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Preclinical Rheumatoid Arthritis (Autoantibodies): An Updated Review

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Abstract

Multiple studies demonstrate that there is a period of development of rheumatoid arthritis (RA) during which there are elevations of disease-related biomarkers, including autoantibodies, in the absence of and prior to the development of RA; this period can be termed 'preclinical RA'. These 'preclinical' autoantibodies including rheumatoid factor and antibodies to citrullinated protein antigens, and more recent studies have also identified a wider variety of autoantibodies and a wide range of inflammatory biomarkers. These findings in conjunction with established and emerging data about genetic and environmental risk factors for RA support a model of disease development where certain factors lead to an initial triggering of RA-related autoimmunity that expands over time to the point where symptomatic arthritis classifiable as RA develops. Herein will be reviewed updates in the field, as well as a discussion of current limitations of our understanding of preclinical RA, and potential future directions for study.

Keywords

Rheumatoid arthritis; Preclinical; Autoantibodies; Antibodies to citrullinated protein antigens (ACPA); Rheumatoid factor; Autoimmunity; Inflammation

Introduction

Multiple studies now demonstrate that there is a period of development of rheumatoid arthritis (RA) that is characterized by abnormalities of autoantibodies and other biomarkers in the absence of clinically apparent inflammatory arthritis that characterizes RA. Although the terminology regarding this period of RA development is currently being debated [1], this period has been termed 'preclinical' RA by many investigators, and several of the key early

Conflict of Interest

Kevin D. Deane has received funding from the Walter S. and Lucienne Driskill Foundation, the American College of Rheumatology Rheumatology Research Foundation, the National Institutes of Health, the Department of Defense, and AbbVie for the study of preclinical rheumatoid arthritis. He and others have submitted a patent application for the use of biomarkers to predict clinically actionable events in rheumatoid arthritis.

Human and Animal Rights and Informed Consent

This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

studies that have helped to define this period of RA development are listed in Table 1. Importantly, the major autoantibody systems described in these early studies have been rheumatoid factor (RF) and antibodies to citrullinated protein antigens (ACPAs), the most common available version of which is the commercially available anti-Cyclic Citrullinated Peptide (CCP) assay for which several generations (e.g., CCP2, CCP3) exist [2]. However, in the past several years, there has been an expansion of our understanding of the autoantibody and other immune responses that occur in preclinical RA. In particular, while the commercial CCP assays do not allow for identification of specific citrullinated antigen targets [2, 3], emerging technologies such as multiplex arrays are allowing for a greater understanding of antibody reactivities to specific citrullinated peptides and epitope spreading over time. In addition, our understanding of preclinical RA changes in autoantibody affinity, avidity and isotype evolution, changes in immunoglobulin effector function through changes such as glycosylation, discovery of novel autoantibody systems, and an ability to test for a wide variety of cytokines, chemokines and other inflammatory markers are leading to a greater understanding of autoimmunity and inflammation in preclinical RA. Herein, will be reviewed several of these key recent findings in preclinical RA, with a focus on autoantibodies. These findings will also be related to an emerging overall model of RA development. In addition will be discussed some areas that need to be explored in order to further advance our understanding of RA development, and ultimately lead us to the point where RA may be prevented.

Early studies identifying autoimmunity and inflammation prior to a diagnosis of RA

Multiple studies have identified that there are abnormalities of autoantibodies and inflammatory markers prior to a diagnosis of RA. Such studies include those by Aho and colleagues who used a Finnish sample bank to identify elevations of RF and antibodies to keratin and perinuclear factor (later determined to be citrullinated filaggrin) prior to the onset of RA [4–6]. In addition, a prospective study included a long-term study of Pima Indians demonstrated that RF precedes the onset of clinically apparent RA [7]. Furthermore, a British prospective family study of patients with RA also demonstrated elevations of RF prior to the onset of RA in previously unaffected individuals [8].

