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Rheumatoid Arthritis: Pathogenesis, Prediction and Prevention – An Emerging Paradigm Shift

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Abstract

Rheumatoid arthritis (RA) is currently diagnosed and treated when an individual presents to health care with signs and symptoms of inflammatory arthritis (IA) as well as other features such as autoantibodies and/or imaging findings that provide sufficient confidence that the individual has RA-like IA (e.g. meeting established classification criteria) that warrants therapy. However, it is now known that there is a stage of seropositive RA during which circulating biomarkers and other factors (e.g. joint symptoms) can be used to predict if and when an individual who does not currently have IA may develop future clinically-apparent IA and classified RA. Indeed, the discovery of the 'Pre-RA' stage of seropositive disease has led to the development of several clinical trials where individuals are studied to identify ways to delay or prevent the onset of clinically-apparent IA/RA. This review will focus on several issues pertinent to understanding the prevention of RA. These include discussion of the pathogenesis of Pre-RA development, prediction of the likelihood and timing of future classified RA, and a review of completed and ongoing clinical trials in RA prevention. Furthermore, this review will discuss challenges and opportunities to be addressed to effect a paradigm shift in RA where in the near future, proactive risk assessment focused on prevention of RA will become a public health strategy in much the same manner as cardiovascular disease is managed today.

Keywords

Rheumatoid arthritis; Pre-rheumatoid arthritis; Pre-RA; Preclinical rheumatoid arthritis; Preclinical RA; Prevention; Prediction

Rheumatoid arthritis (RA) is a common chronic autoimmune disease (1), causing substantial morbidity and decreased quality of life as well as increased mortality and annual costs of billions of dollars (1).

The current clinical management of seropositive RA (e.g. abnormalities of rheumatoid factor [RF] and/or antibodies to citrullinated protein antigens [ACPA]) is focused on initiating

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treatment once an individual develops symptomatic and clinically-identifiable inflammatory arthritis (IA), that may also be classifiable as RA by established criteria (2-4). Importantly, however, due factors including an individual's delay in seeking care for symptoms, and delays of a referral to a specialist, the time between onset of symptoms and initiation of disease-modifying anti-rheumatic drug therapy is often delayed beyond what is ideal especially given that earlier diagnosis and treatment improves outcomes (5, 6). Furthermore, while new drugs and treat-to-target strategies have improved disease control, for many individuals, treatment does not return them to a "pre-RA" state of symptoms (7). These factors, along with the high costs of managing RA, medication side-effects and growing limits of access to rheumatology worldwide (8), make RA a disease that in principle would be benefitted by preventive approaches.

Pathogenesis of RA: detectable autoimmunity before clinically-apparent IA

For most individuals who develop seropositive RA, there is a period characterized by systemic elevations of RA-related autoantibodies prior to the development of clinically-apparent IA/RA that is typically identified on physical examination as a swollen joint consistent with synovitis (9-15). A model of this development, and a series of key case-control and prospective studies that have supported this model are included in Figure 1 and Table 1, respectively. These autoantibodies include multiple isotypes of RF and ACPA, ACPA fine specificities (e.g. antibodies to citrullinated fibrinogen), and antibodies to carbamylated proteins and peptidyl arginine deiminases (16-18).

Based on current data, it appears that this early stage of RA is characterized by early reactivity to a limited number of self-antigens, and limited systemic inflammation, that is followed by evolution over time of expanding innate and adaptive responses and tissue injury until some threshold is crossed and clinically-apparent IA/RA develops. This model has been supported by findings of increases over time in the numbers and type of ACPA (18-21), as well as expansion of other autoantibody systems and increasing systemic inflammation (e.g. cytokines) (22-24). Other processes that occur during this period include altered autoantibody glycosylation (25), and changes in cellular phenotypes such T cell subsets (26). While not consistent across all studies, it appears that in many individuals, ACPA precede RF and other autoantibodies (e.g. anti-CarP), which may indicate that ACPA are reflective of the earliest breaks in tolerance (16, 21), and that development of multiple types of autoantibodies is fundamentally related to a transition to clinically-apparent disease.

Importantly, while expansion of autoimmunity and inflammation characterize this period, the key biologic pathways that drive initial autoimmunity and then a transition to a more pathogenic state and clinically-identifiable IA/RA are not known. Moreover, many purported risk factors for RA have been identified only in individuals with clinically-apparent articular RA; therefore, the role of these factors in the initiation and propagation of autoimmunity and inflammation prior to clinically-apparent IA/RA is not well understood. However, some risk factors that are associated with future risk for RA have been prospectively identified in Pre-RA (Table 2, and reviewed in (27)). In particular, for some individuals interactions between tobacco smoke and the SE may play an important role in these early processes and in increasing the risk for a transition from autoantibody positivity to clinically-apparent IA/RA

(20, 28). In addition, many individuals with systemic elevations RA-related autoantibodies have no evidence of synovitis on physical exam, imaging, or synovial biopsy (29, 30). This strongly suggests that autoimmunity in these individuals is generated outside of the joints, with emerging evidence suggesting this site may be mucosal (e.g. lungs, periodontium, intestine) and related to the microbiome, and is an active area of investigation (reviewed in (31)).

