The Natural History of Rheumatoid Arthritis

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ABSTRACT

Purpose: This article reviews the phases of rheumatoid arthritis (RA) development in terms of the evolution of disease, with a focus on events that occur before the first appearance of clinically apparent inflammatory arthritis. This presynovitis period is defined in individuals who eventually develop classified RA as the pre-RA phase. We include additional discussion of the relevance of this model of RA development to the concept of disease prevention.

Methods: The information provided in this review was identified through searches of the medical literature through MEDLINE and a review of references from published manuscripts as well as information obtained by the authors through attendance at various conferences and working groups related to pre-RA.

Findings: It is now well established that RA develops in a series of phases. The first of these phases is believed to be the presence of genetic and/or environmental risk factors for RA in the absence of detectable systemic autoimmunity in the blood. After this phase, autoimmunity may be detectable through a variety of means (eg, autoantibodies, autoreactive cells) in peripheral blood; in addition, there is emerging evidence that perhaps initiation and early propagation of RA-related autoimmunity may occur at mucosal sites. The presence of autoimmunity detectable in the blood through serologic or other testing is followed in most individuals by a propagation phase that is characterized by an expansion of autoimmunity, inflammation, and symptoms. This transition may be associated with similar or different genetic and environmental factors that initially triggered autoimmunity, as well as continued mucosal inflammation and local RA-related autoantibody production. Eventually, clinically detectable inflammatory arthritis develops that can be classified as RA.

Implications: Understanding the phases of RA development are critical to the development of preventive strategies for this disease. (*Clin Ther.* xxxx;xxx:xxx) © 2019 Published by Elsevier Inc.

Key words: disease prevention, inflammatory arthritis, pre–rheumatoid arthritis, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, inflammatory autoimmune disease that is currently considered largely a disease of the joints (ie, inflammatory arthritis [IA]), although multiple additional organ systems are known to also be involved, including the pulmonary, cardiovascular, ocular, and cutaneous systems. Importantly, however, the presence of IA (defined as tenderness and swelling on examination consistent with underlying synovitis) is still the hallmark of a clinical diagnosis of RA. Indeed, it is joint examination and imaging findings, as well as the presence of RA-related autoantibodies, systemic inflammation, and the duration of joint symptoms and findings, that comprise the established classification criteria (1987 American College of Rheumatology[1] and 2010 American College of Rheumatology/European League Against Rheumatism[2] criteria) for disease. Furthermore, treatment in RA is currently primarily focused on improving IA once it has become clinically apparent.

However, there is now established and evolving research that supports the conclusion that RA-related autoimmunity and inflammation are present long before the first onset of IA during a period that can be termed pre-RA.[3] These observations have

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generated a new understanding of how and when RA-related autoimmunity develops. In particular, these discoveries have raised interest in RA as a disease in which onset of IA could be prevented in individuals identified as at risk for future IA based on the presence of some combination of genetic and environmental risk factors, highly predictive biomarker abnormalities (eg, autoantibody elevations), and potentially joint symptoms. Indeed, as discussed elsewhere in this issue, there are several prevention trials in RA that have been completed or are under way.[4,5] Importantly, studying the evolution of RA-related autoimmunity before the first onset of IA could lead to a new understanding of the pathogenesis of disease and identify novel targets for prevention.

This review discusses the natural history of RA with a focus on what is known about disease development during pre-RA. Notably, this will be a higher-level overview to provide a framework for other articles within this issue of *Clinical Therapeutics* that will provide a more detailed discussion on specific aspects of RA development, including the role of mucosal biology.[6–8]

METHODS

Information contained in this review was obtained through MEDLINE searches with the keywords*rheumatoid arthritis (RA), preclinical RA,* and *pre-RA*. In addition, information included was obtained through conferences and proceedings that have involved the natural history of RA that the authors have attended.

CHARACTERIZATION OF PRE-RA BY EXPANDING AUTOIMMUNITY AND INFLAMMATION

Autoantibodies

Multiple studies of the natural history of RA have been performed. These studies include retrospective case-control studies, analyses of large-scale cohort studies where incident RA has developed, and an increasing number of prospective studies of populations who are at increased risk of future RA. These latter studies have included individuals who have baseline RA-related autoantibody positivity, arthralgia with or without autoantibody positivity, and a family history of RA.[9] A summary of the results of the key studies documenting these findings is included in Table.