With these older studies as background, two landmark studies brought to prominence the field of understanding the natural history of RA prior to diagnosis of disease. These were a study by Rantapaa-Dahlqvist and colleagues published in 2003 demonstrating, in stored serum samples from a Swedish sample set of 83 patients with RA and controls, that RF of various isotypes and CCP were elevated prior up to years prior to a diagnosis of RA [9]. This study was followed shortly thereafter by work by Nielen and colleagues who used stored serum samples from the Dutch Sanquin biobank of samples from blood donation that includes 79 patients with RA and controls to demonstrate similar findings [10]. These studies were supported by additional studies over the next few years all with similar findings, although using slightly different biomarkers (including different assays for autoantibodies) in different cohorts including the United States Military [11], North American nurses [12], and a Norwegian sample set [13] (Table 1). Furthermore, multiple

studies have demonstrated elevations of a wide range of inflammatory biomarkers including C-reactive protein (although variably so), multiple cytokines and chemokines, and gene expression of inflammatory pathways prior to a diagnosis of RA [8,13–21].

While two notable early studies of preclinical RA were prospective (del Puente et al. [7] and Silman et al. [8]; Table 1), most of the early looks at preclinical RA were through studies of fortuitously collected samples from subjects prior to the development of RA; however, there have also been several recent prospective studies of early RA development. Several of these will be discussed below, but one is the Dutch ‘arthralgia’ cohort that consists of individuals with joint symptoms of pain and stiffness who are at baseline without IA based on a 44-joint examination by 2 physicians and who may be positive for RF and/or CCP2 [22]. These individuals are then followed prospectively to evaluate the natural history of arthritis development. Multiple findings have been generated in this cohort, with early work reporting that rates of development of RA in subjects with RF and CCP2 positive at baseline of approximately 40 % over a median of 28 months of follow-up, with incident rates of ~50 % in less than 2 years in patients who had baseline CCP levels above the 75th percentile [22].

Additional biomarker studies in preclinical RA

Building on these earlier works, over the past several years there have been multiple additional studies exploring autoimmunity and inflammation prior to the onset of RA, using additional sample testing from cohorts already evaluated in early studies, as well as prospective cohorts.

In particular, Rantapaa-Dahlqvist and colleagues used their Swedish sample set to identify that IgG, IgA, and IgM isotypes to CCP2 were present prior to a diagnosis of RA, with IgG being most commonly present prior to a diagnosis of RA (35 %), followed by IgA (24 %), and then IgM (12 %). Furthermore, using multiplex technology to identify ACPAs to a wide variety of antigens, Brink, Rantapaa-Dahlqvist and colleagues identified that immune responses to citrullinated proteins appear to be restricted to a small number of targets in early in RA, and expand towards the time of diagnosis of RA [23]. Moreover, while there was not a specific early antigen targeted across all subjects, autoantibodies to citrullinated fibrinogen and vimentin were early and did not seem to rise dramatically over time, while antibodies to other citrullinated antigens including enolase and filaggrin appeared later and rose prior to diagnosis; finally, antibodies to antigens such as citrullinated collagen appeared only immediately prior to a diagnosis of RA, but increased in levels after the onset of clinically apparent arthritis. Similar results have been demonstrated in studies using the Dutch Sanquin biobank and the Dutch ‘arthralgia’ cohort [24], and the United States Department of Defense Serum Repository (DoDSR) [25]. In addition, Suwannalai and colleagues demonstrated that ACPA avidity appears to increase over time during preclinical RA until symptomatic IA develops [26].

Overall, these findings suggest that, early in the natural history of RA, there is an initial break in tolerance to certain citrullinated antigens that expands, and reactivity to different antigens may be more strongly mechanistically linked with the development of arthritis;

furthermore, increasing avidity of ACPAs, and perhaps other autoantibodies, may also play a role in the transition from asymptomatic autoimmunity to clinically apparent IA/RA.

In addition to autoantibody systems of RF and ACPAs, other autoantibodies, and functional aspects of autoantibodies, have been identified in preclinical RA. These include autoantibodies to carbamylated proteins described by Shi and colleagues [27, 28]. In addition, autoantibodies to hinge regions of ACPAs have been described in samples from Dutch 'arthralgia' patients as well as blood donors who later developed RA [29]. Kolfenbach and colleagues have also demonstrated, using serum samples from the United States Department of Defense Serum Repository, that antibodies to the enzyme peptidyl arginine deiminase-4 (PAD4) are present prior to the onset of RA [30]. In addition, using the same DoDSR sample set, Ercan and colleagues demonstrated that the glycosylation levels of autoantibodies change prior to a diagnosis of RA to a more pathogenic, hypogalactosylated state, and similar findings have been demonstrated by in the Dutch 'arthralgia' cohort [31]; these autoantibody changes may have some influence on the transition from asymptomatic autoimmunity to clinically-apparent RA [32].