Nomenclature

Several terms, including Pre-RA, preclinical RA and 'at-risk' are commonly used to describe the period of development of RA before clinically-apparent IA. Of these terms, Pre-RA has been suggested by a European League Against Rheumatism (EULAR) study group in 2014 (32). As such, we will use that term within this review. However, there are some caveats with this term including that the EULAR study group suggested it be applied only when individuals were later known to progress to clinically-apparent RA. It is also not clear how to apply the term to individuals who may have clinically apparent IA even if not classifiable as RA since those individuals are typically clinically treated as RA. Additionally, as discussed in more detail below, as the understanding of Pre-RA evolves, it is likely that different terms to describe stages of RA will be needed that will facilitate research and clinical care, align with the biology of disease and facilitate communication with individuals who may be evaluated for prevention.

Current prediction models for future RA

Multiple case-control studies demonstrate that serum elevations of ACPA and/or RF have high (often >80%) positive predictive values (PPVs) for future IA/RA (12, 13, 24) (Table 1). Moreover, while retrospective case-control studies may overestimate PPVs, in prospective studies that include ACPA (+/− RF), symptoms and other factors, PPVs for the development of IA/RA within 2-6 years range from ~30% to greater than 70%, with the highest PPVs in subjects with high levels of autoantibodies, or dual positivity for ACPA and RF (15, 33).

As an example, in a Dutch study of 347 subjects with RF and/or ACPA positivity and joint symptoms but no IA at a baseline physical examination, 131 (35%) individuals developed IA in a median 12 months (29); furthermore, among individuals with a baseline high-risk score comprised of ACPA, RF and other factors, 74% developed IA/RA within 3 years. In addition, in a study in the United Kingdom of 100 ACPA positive subjects with arthralgia, 50 (50%) developed IA/RA after a median of 7.9 months (33); furthermore, among individuals with a baseline high-risk score comprised of examination findings, symptoms, genetic and autoantibody testing, and an abnormal power-doppler ultrasound finding, ~68% developed IA within 24 months.

Importantly, these two studies have included two aspects of prediction: likelihood (i.e. will someone get IA) and timing (i.e. when will they get IA). As discussed below, these aspects can be used to counsel individuals who are facing decisions regarding their future risk for IA/RA, timing of clinical follow-up, and participating in a trial. Furthermore, these aspects

support clinical trial design where it is essential to have accurate estimates of the expected number of “events” (i.e. incident IA/RA) within a given time frame.

Of note, inflammatory tests such as C-reactive protein have been demonstrated to be elevated in Pre-RA although they have not been consistently helpful in improving prediction models (24, 29, 33); furthermore, while in conjunction with autoantibodies, cytokines/chemokine abnormalities have been shown to be useful in prediction (18, 24), this has not yet been extensively validated.

Prevention: rationale, design and existing studies

Rheumatologists are familiar with many ‘preventive’ approaches in the care of individuals with RA. These include the prevention of worse joint damage in individuals with established RA, osteoporotic fractures, or future flares in individuals who have had acute gouty arthritis. Nevertheless, it is relatively novel concept to consider prevention of the first onset of clinically-apparent manifestation of a disease.

Several factors have underpinned the development of clinical trials that have the “intent to prevent” (phrase courtesy Marvin Fritzler) the onset of clinically-apparent IA/RA. These factors include the predictive ability of autoantibodies, especially ACPA and improved identification of individuals with biomarker elevations through clinical care as well as approaches such as screening in populations at higher risk for RA such as first-degree relatives of individuals with RA (15, 34-36). There are also observations that antimalarials may prevent future flares in “palindromic rheumatism”(37). Furthermore, findings of a ‘window of opportunity’ in RA where earlier treatment in individuals with established IA may lead to improved outcomes and perhaps increases in drug-free remission suggest that the immune system may be more amenable to ‘normalization’ if treated early (5).

Building on these factors, two clinical trials to prevent the first onset of clinically-apparent IA have been completed. In one, 83 ACPA and/or RF positive individuals with arthralgia yet without IA on physical examination were randomized (1:1) to receive two doses of dexamethasone 100 mg intramuscularly 6-weeks apart, or placebo (38). IA rates were not different between arms (20% vs. 21%), although there was a decrease of autoantibody levels in treated individuals. In the PRAIRI trial (Prevention of clinically manifest rheumatoid arthritis by B-cell directed therapy in the earliest phase of the disease) study (39), 81 subjects with baseline ACPA and RF positivity and elevated C-reactive protein (>0.6 mg/L) were randomized (1:1) to receive 1000 mg rituximab for one dose, vs. placebo, and all subjects received methylprednisolone 100 mg intravenously. The rates of IA were not significantly different between arms (34% in treated vs. 40% in placebo); however, the onset of IA was delayed such that the time point at which 25% of subjects in the treated arm developed IA was ~12 months longer compared to placebo.

There are several other prevention studies underway. StopRA (Strategy for the Prevention of the Clinically-Apparent Onset of RA) (40) in the United States is randomizing individuals with ACPA levels >=2x normal to receive hydroxychloroquine vs. placebo for 1 year; subjects are then followed for an additional 2 years to assess durability of response as well

as to evaluate if treatment may result in a less-aggressive form of IA/RA. APPIPRA (Arthritis prevention in the preclinical phase of RA with abatacept) in the United Kingdom and Europe is randomizing individuals with ACPA levels >3x normal or ACPA plus RF, and inflammatory joint symptoms/arthralgia, to receive abatacept subcutaneously weekly for 1-year, versus placebo, with additional 1-year follow-up (41). Other studies that have been launched include one using statins in autoantibody positive subjects (42), and one using glucocorticoids and methotrexate in individuals with arthralgia and no examination evidence of IA but who have 'subclinical' IA per magnetic resonance imaging (43).