Overall, these studies have found that RA-related autoantibodies are detectable in the circulation a mean of 3–5 years before the first clinically detectable IA. The autoantibody systems most studied in pre-RA include rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs); in addition, the presence of anti–peptidyl arginine deiminase antibodies[26] and antibodies to carbamylated proteins[27,28] have also been evaluated in pre-RA.

In general, these studies have found several themes of autoantibody development and evolution in pre-RA. The first is that there is an increasing prevalence of autoantibody positivity as well as increasing autoantibody levels over time as clinically apparent IA and a diagnosis of RA approach. The second theme is that an isotype evolution occurs, with the presence of IgG autoantibody being most specific for classifiable RA and imparting the highest risk for future RA, although there is ongoing IgM RF and ACPA generation even in individuals have IA and during the further transition to classified RA in patterns that suggest ongoing B-cell activation even once IA has developed.[29] The third theme is that there is an expanding number of antigenic targets being identified by the immune system, including additional citrullinated peptides and proteins,[30,31] as well as development of other antibody systems, including RF, anti–peptidyl arginine deiminase antibodies, and antibodies to carbamylated proteins. Most individuals are positive for RF, ACPAs, and other antibodies immediately before they transition from pre-RA to classifiable RA.[16,17,26–28,32–34] Importantly, the dual positivity for RF and ACPA provides stronger prediction for future RA compared with RF or ACPA positivity alone; furthermore, it is likely that the combination of RF and ACPA is an important pathogenic factor in the transition from pre-RA to IA/RA. This is potentially attributable to a greater ability of the combination of RF and ACPAs to form immune complexes, activate macrophages, and upregulate tumor necrosis factor-α and ultimately trigger synovitis.[35] Finally, the pathogenicity of antibodies also appears to evolve in pre-RA. Specifically, there appears to be altered antibody affinity[36] and other changes, such as changes in glycosylation of the Fc domain[37] and the

Table. Key studies of the prearthritis phases of RA development.

Study	Summary
del Puente et al,[10] 1988	Approximately 2700 Pima Indians from the Southwestern United States were followed up for up to 19 years with biennial examinations; 70 individuals (approximately 2.6%) developed incident RA with the highest rate of 48 per 1000 person-years in individuals with baseline RF titer of >1:256 (ACPA testing not available).
Aho et al,[11–14] 1991–2000	Approximately 19,000 adults in Finland initially evaluated from 1973 to 1977 in a population-based study. By 1989, 124 developed RA, 89 with RF-positive RA and had pre-RA diagnosis serum available; findings from these individuals were published in multiple publications and included elevations of IgG, RF, and antibodies to keratin and perinuclear factor (later determined to be varieties of ACPAs) before RA.
Silman et al,[15] 1992	370 unaffected first-degree relatives from families in Great Britain with multiple cases of RA were followed up; 14 individuals developed incident RA, for an overall rate of 8 per 1000 person-years; incidence was highest in those with RF positivity.
Rantapaa-Dahlqvist et al,[16] 2003	Swedish biobank study of 83 cases with RA and 382 controls, most with one stored serum sample available from before RA diagnosis. At any time before a diagnosis of RA, anti-CCP2 test results were positive in approximately 34% of individuals with RA: RF-IgA, approximately 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 before diagnosis.
Nielen et al,[17] 2004	The Dutch Sanquin biobank was used to identify 79 cases with RA with a median of 13 samples available and 2 control samples per case; anti-CCP1 and RF-IgM were tested. Overall, 49% of patients with RA tested positive for anti-CCP1 or RF-IgM a median of 4.5 years before diagnosis. Using a 0- to 5-year window before diagnosis and comparison with controls, anti-CCP1 or RF-IgM positivity was approximately 36% sensitive and approximately 97% specific for RA, with a PPV of approximately 97%. Increased sensitivity, increased rates of simultaneous positivity for anti-CCP1 and RF-IgM, and higher levels were present in the most immediate prediagnosis period. Anti-CCP1 appeared to be positive before RF-IgM.
Majka et al,[18] 2008	The US Department of Defense Serum Repository was used to identify stored serum samples from 83 military personnel who developed RA and 83 matched controls. RF and anti-CCP2 levels were elevated in 57% and 61% of individuals before a diagnosis of RA, respectively. The median time of appearance of RF was earlier CCP2 (6.0 vs 5.4 years), although not statistically different. Notably, younger patients (<40 years old) appeared to have a shorter duration of preclinical autoantibody positivity compared with older patients (≥40 years old).
Chibnik et al,[19] 2009	The prospective Nurses' Health Study based in the United States was used to identified 93 cases of incident RA, along with 3:1 matched controls; a single

