in addition, these studies can develop the infrastructure to identify individuals at high-risk for future RA who can be enrolled in clinical prevention trials once developed.

Developing such an infrastructure may be the most important aspect of clinical trials in RA prevention given the prevalence rates of RA and need to screen large numbers of subject to find those who are exhibiting biomarker evidence of preclinical RA. In this regard, a lesson can be learned from studies in type 1 diabetes which has a similar model of development of RA where autoantibodies precede the clinical onset of disease, and can be used in a highly accurate fashion to predict future onset of disease (101–103). T1DM investigators have formed large-scale study networks to study both the natural history of T1DM as well as identify subjects for prevention trials. Specifically ‘TrialNET’ is a multi-site international collaborative effort that has been able to screen tens of thousands of individuals for risk for T1DM and serves as a highly important mechanism for performing clinical prevention trials in this disease(104). Such a model would be highly applicable to RA prevention studies

although it would take considerable investment by the rheumatologic community and funding agencies to create.

However, while more information about the natural history and mechanisms of RA development should be obtained, while this information is being obtained, the results of the Dutch PRAIRI trial may lead to a near-term paradigm shift in the management of RA. If this study shows that identifying subjects at-risk for RA through biomarker testing, and treating them with rituximab, has a good balance of efficacy, safety and cost-effectiveness, prevent RA, will this approach be the new way forward to managing RA? It is hard to imagine that the specific approach of using rituximab would become widespread, but the findings from this study may spur the development of similarly designed trials, even if the intervention is different. But what if the PRAIRI study fails to show that RA can be prevented in a safe and effective manner? Will that end thoughts of RA prevention, at least for the near future? One would hope that would not happen, and instead that any lessons learned from a failure would only drive the development of a better trial in the near future.

Importantly, while they have inherent difficulties and are expensive, clinical prevention trials may be the best way forward to advance the understanding of the natural history of RA development and mechanisms of disease. In particular, while as discussed above, certain biomarkers may be highly predictive of the onset of clinically apparent RA within a short period of time, it may be that that is too late in the development of RA to be easily modulated to prevent disease; as such, the optimal time to intervene to prevent RA may be some years prior to the onset of RA, although biomarker profiles that identify the 'optimal' period to intervene to prevent RA will need additional investigations that can only be carried out within a clinical trial. In addition, the cost-effectiveness of preventive approaches for RA will be highly important to moving the field of RA prevention forward; cost-effectiveness of prevention of RA can be carried out using estimates of efficacy; however, such studies should ultimately be performed using data obtained from well-designed clinical trials that can use 'real' data regarding efficacy in analyses. Furthermore, while laboratory studies may demonstrate a relationship between *Porphyromonas gingivalis* and RA, a clinical trial that demonstrates that modification of this organism leads to RA prevention would provide powerful proof of its causative relationship to RA.

Conclusion

Identification of a preclinical phase of RA development and a growing understanding of the natural history and mechanisms of RA development as well as potential preventive interventions lead to the hope that this disease can be prevented in the near future. While optimal methods for RA prevention require further study, the results of the ongoing PRAIRI study will likely have a strong impact on how RA is approached and should spur forward progress into RA prevention. Furthermore, approaches to RA prevention could ultimately be applied to other rheumatic diseases that may have similar models of development (e.g. lupus(105)), leading to a broad change in how rheumatic diseases are approached, and ultimately substantial improvements in public health.

Acknowledgments

Grant Funding

This work was supported by funding from the American College of Rheumatology Rheumatology Research Foundation, the Walter S. and Lucienne Driskill Foundation and the National Institutes of Health (AI103023).

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Figure 1. Phases of development of rheumatoid arthritis (RA)

In this model of RA development, disease begins with genetic and environmental risks (**Phase 1**), followed by asymptomatic inflammation and autoimmunity (e.g. autoantibodies, cytokines and chemokines; **Phase 2**), with progression to symptoms that may be present in absence of inflammatory arthritis (IA) on physical examination (Phase 3), and eventual development of undifferentiated IA (**Phase 4**) that may progress to classifiable RA (**Phase 5**). **Phase 6** is defined as evolution of disease (e.g. exacerbations, remissions, and response to therapy) after clinically apparent articular disease has developed. **‘Preclinical’** RA is defined as Phases 2 and 3 as they are identifiable by biomarker testing and prior to IA that is identifiable by joint examination. This developmental process is characterized by expanding autoimmunity and inflammation, detectable through assessment of circulating biomarkers, although Phase 1 could also be included. The double-headed arrows indicate that progression of RA may be halted, or reversed, perhaps through immunomodulatory pharmacologic intervention(s), especially if initiated prior to the onset of clinically apparent IA (Phase 4).