Paradigm shift to RA prevention – challenges and opportunities

While it represents a great advance that several clinical prevention trials in RA have been completed or are underway, challenges and opportunities remain in further advancing prevention (Table 3), and several of these are discussed below.

Improving prediction

Accurate prediction of future IA/RA is a critical aspect of prevention. While models to-date have supported clinical trials, there are several important challenges. First, not all subjects with abnormalities of RA-related autoantibodies, even ACPA, or other factors (e.g. articular symptoms) develop IA/RA within the time-periods of prospective study (Table 1). This could be because retrospective studies have shown that autoantibodies may be elevated >10 years prior to RA diagnosis (12, 21), and few prospective studies have been conducted that long. However, this also suggests that some individuals may develop RA-related autoimmunity and even some articular symptoms, yet never develop clinically-apparent IA. Moreover, there is a growing understanding that RA-related autoantibody positivity may be lost over time in at-risk individuals (35) (although in one study some individuals lost autoantibody positivity Pre-RA yet still later developed RA (21)), or that autoantibodies may only be detectable after IA has developed (44). Furthermore, while there are multiple commercial assays for ACPA available, they do not have the same diagnostic accuracies in established RA, and these differences may be more pronounced in Pre-RA (45). Also, given most biomarkers in RA have been developed in established disease, there may be additional discovery of biomarkers that are more appropriate for understanding Pre-RA and in particular to identify transitions from benign to pathogenic autoimmunity.

Some additional challenges in prediction are that most prospective studies utilize autoantibody positive subjects identified because they sought care for joint symptoms; therefore, studies are needed to understand prediction in individuals who have minimal joint symptoms, or who are asymptomatic, because these are types of individuals who might be identified if population-based testing for RA biomarkers was performed. In addition, while most predictive models have primarily focused on autoantibodies, an entity termed Clinically Suspect Arthralgia (CSA) has been identified that uses a combination of self-reported symptoms and examination findings that has a PPV for future RA of ~30%, although in some scenarios, much lower (~3%)(46). Furthermore, some models have utilized genetic factors instead of autoantibodies to estimate risk of seropositive as well as sero-negative RA (47). As such, going forward, if diagnostic accuracy is sufficiently high,

symptoms and other non-autoantibody factors may be used to identify individuals at sufficiently high risk for future RA that preventive interventions may be considered; importantly, these approaches may be especially helpful for prediction of seronegative RA.

Physical examination has been the primary method to identify clinically-apparent IA/RA; however, imaging, is playing an increasing role in RA management to identify IA when examination is uncertain, as well as to follow response to therapy (48). Furthermore, imaging has been used to predict the development of future physical examination-apparent IA (33, 48). However, if imaging is used to define IA that is not identifiable on examination (i.e. subclinical IA), that may change the approach to prevention where “treatable” IA is identified earlier that physical examination is able to do. While potentially beneficial, that approach could also lead to overtreatment, in particular because of the known high variability in interpreting images, and also because ‘synovitis’ on imaging can be detected in symptom-free individuals from the general population (49, 50). As such, it may be some time before the appropriate role is understood of imaging for use in defining the presence of current ‘actionable’ disease in absence of examination findings of IA, as well as prediction and prevention in IA/RA.

In sum, prediction is a critical part of prevention, and it is important that existing clinical trials, ongoing natural history studies (e.g. FDRs, indigenous North Americans and the Dutch ‘Lifelines’ study (15, 34-36, 51)) as well as future studies, optimize diagnostic accuracies of models for the likelihood and timing of future RA. These models should also account for cross-test interpretation, with consideration for a standardization of testing, similar to that done in autoantibody testing in T1D (52, 53). Specifically, one could envision a model, perhaps developed through advanced analytic technics such as artificial intelligence/machine learning (54), that incorporates multiple dimensions including demographics, family history/genetics, environment, autoantibodies and other biomarkers, symptoms and examination findings and imaging to accurately and clearly inform about an individual’s likelihood and timing of future RA. This could even be a two-step model where a relatively inexpensive test (e.g. serum ACPA) could be evaluated first to determine an overall risk, and then in follow-up, additional factors could be assessed to determine current clinical status, more specific level of risk, as well as potential timing of onset of disease (24). Furthermore, as discussed in more detail below, potentially identify what specific pathways should be targeted to prevent disease.

Novel targets for prevention—The current clinical trials in RA prevention are evaluating agents that have been used in established RA. This is in part because these agents have known efficacy, safety and tolerability profiles in RA, and have regulatory agency support. These agents may also successfully be able to alter antigen presentation, innate and adaptive responses (e.g. B and T cell interactions), expansion of autoantibodies (e.g. ACPA fine specificities, RF) and expansion of inflammation that appear critical in Pre-RA development. However, these agents have been studied to determine their efficacy in established RA; therefore, it may be that they do not address key biologic pathways in Pre-RA. Indeed, it may be that novel pathways, even mucosal-based, need to be targeted for effective prevention (31).