(*continued on next page*)

Table. (*Continued*)

Study	Summary
	pre-RA diagnosis serum sample was tested for CCP2. At its standard cutoff level (>5 units), CCP2 positivity was 28% sensitive and 100% specific for future RA and 100% specific, and higher levels predicted a shorter time to diagnosis.
Bos et al,[20] 2010 and van de Stadt et al,[21] 2012	147 Dutch clinic patients with arthralgia defined as joint symptoms in the absence of inflammatory arthritis at baseline based on a 44-count joint examination by 2 physicians were followed up prospectively; at baseline, 50 were CCP2 positive, 52 RF-IgM positive, and 45 positive for both autoantibodies. Of those with positivity for CCP2 and RF-IgM, 45% developed RA after a median of 28 months of follow-up. Longer-term follow-up has allowed for the development of a prediction rule for future RA.[21]
de Hair et al,[22] 2013	55 ACPA- and/or RF-positive Dutch patients were identified in clinics and followed up prospectively. A total of 27% developed IA/RA after a median follow-up time of 13 months. Nonsmokers and those with normal eight had the lowest rates of progression to IA/RA.
Ramos-Remus et al,[23] 2015	819 First-degree relatives of Mexican patients with RA were tested for ACPA and RF, and individuals were followed up longitudinally for approximately 5 years. ACPA positivity with or without concomitant RF positivity had PPVs of 58%−64% for development of RA during this follow-up.
Rakieh et al,[24] 2015	100 Individuals in Great Britain with arthralgia and CCP2 positivity without clinically apparent synovitis at baseline were followed up for a median of approximately 20 months. A total of 50% developed IA after a median of 7.9 months. Highest risk for progression to RA was in individuals with ultrasonographic findings of joint inflammation, tender joints on examination, and high levels of RF and CCP2.
Gan et al,[25] 2017	35 CCP3-positive individuals from the United States without clinically apparent synovitis at baseline were followed up for approximately 2.5 years. A total of 40% developed IA/RA within this follow-up. Progression to IA/RA was associated with higher age, shared epitope positivity, and lower blood levels of ω-3 fatty acids.

Abbreviations: ACPA, anticitrullinated protein antibody; CCP, cyclic citrullinated peptide; IA, inflammatory arthritis; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor.

F(ab) around the antigen combining site,[38] with these changes potentially rendering antibodies more pathogenic.

What is not yet clearly known is what antibody system appears first in RA, with *appears* being defined as which antibody is positive first, either on an individual level or by prevalence of positivity within groups. Several studies have suggested ACPAs come first, but others suggest RF is first or that there is near simultaneous development of RF and ACPAs.[16,17,32,39] There is some evidence that RF and ACPAs precede systems such as antibodies to carbamylated proteins[28]; however, more definitive studies are needed. This is important because knowing which system appears first may help understand the pathophysiology of early disease initiation and may facilitate the identification of new opportunities for prevention. In addition, distinct processes may drive the development of each antibody system, and linking the specific autoimmune response to pathogenic processes that could be modified in prevention strategies could provide

additional opportunities and targets. Furthermore, the earliest antigenic targets within citrullinated proteins, which citrullinated (or other) proteins are initially targeted, and the key antigenic targets or modifications of the immune system and/or target tissue(s) that allow a transition from pre-RA to IA and classifiable RA are not known. These are active areas of research.

Inflammation

In parallel with the evolution of autoantibodies in pre-RA, there is an expansion of inflammation. Inflammation has largely been measured systemically in pre-RA using stored serum and/or plasma samples and has focused on cytokines and chemokines.[19,32,40] In aggregate, these studies have found an increase in the levels of a variety of cytokines and chemokines, with the general trend that more cytokines and chemokines are elevated most proximal to the transition from pre-RA to IA and classified RA.

In addition, several studies have found that a measure of inflammation that is commonly used in clinical practice, C-reactive protein (CRP), increases over time in pre-RA.[39,41] However, the levels of CRP are often only minimal elevated until classifiable RA has developed, likely consistent with studies that have found that a substantial proportion of individuals with classified RA early in the disease course have normal clinically tested markers of inflammation, including CRP.[42] That said, most studies support that if individuals in the pre-RA phase has elevations of autoantibodies as well as systemic inflammation by measures such as CRP, then they are highly likely to imminently develop RA; this finding has underpinned the development of inclusion criteria in several clinical prevention trials for RA that are discussed in detail elsewhere in this issue.