Table 1

Examples of studies of autoantibodies and other biomarkers in preclinical ARDs

Study	Biomarkers	Findings
Rantapaa-Dahlqvist et al 2003 (12)	RF, CCP	PPV 100% for a diagnosis of RA within 1.5 years if RF-IgA and CCP positive (based on case-control data);
Nielen et al 2004(13)	RF-IgM, CCP	PPV up to 100% for RA diagnosis within 5 years based on 5-year incidence rates of 0.001 (general population) or 3.9% (estimated from high-risk multicase RA families)
Deane et al 2010(106)	RF, CCP, multiple cytokines, chemokines & CRP	ACPA and/or 2 or more RF isotypes >96% specific for future RA; highest levels of autoantibodies <3 years prior to diagnosis.
Bos et al 2010(68)	RF and CCP	27% of subjects with CCP(+) developed IA after a median of 11 months of follow-up; rates of over 50% within ~1 year were seen in patients with highest CCP titers.
Karlson et al 2013(72)	Multiple genetic and environmental factors	Genetic and environmental factors ascertained prior to the onset of RA in the Nurses' Health Studies were used to predict future RA with an AUC of 0.716.
van de Stadt et al (69)	Multiple environmental factors, symptoms and biomarkers	Subjects with joint pain in absence of inflammatory arthritis on examination followed in rheumatology clinics; factors including sex, lack of alcohol use, symptom duration and distribution were predictive of developing RA; however, the strongest risk factors were elevations of RF and ACPAs, especially high-titer.

A caveat is that these are applied to a general example, Rantap PPV for future RA the high specificity of these general population where the Rantap and colleagues found, although in a population biomarkers for disease were determined in case-control studies. When these tests the estimated prevalence disease may be low, the PPVs may fall substantially. For example, in their case-control study that positivity for anti-CCP and RF-IgM has a 100% with a frequency of RA of 1%, the PPV fell to 16%.

Table 2**Risk factors for rheumatoid arthritis**

<p>Genetic</p> <p>MHC alleles (107, 108)</p> <p>PTPN22 polymorphisms (109)</p> <p>Epigenetic factors (e.g. DNA methylation)(110, 111)</p> <p>Race/ethnicity: high rates of RA in certain ethnic/racial groups including Native Americans; genetic vs. environmental?(99, 112–115)</p>
<p>Environmental</p> <p>Socio-economic status (114)</p> <p>Tobacco smoke (116)</p> <p>Occupational dust (117)</p> <p>Dietary/nutritional factors (55)</p> <p>Microbes (47, 118–122)</p> <p>Hormonal factors RA (55, 114)</p> <p>Alcohol use (protective) RA (58, 123)</p> <p>Statin use (mixed; one study suggests protective(124); another suggests increased risk(125))</p> <p>Sex (RA is more prevalent in women(2, 117); unclear if this is due to hormones or other factors)</p> <p>Life stress (126)</p>
<p>Environmental factors associated with risk for RA-related biomarkers or future RA in subjects without current known articular disease:</p> <p>Exposure to tobacco smoke associated with RF positivity in absence of RA (127–129).</p> <p>Oral contraceptive use associated with decreased risk for RF positivity in absence of RA (129).</p> <p>Smoking and HLA alleles associated with increased risk for future RA in the Nurses' Health Study (130).</p>

Table 3

Summary of studies supporting that early treatment of RA results in improved outcomes

Anderson et al, 2000 (131)	Meta-analysis demonstrating that RA patients with shorter disease duration respond better to similar therapies as compared to patients with longer-term disease.
Lard et al, 2001 (132)	In this non-randomized study, the initiation of treatment of RA at a median of 15 days after diagnosis resulted in improved disease activity at 2 years compared to treatment initiated a median of 123 days after diagnosis.
Mottonen et al, 2002 (133)	Delay of initiation of RA therapy by 4 months after the onset of symptoms decreased the ability for a single drug to induce remission in early RA.
Nell et al, 2004 (134)	A case-control study demonstrating that patients with a median RA duration of 3 months had improved outcomes with similar therapies when compared to patients with a median duration of disease of ~12 months.
Finckh et al, 2006 (135)	Meta-analysis demonstrating that early treatment of RA (<1 year) results in reduced long-term radiographic progression rates compared with patients treated later (>1 year).
Cush, 2007 (136)	Review article that summarizes data from subanalyses of several trials of biologic therapies in RA. Shows that early treatment (<2–3 years of disease duration) results in improved outcomes compared to treatment initiated in disease of >2–3 years duration.
van der Woude et al, 2009 (137)	Data from two large early arthritis cohorts demonstrated that sustained, DMARD-free remission of RA was significantly associated with shorter duration of symptoms of IA at time of initiation of therapy.
van der Linden, et al 2010 (138)	In a study of an early arthritis cohort, only 31% of patients with RA were assessed within 3 months of symptom onset; assessment and treatment of RA within 3 months of symptom onset was associated with increased chance of DMARD-free remission and less joint destruction.