As such, it will be important to explore biologic pathways in Pre-RA in conjunction with the existing (and future) clinical trials and other studies so that the next round of trials will target the most relevant pathways. To that end, a growing interest in using animal models to understand the mechanisms of “Pre-disease’ may provide means to validate pathways identified in human studies, as well as potentially identify novel targets for prevention. For example, Jubair and colleagues have demonstrated in a murine model of arthritis that microbiome-directed interventions prior to the onset of IA can greatly diminish arthritis, even if administered after systemic autoimmunity has developed (55).

While results are conflicting and have not been evaluated in randomized, prospective fashion, there are a growing number of studies identifying lifestyle factors that may reduce risk for RA. These include smoking cessation, a healthy diet (and likely one enriched in fish consumption and fatty acids), weight loss, and increased exercise (Table 2, and reviewed in (56)). Because these interventions may take years to see beneficial effects, they may never be formally studied alone in interventional prevention trials. However, given the potentially broad beneficial effects, these factors may need to be included as ‘general’ preventive recommendations in conjunction with other interventions; furthermore, they may be important to optimize risk-benefit ratios of interventions in individuals with only modest autoimmune abnormalities and risk for future RA.

Importantly, while precision/personalized medicine in the management of individuals with established RA has not yet reached fruition, one could envision that in Pre-RA there may be an ability to identify a specific pathway for an individual that could be optimal to target, either pharmacologically and/or through lifestyle modifications, to optimize prevention.

Prevention trial design and duration of intervention

The current and completed trials for RA prevention are relatively simple – 1:1 randomization comparing active drug and placebo. Furthermore, the interventions are of limited duration (e.g. in PRAIRI a single dose of rituximab was given). In addition, the primary outcome for these trials is the development of classifiable RA.

These approaches are appropriate in these early days of prevention to address safety and ethical concerns, costs and the preferences of individuals who are participating in trials. The outcome of classifiable RA is also a clinically-meaningful and agreed-upon disease state. In addition, the use of placebo is important because the prediction of future RA is not perfect, and it is expected that a number of individuals, even with high-risk features, may still not progress to clinically-apparent IA/RA during the time period of a study and therefore one needs to know if the study drug truly resulted in benefit.

However, for several reasons, the next round of prevention trials will likely have different designs. First, RA is a relatively rare disease and there are difficulties in finding individuals in a Pre-RA state; furthermore, there are multiple possible pathways that may be addressed to delay or halt the development of RA. As such, adaptive trials may be considered, where multiple interventions can be tested within a single trial that can optimize small subject numbers (57). Second, instead of classifiable RA, trials may need to use other informative outcomes such as levels of autoantibodies or cytokines/chemokines, especially since these

outcomes may be able to shorten clinical trials given that outcomes of classifiable RA may take years to develop. Specifically, given it appears that an important feature of the pathogenesis of Pre-RA is expansion of ACPA and new antibody formation (e.g. RF) and inflammation, of interest for prevention is the efficacy of approaches to arrest the expansion of autoimmunity and inflammation, as well as to use measure of biomarkers to provide insights into the success of an intervention. For example, an intervention may be considered a success in an ACPA positive individual who does not develop future abnormalities of RF.

Furthermore, it is important to consider that there are symptoms and other impactful medical issues that have been identified prior to IA/RA, and potentially related to autoimmunity. Some of these features may be termed an ‘RA prodrome’ and include arthralgia (the etiology of which in absence of definable IA is as of yet unclear), functional limitations, fatigue, sleep abnormalities, work absences, mental health disorders, and potentially other non-articular manifestations of autoimmunity such as lung and cardiovascular disease, and sicca symptoms (58-61). Understanding these potential non-IA manifestations of RA could impact the development of prevention approaches in RA, resulting in treatment of a current “autoimmune-opathy” and also prevention future IA/RA - similar to the concept of treating a ‘diagnosis’ of hypertension to prevent a future heart attack. These non-IA features could also be used as endpoints themselves. Nomenclature pertaining to Pre-RA could also be expanded to include non-articular manifestations of disease.

Finally, it would be ideal if a time-limited intervention had lasting benefit for prevention; however, the development of IA/RA was only delayed in the rituximab-treated group. As such, while the ongoing trials will further inform this issue, it may be that longer-term interventions are needed to more effectively delay or prevent IA/RA. This would be akin to statin treatment in hypercholesterolemia where the drug is continued indefinitely to provide long-term benefit. However, even if it takes a prolonged intervention to delay or halt the first appearance of IA, there may be substantial benefit in improved symptoms, and reduced long term damage and disability. Furthermore, while the issue of lead-time bias needs to be considered, it could be beneficial if the IA/RA that develops is a less-aggressive form that ultimately requires less expensive or toxic interventions for control. These issues should be evaluated as part of studies going forward.

Participation: individuals at-risk for future RA

The current trials in RA prevention have used criteria to select individuals who are at high-risk for RA within a relatively short time and combinations of autoantibody elevations and symptoms, with those subjects largely identified through clinics, although some studies include recruitment from FDR and general populations.