Notably, thus far no specific inflammatory pathway has been robustly identified as key in pre-RA, which appears to be necessary or sufficient for the development of systemic autoantibodies or the transition to RA, although there have been some findings suggesting that type 1 interferon[43] and B- and T-cell signatures exist.[40,44] The lack of identification of key signatures may be attributable to limits in detecting inflammatory markers as well as relatively small sample sets and will need to be studied further. As for which process comes first in pre-RA, autoantibodies or inflammation, on the basis of existing studies there appears to be a near simultaneous development of early autoantibodies and inflammation albeit all at low levels early in pre-RA, with expansion over time. Moreover, some studies have identified elevations in certain cytokines and chemokines, including interleukin (IL) 1α and interferon γ—induced protein 10, before RF and ACPA positivity in pre-RA.[32]Furthermore, in a study of an indigenous population in Canada, which has a high prevalence rate of RA, first-degree relatives had systemic elevations of monocyte chemoattractant protein 1 even in absence of autoantibody positivity.[45] Although this study was limited by its cross-sectional design, it raises the possibility that there may be some baseline inflammatory state that serves to potentiate future autoantibody development and ultimately RA development.

Several additional inflammatory-related biomarkers have been found to be abnormal in pre-RA. In particular, the level of survivin, which can be expressed by macrophages, T cells, and B cells, was elevated in individuals with arthralgia, some of whom were also RF and/or ACPA positive, and elevated survivin levels predicted which individuals would transition from pre-RA to IA and classifiable RA.[46] In addition, the marker 14-3-3eta is elevated in RF- and/or ACPA-positive individuals and was associated with future development of IA and classified RA; furthermore, 14-3-3eta elevation was associated with the future development of IA even in RF- and ACPA-negative individuals.[47] Given that both survivin and 14-3-3eta can be generated within joints, it remains to be seen if their elevations are an indication of IA that joint examination is initially unable to detect, although the same may be true for many of the cytokines and chemokines studied in pre-RA.

Identifying the association between early autoimmunity and inflammation in pre-RA, as well as pathways that may be related to propagation of autoimmunity and transition from pre-RA to classified RA, remains an area of active research because identifying a key pathway in pre-RA could lead to specific targeting of that pathway for prevention.

Cells

Most studies of pre-RA have focused on stored serum or plasma; as such, there is as yet limited

understanding of cellular processes in pre-RA. However, there are several prospective studies of ACPA-positive individuals or other individuals who are at risk for future RA based on family history of RA, where peripheral blood cells have been evaluated through methods such as flow cytometry. In a study of 113 RF- and/or ACPA-positive individuals with arthralgia, 40 (35%) of whom developed IA during follow-up, at baseline, those who developed incident IA had lower peripheral cytotoxic T cells and some B-cell subsets with the lowest levels in those who developed IA within 1 year.[48] This was interpreted as potentially indicating that peripheral cells migrated to tissue during the transition from pre-RA to IA.

An additional British study evaluated peripheral blood mononuclear cell (PBMC) profiles with flow cytometry in 103 individuals, all of whom were ACPA positive without IA at baseline and 48 (approximately 47%) of whom developed incident IA; T-cell subsets within these individuals were compared with subsets in a group of healthy controls.[49] At baseline, approximately two-thirds of the ACPA-positive individuals had abnormalities in T-cell subsets compared with controls; these changes included reduced peripheral CD4 naïve T cells, reduced T-regulatory cells, and an increased population of a novel T-cell subset termed inflammatory-related cells. Furthermore, the presence of $\geq$2 of these T-cell subset abnormalities were predictive of incident IA, suggesting that they may be pathologically related to the transition from pre-RA to IA/RA.

In an additional study of 21 individuals at risk for RA based on serum RF and/or ACPA positivity and expansion of $\geq$5 B-cell receptor (BCR) clones (determined by BCR sequencing) in peripheral blood was found preferentially in those individuals who progressed to IA and classified RA when compared with those autoantibody individuals who did not.[50] In addition, in a subset of 8 individuals who transitioned to IA, paired PBMCs and synovial biopsies were performed *after* they developed IA. Within the synovium of a subset of these patients were a number of BCR clones that were seen in the pre-RA blood sample; however, in the post-IA blood sample, none of the BCR clones were identified that were previously seen in the pre-RA samples. This finding suggested that the B cells may have migrated from the peripheral blood to the joints once IA developed.