Table 4

Potential approaches to prevention of RA

Approach	Examples
Risk factor modification prior to the development of autoimmunity (primary prevention)	<p>Smoking cessation, perhaps targeted in subjects at high genetic risk for a specific ARD (e.g. family history of RA)</p> <p>Antimicrobial therapy targeted causative organisms (e.g. <i>Porphyromonas</i>?)</p> <p>Risk factor modifications may be difficult to study efficacy because intervention may take years to show clinical benefit, although biomarkers of immunity and inflammation may be used as surrogate markers.</p> <p>Immunomodulatory therapy may used at this point in the natural history of RA may be used as well; however, targeting individuals who do not yet have biomarkers of autoimmunity would be problematic in terms of estimating risk-benefit of pharmacologic therapy.</p>
Risk factor modification or pharmacologic intervention after the development of autoimmunity, but prior to autoimmune disease (secondary prevention)	<p>Smoking cessation (if this is indeed a propagating factor)</p> <p>Immunomodulatory therapy that can abrogate autoimmunity and inflammation. To implement, requires accurate prediction of risk for future RA, and selection of agent with sufficient balance of efficacy, safety, tolerability, and subject willingness to take.</p>
Tolerance induction in preclinical disease – may be applied at several time points in the natural history of RA	<p>Tolerance to citrullinated proteins that may be crucial to early initiation and propagation of RA. Several tolerizing approaches to ARDs have been tested, and such approaches may be feasible in preclinical disease (139, 140)</p>

Table 5**Issues in RA prevention**

Issue	Discussion
<p>Sufficient understanding of the natural history of RA in order to:</p> <ol style="list-style-type: none"> 1 Identify appropriate targets for prevention 2 Accurate prediction of future disease for individuals (e.g. "personalized medicine") 	<p>Natural history studies of preclinical RA that target high-risk populations such as relatives of patients with established disease, or broad population screening to identify subjects with high-risk genetic or biomarker factors to enrich prevalent and incident autoimmunity and clinically apparent disease (44, 68, 141). Also, relevant animal models to evaluate specific mechanisms of disease development are necessary.</p>
What should be included in prediction models for disease?	Genetic, environmental, biomarkers and other factors (e.g. symptoms) can be used in combination to identify risk for RA (19, 69, 72). Combinations of autoantibody and inflammatory markers can also be used to predict the likelihood and timing of future RA (19, 34). But what is the ideal predictive model? Should it rely on simple, readily obtainable tests such as clinically available biomarkers rather than complicated algorithms?
What are appropriate public health efforts to identify subjects at-risk for ARDs in whom prevention would be reasonable approach?	How should individuals who are at-risk for future RA be identified in the population? Through public health efforts similar to those used for such diseases as cancer or heart disease? The cost-effectiveness of preventing RA need to be evaluated, with such analyses including costs of identify at-risk individuals, the possibility of treating individuals who may have markers of risk for RA but never develop clinically apparent disease, and potential adverse effects of treatment as well as potential short and long-term benefits.
How high should the likelihood of future RA be prior to initiating preventive therapy?	This depends on the nature of the prevention: low-risk lifestyle intervention may be palatable with relatively low risk for future RA; high-risk pharmacologic therapy will likely require higher likelihood of disease development although if the risk for future disease is too high, the effectiveness of relatively simple and safe interventions may be limited to prevent RA.
What is the optimal cost-effectiveness and safety for approaches to prevention?	Lifestyle changes may offer greatest safety, but will they be effective? And, will they be effective in a time frame that is reasonable to study in a clinical trial?
What will subjects who are at-risk for a future ARD be willing to undergo for prevention?	Will require study to determine what level of risk a subject would need in order to undergo therapy, and to determine what types of interventions would be acceptable. Published work suggests that relatives of patients with RA would be willing to participate in a pharmacologic prevention trial if their risk for RA was >30% within 5 years (142).
Is it worthwhile to intervene on subjects with autoimmunity in absence of autoimmune disease, even if they have low risk of progression to clinically apparent RA?	This in part is determined by how tissue injury and disease is evaluated and classified. For example, if a subject with elevations of RA-related autoantibodies has joint pain but no definable inflammatory arthritis on physical examination, should additional measures such as imaging be performed to assess for subclinical tissue injury? It may be that autoimmunity is not benign, even if classic manifestations of RA-related tissue injury (e.g. synovitis) are not present. Also, emerging data suggesting that autoantibodies may be associated with increased CVD risk and therefore treating autoimmunity even in absence of classic disease findings such as synovitis may be beneficial (143).
At what point in preclinical autoimmunity is it most reasonable to intervene?	It may be easiest to halt autoimmunity if intervention is very early in the process; however, the clinical benefit of early intervention may take years to identify and therefore be impractical to evaluate in a clinical trial; however, intervention in late preclinical disease may be too late to halt/abrogate autoimmunity
What do we hope to achieve with preventive interventions?	Is a reset of the immune system and drug-free remission possible? It is acceptable to start immunomodulation early and prevent tissue damage, even if the immunomodulation must be continued to maintain control of autoimmunity and prevention of clinical manifestations of disease?
Ethical considerations	Will identification of risk for RA put subjects in jeopardy of losing the ability to get insurance coverage for illness? What is the psycho-social impact of identifying risk for future RA if there are no clearly effective prevention strategies? Could identification of risk lead to early treatment even if prevention strategies do not exist? For example, could ACPA(+) subjects identified through screening be followed closely and treated once clinically apparent RA develops?