Selecting such high-risk individuals largely from clinics is reasonable for the first round of prevention trials to meet trial design and ethical requirements; furthermore, a trial can be spared from having to develop costly infrastructure to identify at-risk individuals through population-based approaches such as broad testing for autoantibodies. However, such approaches may identify individuals who are so far along in the development of RA that prevention is difficult to attain, as well as miss high-risk individuals who have few symptoms or lack access to clinical care. As such, in future trials additional inclusion criteria

may be considered that have perhaps a lower (yet still definable and accurate) risk for RA, but also identify a stage of RA development that is more amenable to halt or a change to a more benign state. This could entail study design and enrollment strategies, such as broad population-based autoantibody testing, to identify individuals who may be asymptomatic and/or with only modest elevations of autoantibodies (Figure 2). Such trials may use 'safer' interventions such as low toxicity medications, or lifestyle changes yet still be effective if indeed the immune system at stages of RA where only modest dysregulation is present and more amendable to keeping or returning to a 'normal' state. Importantly, RA would benefit from efforts similar to those in T1D where networks such as 'Trialnet' have been developed including FDRs and general population screening to create a pool T1D-related autoantibody positive individuals who can readily be recruited for T1D prevention trials such as the teplizumab study (62, 63).

Another consideration is that individuals who sought clinical care for joint symptoms and were found to be in a Pre-RA state may be more interested in participation in prevention that someone who is at-risk but is asymptomatic and/or has little understanding of what RA is - which may be the type of individual identified if broad population-based screening for RA risk was implemented. Informing these issues to some extent, there are studies that have explored 'preferences' for prevention in at-risk individuals (64, 65). General themes that have emerged include that at-risk individuals would like clarity around what RA is as a disease, their absolute risk for IA/RA, and to know that interventions are highly likely to be successful as well as well-tolerated and safe. Following this, if prevention is to be implemented in asymptomatic individuals, or who are unaware of RA, there will need to be additional efforts to educate these populations about RA, and what screening and prevention may mean to their health. This will require broad public education about RA. These educational activities could be encompassed under a 'rheumatology preventionist' (term courtesy Frederick Miller). Importantly, a collateral benefit of increased prevention-related public awareness programs may also help reduce delays in individuals seeking treatment for clinically-apparent IA/RA (6). Notably, the aforementioned prevention trial of statins terminated early due to slow enrollment that was in part due to subject reluctance to participate (personal communication Dirkjan van Schaardenburg)(42)). This highlights the importance of fully understanding and addressing subject's preferences in order to complete robust clinical trials.

Importantly, having clear and informative nomenclature regarding Pre-RA would help facilitate education in prevention individuals who are at-risk for RA as well as health-care providers, and other stakeholders (66). This may ultimately include nomenclature pertaining to non-articular manifestations of RA. An example that may provide insights for RA is from T1D where autoantibody positive states, even in absence of a need for insulin therapy, are now considered disease (67), with this designation facilitating education of individuals at-risk for T1DM and the performance of interventional studies. Notably, International Classification of Diseases (ICD)-10 codes already exist for some aspects that could be applied to Pre-RA including ACPA positivity (R79.89) and family history of RA (Z82.61). A caveat is that naming a condition, or risk for a future condition, may also have implications on an individual's ability to obtain insurance coverage.

Participation: rheumatologists

Rheumatology practitioners will play a key near and long-term role in prevention because of their expertise in RA; furthermore, they are currently best positioned to identify individuals with joint symptoms and autoantibody abnormalities yet no clinically-identifiable IA who are likely to be “first in line” for prevention. In addition, if ‘standard’ RA medications are used in prevention, rheumatologists are best situated to work with individuals around the use, risks and benefits of these agents. However, given most rheumatology practices now entail treating individuals who have substantial illness and are already limited by provider shortages and long wait-times (8), practice patterns may have to change to accommodate prevention. Furthermore, it may be that some aspects of prevention would ultimately be supported by primary care.

In addition, there will need to be new ways to evaluate and follow individuals in Pre-RA to gauge effectiveness of an intervention, or even to know when an intervention could be tapered or stopped. These approaches have yet to be determined but will likely include joint examination although that may be less informative to follow responses in individuals who have never developed clinically-apparent IA; as such, follow-up may be more reliant on careful imaging, and assessment of informative biomarkers as well as subject-reported outcomes that quantify symptoms such as pain, stiffness and swelling as well as non-articular disease such as fatigue. These assessments could be through wearables, application or web-based (e.g. telemedicine), especially given the growing use of these platforms in RA (68).

Participation: other stakeholders

Other stakeholders critical to advancing prevention include epidemiologists, trialists and outcomes researchers and translational and basic science researchers who can help discover new targets and implement informative clinical trials. Support from governmental funding and regulatory agencies is needed to promote prevention research. Similarly, pharmaceutical industry involvement is essential to support target identification and drug development, trials, and importantly to create sustainable business models that include prevention. The biotechnology and diagnostic industries will also need to support the development of platforms and biomarkers useful in predicting RA, as well as measuring outcomes. Finally, stakeholders need to include health care and insurance systems, health economists and governmental agencies (e.g. United States Preventive Task Force) that can help enact screening and prevention into routine clinical care, and convince payors to implement prevention (69, 70).