Cross-sectional studies of cells from individuals at risk for future RA have identified additional cellular abnormalities that may play a role in the risk of future RA. These abnormalities include a finding of PBMC hypercitrullination of multiple proteins in arthritis-free first-degree relatives (FDRs) with or without serum RF or ACPA positivity and compared with controls.[51] In this same study, anti-CD3 stimulation of PBMCs also resulted in increased generation in $CD4^+$ T cells of several cytokines, including IL-2, IL-17A, and IL-17F, but reduced production of IL-4 and IL-13, in FDRs compared with controls. These cytokine responses were irrespective of serum ACPA-positive status within FDRs and furthermore appeared to be related to PTPN22 pathway function that in turn may have been affected by intracellular citrullination. These findings need replication and deeper exploration; however, similar to the finding mentioned above of elevated circulating monocyte chemoattractant protein 1in indigenous Canadian populations,[45] these cell study—based findings suggest that groups such as FDRs who are at risk for future RA may have underlying immunologic abnormalities even in the absence of serum autoantibody positivity that may prime them for development of RA in the future. These are important pathways to explore because they could help improve our understanding of the pathogenesis of RA and ultimately offer targets for preventive interventions.

Finally, a cross-sectional study of PBMCs from RF- and/or ACPA-positive individuals compared with autoantibody-negative controls found that although total plasmablast numbers were indistinguishable in these groups, the autoantibody-positive individuals had a greater percentage of IgA plasmablasts.[52] This finding suggested that these individuals had mucosal-based immune responses in pre-RA, perhaps mechanistically related to their RA-related immune responses. This concept will be explored further in the next section.

MUCOSAL ORIGIN OF RA-RELATED AUTOIMMUNITY

Importantly, although the generation of RA-related autoantibodies has been found within inflamed joints in individuals with established RA,[53] the circulating

autoimmunity and inflammation in pre-RA can occur in the absence of definable joint inflammation. This has been found in several studies of individuals who exhibit serum RA-related autoantibody positivity by (1) the absence of self-reported joint symptoms,[24] (2) the absence of joint examination findings of IA (tenderness and swelling),[24,54] and (3) absent imaging evidence of IA using modalities such as ultrasonography, magnetic resonance imaging, and positron emission tomography.[55–57] In addition, one study found that some individuals with circulating RF and/or ACPA do not have histologically definable inflammation on synovial biopsy of the knee.[58] Overall, these findings suggest that autoimmunity in RA originates outside the joints.

As to where that site (or sites) is, this is an area of active investigation, although there is some established and emerging evidence that it may be a mucosal site. This conclusion is supported by findings, such as those mentioned above, that indicate IgA plasmablasts are enriched in RA-related autoantibody-positive individuals without IA,[52] as well as cross-sectional studies that have found increased IgA-isotype positivity of RF and ACPA in individuals who are at risk for future RA, such as FDRs.[23] As for which specific mucosal sites are involved in pre-RA, most evidence to date implicates sites such as the lung, periodontal surfaces, and gut, although there are numerous other candidate mucosal sites.[59] In particular, the generation of RA-related autoantibodies in the lung has been found in a subset of serum RF- and/or ACPA-positive individuals.[60] Furthermore, although not pre-RA, differences in periodontal and/or gut microbiome findings in individuals with new-onset RA compared with controls suggest that the gastrointestinal tract and specifically gut microbiota may play a role in the transition to RA,[61,62] although the question of whether microbiota change because some get ill from RA or because they cause someone to get RA still needs to be worked out. The role of mucosal surfaces in the natural history of RA is reviewed in detail by Demoruelle[6] in this issue, and certainly this area needs additional research. However, overall, it is compelling to think that mucosal surfaces may play a key role in the initiation and propagation of autoimmunity in pre-RA and that mucosal-related processes may also serve as targets for prevention.

ENVIRONMENTAL AND GENETIC FACTORS

There are numerous genetic and environmental factors associated with RA.[63] It is beyond the scope of this article to review these factors in depth, and a commentary in this issue is dedicated to targeting environmental factors in RA prevention.[64] However, a critical point is that most of the genetic and environmental factors that have been linked to RA have been studied in case-control studies that include individuals with established classified RA. With the understanding that RA-related autoimmunity begins years before the onset of incident IA and classified RA, it is therefore highly likely that factors that trigger and propagate RA-related autoimmunity as well as drive the transition from pre-RA to IA are acting years before a diagnosis.

As such, the field needs to reevaluate in appropriate studies of pre-RA what factors drive the development of RA. Importantly, the field also needs to evaluate *when* these factors are acting in the natural history of RA development because it could well be that certain factors are triggering early autoimmunity in RA (eg, autoantibody positivity), and other factors are promoting the propagation of autoimmunity and ultimately the development of IA. Understanding these factors will provide not only clues to mechanisms of disease development but also targets for prevention.