Current management of Pre-RA

In terms of what can be done now for individuals in Pre-RA, if an individual has sufficient symptoms and is autoantibody positive, there is a tendency to treat, even if clinically-apparent IA is not identified. However, given that a number of individuals with symptoms and autoantibodies may not progress to IA, it is critical to perform trials to help guide the type and duration of interventions. As such, if available, clinicians should consider referring appropriate individuals to clinical trials. If such referral is not possible, while not well-

proven, recommendations for risk reduction could include tobacco cessation, exercise, a healthy body weight and a Mediterranean-type diet that may also broadly beneficial to other aspects of health (e.g. cardiovascular disease)(56, 71). Recommendations on supplements should be avoided until more data is available; however, as several studies have shown that omega-3 levels and supplement intake are inversely associated with risk of autoantibodies and progression to IA, this particular approach deserves additional study (72). In addition, while periodontal disease has been identified in Pre-RA (73), and higher levels of perceived stress have been associated with incident IA/RA (60), more data is needed before interventions such as stress reduction and dental care are recommended as preventive interventions. Finally, and most importantly, subjects at-risk for IA/RA should be counseled to seek medical attention if joint symptoms develop or worsen, and it is reasonable for periodic follow-up (perhaps annually) with rheumatology to evaluate the joints and offer ongoing counseling.

Conclusion

The understanding of Pre-RA, and an ability to predict development of future IA/RA, has advanced to where trials to prevent IA/RA have been completed, with others underway. The findings from these trials, and other studies evaluating the natural history of RA, will provide important knowledge for future preventive trials as well as potentially clinical care, moving the field in the near future to a paradigm where RA, and soon other autoimmune rheumatic diseases, may follow similar models where an at-risk state can be identified and approached with an ‘intent to prevent’.

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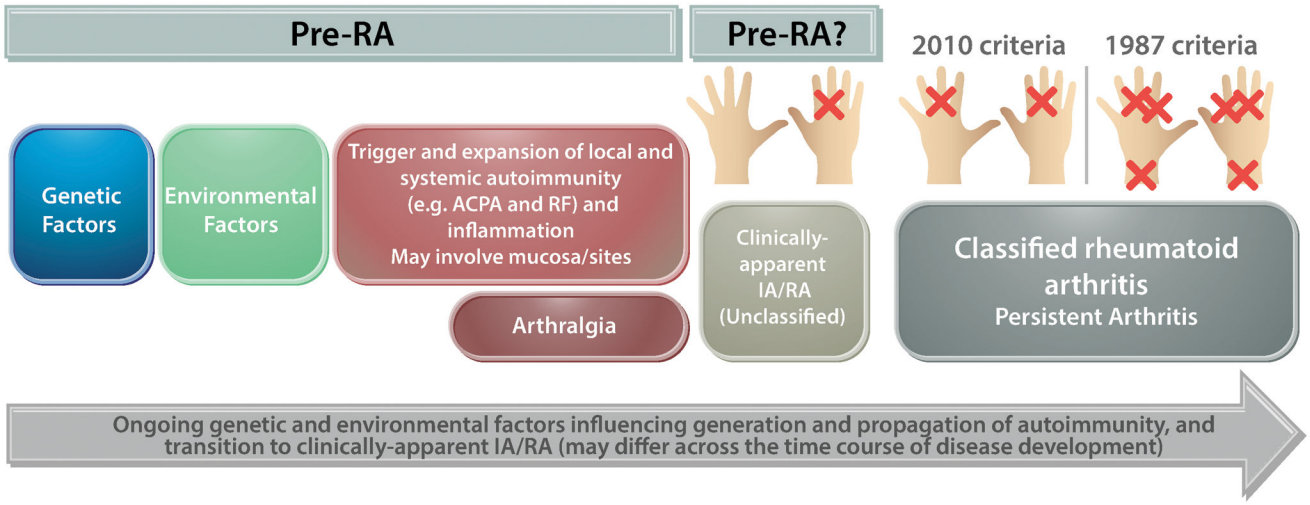

Figure 1. Model of Rheumatoid Arthritis (RA) Development

In this model, genetic and environmental factors lead to initiation and expansion of autoimmunity that may progress to clinically-apparent IA/RA and classified RA. There is some controversy whether the term Pre-RA should be applied once clinically-apparent IA is present if not classifiable as RA. Abbreviations: ACPA=antibodies to citrullinated protein antigens; IA=inflammatory arthritis; RA=rheumatoid arthritis; RF=rheumatoid factor

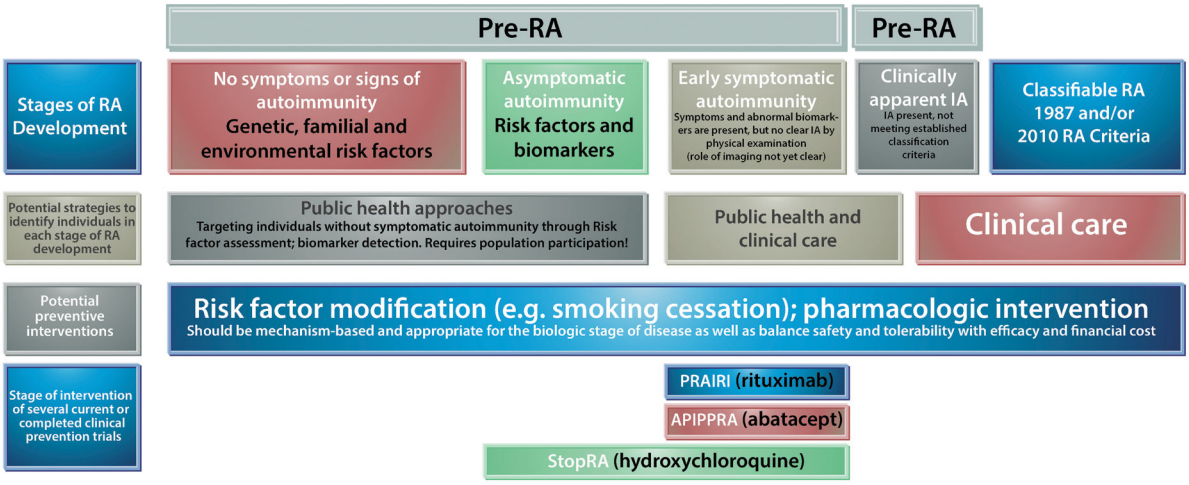

Figure 2. Strategies for identification and intervention for rheumatoid arthritis (RA) prevention

Differing approaches are needed based on stage of RA development. There is some controversy whether the term Pre-RA should be applied once clinically-apparent IA is present if not classifiable as RA. Abbreviations: IA=inflammatory arthritis; PRAIRI=Prevention of clinically manifest rheumatoid arthritis by B-cell directed therapy in the earliest phase of the disease; APIPPRA=Arthritis Prevention in the Preclinical Phase with Abatacept; StopRA=Strategy for the Prevention of the Clinically-Apparent Onset of RA

Table 1.

Key longitudinal studies of pre-rheumatoid arthritis

Authors and year published	Country of origin/ population	Study type	Number of subjects and incident IA/RA	Key findings
del Puente et al 1988 (9)	USA, Pima Indians	Prospective cohort study	2,712, 70 (~2.6%) with incident IA/RA after up to 19 years of follow-up.	The highest rate of development of RA (48 per 1000-person years) was in subjects with baseline RF titer of >1:256.
Aho et al 1991 to 2000 (10, 74)	Finland	Retrospective biobank study	19,072, 124 with incident RA.	Findings were published in multiple publications and included elevations of immunoglobulin G, RF and antibodies to keratin and perinuclear factor (later determined to be varieties of ACPAs) prior to RA.
Silman et al 1992 (75)	United Kingdom	Prospective cohort study	370 unaffected first-degree relatives from families with RA; 14 with incident RA	Incident RA was highest in subjects with RF positivity.
Rantapaa-Dahlqvist et al 2003 (12)	Sweden	Retrospective biobank case-control study	83 cases with incident RA, 382 controls	At any time prior to a diagnosis of RA, anti-CCP2 was positive in ~34% of subjects RA, RF-IgA ~34%, RF-IgM 19% and RF-IgG 17%. A combination of anti-CCP2 and RF-IgA positivity at any point in preclinical RA had a sensitivity of 21%, specificity of 99% and PPV of 87% for future RA. Sensitivity and levels of autoantibodies were highest in the period <1.5 years prior to diagnosis.
Nielen et al 2004 (13)	The Netherlands	Retrospective biobank case-control study	79 cases with incident RA, 2,138 controls.	Overall, 49% of RA subjects positive for anti-CCP1 or RF-IgM a median of 4.5 years prior to diagnosis. Using a 0 to 5-year window prior to diagnosis and comparison to controls, anti-CCP1 or RF-IgM positivity was ~36% sensitive and ~97% specific for RA, with a PPV of ~97%. Increased sensitivity, increased rates of simultaneous positivity for anti-CCP1 and RF-IgM and higher levels were present in the most immediate pre-diagnosis period. Anti-CCP1 appeared to be positive prior to RF-IgM.
Majka et al 2008 (14), Deane et al 2010 (24), Ercan et al 2010 (76), Kolfenbach et al (17), Gan et al (16) and Sokolove et al 2012 (18)	USA	Retrospective biobank case-control study	83 cases with incident RA and 83 controls.	A series of studies were performed in this cohort demonstrating: • RF and anti-CCP2 are elevated in 57% and 61% of subjects prior to a diagnosis of RA, respectively. Notably, younger subjects (<40) appeared to have a shorter duration of preclinical autoantibody positivity compared to older subjects (≥40). • An increasing number of abnormal cytokines/ chemokines was associated with a shorter time to future diagnosis of RA in an age-dependent manner. • Pre-RA abnormalities of anti-CarP and anti-PAD antibodies, and abnormalities of glycosylation. • A panel of elevated ACPA fine specificities and cytokines were ~58% sensitive and ~87% specific for onset of RA within 2 years.
Karlson et al 2009 (77)	USA	Nested case-control study within the Nurses' Health Study and Women's Health Study	170 cases with incident RA, with 506 controls.	Soluble tumor necrosis factor receptor II, and interleukin-6 were elevated prior to a diagnosis of RA.
Van de Stadt et al 2012 (78)	The Netherlands	Prospective study of individuals	347 subjects with RF and/or ACPA	A score was developed assigning 1 point for each of the following that were present: positive FDR status, no alcohol