Following this, as of yet, prospective studies of pre-RA involve a relatively small number of individuals who have transitioned from pre-RA to classified RA, especially when compared with the numbers of individuals with classified RA who have been studied in epidemiologic studies and clinical trials. A best estimate is that our current knowledge of pre-RA is based on approximately <1500 individuals who have been studied across the transition from pre-RA to clinically apparent IA and RA. That said, there are some genetic and environmental factors emerging that appear to increase an individual's risk for transitioning from an autoantibody positive pre-RA state to IA and classified RA. These factors include that continued smoking and obesity are risks for progressing from ACPA positivity to IA/RA.[22] In addition, modest alcohol consumption in autoantibody-positive individuals has been identified in prospective studies as a protective factor against the development of future RA.[54] The presence of the

major genetic factor that is associated with RA, the shared epitope,[65] is also a factor for progressing from ACPA positivity to IA/RA, although the effect of this has been variable across studies.[29,54] With additional study, these factors may help understand the pathogenesis of RA and, importantly, provide lifestyle modifications that could improve risk.

Furthermore, in cross-sectional studies of FDRs, the use of hormone-based oral contraceptives is protective against RF presence[66]; because this is in line with case-control and populations studies that have also found the oral contraceptive use is associated with decreased risk for RA, it may well be related to a true protective effect,[67] although further study is needed to identify mechanisms and potentially apply this therapy to preventive approaches to RA. In addition, in a cross-sectional study, increased dietary intake and higher red blood cell membrane levels of ω3 fatty acids are protective against ACPA positivity,[68] and within ACPA-positive individuals at baseline, increased dietary intake and higher levels of red blood cell membrane levels were protective against the development of incident IA and classified RA.[25] As with oral contractive use, these findings align with case-control and population studies where intake of ω-3 fatty acids, including through foods such as fatty fish, are protective against RA,[63] but again this will require additional studies to uncover specific mechanisms underlying the associations and to implement in prevention.

Currently, some of these risk (and protective) factors are built into prediction models for future RA, which is discussed in more depth elsewhere in this issue.[7] Furthermore, more studies are needed of the genetic and environmental factors that influence the pre-RA natural history. However, the studies thus far provide support that indeed there may be factors that can be identified that shed light on the pathophysiology of RA development and that may be potential modifiable factors to promote prevention.

SYMPTOMS AND DEVELOPMENT OF RA

A number of studies of pre-RA have identified that individuals can have variable levels of joint-related or other symptoms (eg, fatigue) compared with other individuals in pre-RA. The fatigue may be related to systemic inflammation. However, often the joint symptoms are not associated with objective findings of synovitis, such as joint swelling (or even joint tenderness) on examination or synovitis on imaging. There is emerging evidence that some of this pain may be attributable to inflammation in nonarticular sites, such as the tenosynovium.[69] In addition, there is emerging evidence that ACPA may induce pain perhaps through a mechanism of IL-8 release,[70,71] and this may occur in the absence of detectable synovitis. However, some of these symptoms are not yet well understood in terms of direct tissue injury.

What this means to the pathophysiology of RA is unclear. One suspects that these symptoms are attributable to joint inflammation or damage that is not detectable on current modalities, such as physical examination and imaging, but it is possible that there are other processes at work, such as cytokine effect on pain mentioned above or other, perhaps centrally mediated pain. These theories will need further exploration.

However, despite their true origin, the symptoms present in the absence of definable IA seem important because an increasing number of studies have found that symptoms plus autoantibody positivity are more predictive of imminent clinically apparent IA and classifiable RA than autoantibodies alone.[24,54] In addition, joint symptoms alone may be predictive of future RA even in the absence of baseline autoantibody positivity, and this finding has underpinned the development of clinically suspect arthralgia, which is described elsewhere in this issue and is now being further studied to identify individuals at high risk of progressing to IA and classifiable RA.[72,73] A caveat is that some of the importance of symptoms may be related to the method by which some studies of pre-RA have been developed. In particular, many studies have initially identified individuals who have persistent joint symptoms at their entry into clinical care who were then tested for RF and ACPA. The studies then enrolled these individuals with autoantibody positivity. This is a reasonable approach when standard clinic assessments are used to identify individuals at risk for future RA; furthermore, individuals with symptoms may more readily participate in prevention studies with the hope of feeling better, and ethical review boards may more readily approve prevention studies in symptomatic individuals because they may have a higher risk for imminent disease as well as potentially benefit more from an intervention. However, the approach of first identifying symptomatic individuals for autoantibody

testing may bias studies toward demonstrating a stronger role of persistent symptoms in pre-RA development. Indeed, older literature suggests that RA may develop differently in different people, including individuals with palindromic-type disease in whom symptoms are present then resolve or individuals with explosive disease in whom symptoms are largely absence until the onset of IA[42]; these latter types of pathways from pre-RA to IA and classifiable RA may not be captured well in approaches that focus on initial identification of individuals with symptoms.