Authors and year published	Country of origin/ population	Study type	Number of subjects and incident IA/RA	Key findings
		presenting to rheumatology clinics	positivity but no IA at baseline; 131 with incident IA/RA after a median of 12 months.	consumption (use of alcohol was protective), symptoms starting <12 months prior, intermittent symptoms, symptoms in upper and lower extremities, visual analog pain score of >=50 millimeters, more stiffness >=60 minutes, self-reported swelling in any joint; in addition, up to 4 points were assigned if both RF and ACPA were positive. In individuals with scores of >=7, 74% developed IA/RA within 3 years.
de Hair et al 2013 (79)	The Netherlands	Prospective study of ACPA and/or RF positive subjects	55 subjects, 15 (27%) with incident IA after a median of 13 months.	Non-smokers and those with normal body weight had the lowest rates of progression to IA/RA.
Ramos-Remus et al 2015 (15)	Mexico	Prospective study of unaffected FDRs of patients with RA	819 FDRS, 17 (2.1%) with incident IA/RA over 5 years.	ACPA positivity with or without concomitant RF positivity had PPV's of 58-64% for development of RA during follow-up.
Rakieh et al 2015 (33)	United Kingdom	Prospective study of ACPA+ (CCP2) subjects with arthralgia referred to rheumatology clinics	100 ACPA+ individuals, 50 with incident IA/RA after a median of 7.9 months	A score was developed assigning 1 point for each of the following: tender joints, morning stiffness >30 minutes, presence of the shared epitope, high levels of RF and/or ACPA, and the presence of ultrasound power doppler findings in >=1 joint. In individuals with the highest scores (>=2), >41% developed IA/RA within 24 months, and individuals with scores of >=4, 68% developed IA within 24 months.
Burgers et al 2017 (80)	The Netherlands and Sweden	Prospective study of subjects with arthralgia	178 subjects with arthralgia meeting EULAR criteria for CSA at baseline, 44 (18%) developed with incident IA/RA after a median of 16 weeks.	This was a study to validate the EULAR definition for Clinical Suspect Arthralgia (46). The presence of 3 or more of the following factors was ~84% sensitive and had a PPV of ~30% for IA/RA within 2 years: duration of onset of symptoms <1 year, symptoms in MCP joints, morning stiffness >=60 minutes, more severe morning symptoms, having an FDR with RA, and on examination, difficulty making a fist and tenderness with an MCP squeeze. However, PPV for IA was much less if the criteria were applied by a non-rheumatologist practitioner (PPV ~3%).
Gan et al 2017 (81)	USA	Prospective cohort study	35 ACPA+ (CCP3) subjects with baseline IA identified through health-fair screenings; 14 with incident IA/RA after a mean of 2.6 years.	Progression to IA/RA was associated higher age, shared epitope positivity, and with lower blood levels of omega-3 fatty acids.

Abbreviations: RA=rheumatoid arthritis; IA=inflammatory arthritis; Ig=immunoglobulin; RF=rheumatoid factor; ACPA=antibody to citrullinated protein antigen; CCP=cyclic citrullinated peptide; USA=United States of America; MCP=metacarpal phalangeal joints; EULAR=European League Against Rheumatism

Table 2.

Purported genetic, environmental and other risk and protective factors for future RA development evaluated in prospective studies or cross-sectional studies of at-risk individuals/Pre-RA

Genetic and familial risk factors Shared epitope associated with higher risk for transition to RA in ACPA positive individuals at baseline (33) First-degree relative status increased risk of progression to articular RA in arthralgia cohort (29) Certain populations with high-risk for RA, including populations indigenous to the Americas who have ~5-7 fold increased risk for RA compared to non-indigenous populations (82)
Sex-related factors Female sex given women have 2-3 fold higher risk for RA compared to men (27) Longer duration of breast-feeding and higher parity are protective (83) Oral contraceptive use associated with decreased autoantibody positivity in at-risk individuals without RA (first-degree relatives)(84)
Environmental (and potentially modifiable)(reviewed in (27) and (56)) Increased risk for RA Tobacco exposure, especially long duration and high intensity smoking Obesity Inflammatory diet Protective against RA Moderate alcohol consumption High fatty fish intake and intake of omega-3 fatty acids
Other Lung disease (airways, parenchymal) present in RA-related autoantibody individuals and in some cases preceding articular RA (85) Periodontal inflammation is present in RA-related autoantibody positive individuals, and increased in comparison to controls (73)

Abbreviations: Pre-RA=pre-rheumatoid arthritis; ACPA=antibodies to citrullinated protein/peptide antigens

Table 3.

Key challenges and opportunities in implementing prevention in RA

- Completion of ongoing clinical trials to learn the efficacy of the agents and approaches that are evaluated
- Development of improved prediction models (including for seronegative RA)
- Identification of relevant biologic pathways for prevention that may be unique to the Pre-RA period
  - May be from ongoing or future trials and observational studies and include biology of non-articular sites (e.g. mucosal sites)
  - Includes understanding of the pathophysiology of autoimmunity and joint symptoms in absence of clearly definable IA
- Effective strategies to identify individuals who are at sufficiently high risk for RA that preventive approaches may be considered
  - Incorporates accurate prediction models and individuals' preferences
  - May include public health awareness campaigns and broad population screening
- Clear understanding of the role of imaging in diagnosis and management in Pre-RA
- Development of clear and informative nomenclature
  - Aligns with biology of disease
  - Effective in communicating with stakeholders
- Optimization of stakeholder participation in prevention
  - Individuals at-risk
  - Clinical rheumatologists
  - Research community
  - Funding agencies
  - Pharmaceutical, biotechnology and diagnostic industries
  - Health care and insurance agencies
  - Governmental agencies who can implement policy around prevention