CLASSIFIED RA: INSIGHTS FOR PREVENTION

This review focuses on the natural history of RA in the pre-RA period. However, there is ample evidence that RA continues to evolve immunologically even after IA and classified RA is present. In particular, studies have found that autoantibody levels in the blood can become positive or negative even after several years of disease.[74,75] These findings may be related to treatments, potentially different assays or cutoff for positivity, or other factors that are not yet well known. However, perhaps most compelling when contemplating RA as a preventable disease is that one of the strongest predictors of good response to therapy and remission (when taking the drug or not) is initiation of therapy within a short time frame from the onset of RA-related symptoms and the identification of the first synovitic joint, even before classifiable RA is present.[76–78] The reasons for this are not clear, but it is compelling to think that a great part of this finding is that because in early RA the immune system has developed enough abnormalities to result in IA but still may be malleable enough to return to a relatively normal state. This theory needs to be studied further but provides a potential rationale that moving therapy from its current use in individuals with IA and classified RA to the pre-RA state may have a strong chance at being effective in prevention or even a reset of the immune system where interventions may not be needed forever, which is currently the case for most individuals with RA who undergo standard of care where treatment is initiated only once the first clinically apparent IA has developed.

OVERALL MODEL OF RA DEVELOPMENT

Taking into account all the information discussed above regarding autoantibodies, inflammation, cells, and genetic and environmental factors and symptoms, an overall model of the natural history of RA development can be developed as presented in Figure. In this model, genetic and environmental factors can combine, perhaps initially at a mucosal

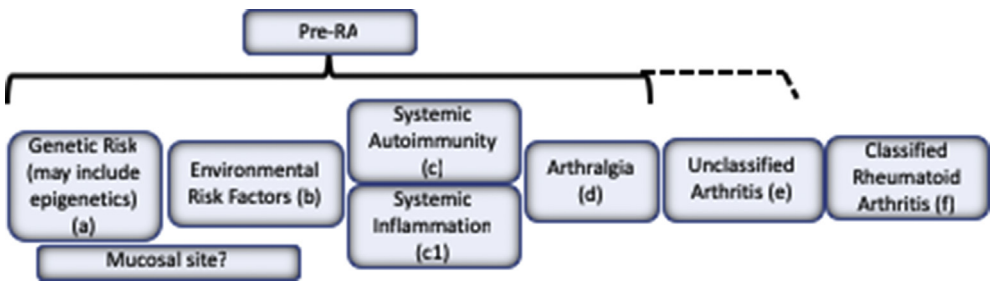

Figure. Natural history of rheumatoid arthritis (RA). In this model, various phases of RA development exist that could potentially be identified and then targeted for prevention of future phases. The phases are adapted from the European League Against Rheumatism's recommendations for terminology and research in individuals at risk of RA.[3] In this model, genetic (a) and environmental (b) factors trigger then drive propagation of autoimmunity and inflammation (c, c1), with these early processes perhaps occurring at mucosal sites. The disease can then evolve to arthralgia (d), unclassified arthritis (e), and then classified RA (f). Of note, genetic and environmental risk factors likely operate throughout the natural history of RA; however, the specific factors may differ along the course of disease development. In addition, multiple phases can exist simultaneously, and individuals may not progress through all phases. Finally, the dotted line indicates that some may not consider an individual with inflammatory arthritis (IA) (e) pre-RA.

site, to trigger initial autoimmunity and inflammation that can propagate over time. Then autoimmunity and inflammation can evolve with expanding antigen target systems (eg, RF and ACPA), isotypes, and inflammatory markers. In parallel, symptoms of joint inflammation as well as other symptoms (eg, fatigue) can develop. Furthermore, this may also be a period when nonarticular tissue may be involved in autoimmunity-related injury or effects; this will be discussed in the article by Giles in this issue,[79] but these tissues include the cardiovascular system where myocardial infarctions and strokes may be increased in pre-RA compared with control populations,[80] lung disease may precede articular RA,[55,81] and depression and other mood disorders may be increased.[82]

This RA prodrome is then followed by clinically detectable IA and then ultimately classifiable RA. Notably, in this model, multiple phases can be present at a single time, and particular factors, such as genetic and environmental factors, may differ at separate time points. In addition, an individual may not progress through all phases or may progress but then return to an earlier phase through an intervention, such as immunotherapy (eg, developing seronegativity for RF and/or ACPA after receiving medications for RA[74]), or without obvious therapy, such as spontaneous remission of autoimmunity, which has been found, albeit in a limited fashion in several pre-RA studies especially within control populations.[16,32]

There are some caveats to the interpretation of this model as well as its content. In particular, there is some controversy about which phases should be referred to as pre-RA. Specifically, a substantial portion of the population has some genetic and environmental risks for RA yet likely do not exhibit any of the other phases (eg, autoantibodies, arthralgia), and whether they could be considered pre-RA in a similar way to someone who exhibits seropositivity for RF and ACPA remains to be determined. Furthermore, an individual with IA even if not classifiable as RA may be considered to have evolved past pre-RA.

Defining systemic autoimmunity can also be difficult because there is a wide range of autoantibodies available in clinical care and for research, and these assays do not perform the same in classified RA, especially if the autoantibodies assess different isotypes; in addition, the variability of agreement of autoantibody tests can be higher in pre-RA when immune responses may be less mature.[83] There are also issues such as potential cross-reactivity of autoantibodies; notably, ACPA may bind to a variety of proteins that contain citrulline and even antibodies that contain similar structures such as homocitrulline.[84] Furthermore, there are ever-evolving types of autoantibodies being discovered and made available, which could further change the landscape of what we know about autoimmunity in pre-RA. As such, as the field of pre-RA moves forward, there may need to be efforts to harmonize and standardize what specific testing needs to be performed to establish that each of the phases is present, much like what has been done in other autoimmune diseases that have a definable predisease state, such as type 1 diabetes for which autoantibody testing is closely evaluated to ensure homogeneity. Similar comments can be made about systemic inflammation for which numerous assays exist with varying performance to identify inflammatory abnormalities. In addition, some data have suggested that localized mucosal autoantibody production may in fact be protective and assist in the clearance of inflammation, which is a hypothesis that requires additional investigation to understand what autoimmunity may be beneficial versus harmful and what processes may drive the transition between these 2 states.[59]

Furthermore, although existing studies suggest that a high percentage of individuals who develop RF and/or ACPA-positive RA will have seropositivity of these antibodies before IA, not all individuals who develop IA have detectable seropositivity for autoantibodies preceding their arthritis. This finding could be because a pre-RA sample that was from a period when pre-RA autoantibody positivity was present was missing; however, some studies have found that up to approximately 11% of individuals who present with IA and are initially negative for ACPA will develop ACPA positivity many months after their initial presentation.[74] This finding could mean that RA-related autoantibodies that are detectable in the blood develop after clinically apparent synovitis or that current assays are insufficient to identify all forms of pre-RA autoimmunity; this finding will need exploration in future studies. Furthermore, seronegative RA does not readily fit into this model in that there are not yet biomarkers that can detect pre-RA autoimmunity, although this may change with development of new assays.

Finally, the specific mechanisms by which individuals transition among the various phases of pre-RA to IA and classifiable RA are not yet known. As discussed above, it may be that genetic and environmental factors converge at mucosal sites to initially trigger autoimmunity, which is later followed by expansion of immunity in regional lymphatics with eventual appearance of circulating autoimmunity. It may be that circulating autoimmunity then triggers arthritis through the formation of immune complexes or other activating inflammatory processes (eg, platelet activation[85]) when the right levels and antigenic targets are reached; autoantibodies or other immune cells evolve through epitope spreading or somatic hypermutation to target joint proteins; autoantibodies evolve to be more pathogenic through mechanisms such as glycosylation changes; or the joint changes through some event, such as trauma or infection, to be more susceptible to circulating autoimmunity. It may be a combination of some of or all these factors. Defining these transitions and how to alter them to delay or halt individuals from progressing through these phases is critical to developing effective preventive strategies for RA.

CONCLUSION

RA develops in a series of phases, several of which occur before the clinical appearance of IA. These pre-RA phases can be evaluated to understand the pathophysiology of RA development and, perhaps most importantly, targeted for prevention.

CONFLICTS OF INTEREST

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