Expanding prospective studies of preclinical RA

A major issue in the prospective study of 'preclinical' RA is finding subjects with abnormal RA-related autoimmunity in absence of arthritis. This can be addressed in part by finding cohorts of subjects with established RA, and then hoping they have blood samples available from prior to the onset of their disease (or conversely, and perhaps more commonly, finding biobanks, and hoping that some subjects later developed RA); importantly, such studies form the bulk of our knowledge of autoimmunity in early RA. However, such studies may miss subjects who have undiagnosed synovitis at the time of their biospecimen collection, and therefore serum samples may not truly be 'preclinical' RA. Therefore, finding people in 'real-time' who can be simultaneously evaluated for RA-related autoantibodies and joint symptoms and findings of RA is important to understanding the development of early RA. However, finding such individuals is difficult because the number of people who are in a preclinical phase of RA development is likely quite low, and it would be expensive to find them in broad community-based approaches. Therefore, focusing on groups that may be at particularly high risk for future RA can improve the yield of finding those in the 'preclinical' phase of RA.

As mentioned above, the Dutch 'arthralgia' cohort has used clinics to identify and follow individuals who exhibit RA-related autoimmunity in absence of definable IA; moreover, important data regarding the natural history of RA and prediction of future onset of IA/RA using a novel prediction rule have been found using this cohort [33]. In addition, several studies have sought to study preclinical RA by evaluating first-degree relatives (FDR) of probands with RA. These include the multi-center Studies of the Etiology of Rheumatoid Arthritis (SERA) project that includes FDRs as well as individuals identified with anti-CCP positivity through health-fair screening [3, 34, 35]. This project has found that RA-related autoantibodies are indeed elevated in individuals in absence of clinically apparent inflammatory arthritis based on real-time joint evaluations [34]; in addition, it has noted that inflammatory markers are elevated in relationship to these autoantibodies suggesting that

autoimmunity is developing in the setting of systemic inflammation [36, 37]. Another prospective project headed by Hani El-Gabalawy in Manitoba, Canada, has utilized the high prevalence rate of RA in North American Natives (NAN) to examine the early natural history of RA [38]. This NAN project has demonstrated several important findings related to preclinical RA. In particular, it has demonstrated that there are differences between specific ACPA reactivities in individuals with established RA and their FDR [39], suggesting that there is a fundamental difference in the type of peptides and proteins targeted by autoantibodies in subjects at risk for RA, and those with established disease. The NAN project has also noted that elevations of certain inflammatory markers such as MCP-1 are present in FDR, even in the absence of detectable autoimmunity [40], perhaps indicating that autoimmunity can arise in families out of an inflammatory background.

Other studies of FDR have also demonstrated that RA-related autoantibody positivity is present in individuals in absence of definable IA. These include work from by Kim and colleagues from Korea [41], Barra and colleagues from Canada [42], and Arlestig and colleagues from Sweden [43]. In particular, Arlestig and colleagues found that IgA and IgM isotypes to CCP2 were predominant in FDR without IA, while the IgG isotype was predominant in patients with established RA. In addition, Barra and colleagues also found that IgA isotypes of ACPA were most common in FDR, and they also identified that FDR had fewer autoantibodies to specific citrullinated proteins when compared to patients with clinically apparent RA. Overall, these findings suggest that isotype switching may be a factor in progression to clinically-apparent RA, and that epitope spreading may be part of the transition from asymptomatic autoimmunity to clinically-apparent RA.

Interestingly, several studies have shown that epitope spreading appears to slow or halt after a clinical diagnosis of RA. Notably, these studies have utilized specific ACPA tests instead of the commercially available CCP assays. This is because the commercial CCP assays utilize combinations of likely several citrullinated antigens that have been made into a cyclic form to promote stability; while these CCP assays have high diagnostic accuracy for RA, they do not provide data regarding autoantibodies to specific citrullinated proteins [2, 3]. In particular, van der Woude and colleagues found using an array of 5 ACPAs to specific citrullinated antigens that, between blood drawn at baseline in patients with established RA and 7-year follow-up, there were basically stable numbers of ACPAs recognized; furthermore, the number of ACPAs recognized did not significantly change in patients who initially presented with undifferentiated IA and later progressed to classifiable RA [44]. Sokolove and colleagues showed a similar finding in a comparison of pre-RA diagnosis and post-diagnosis samples in military samples where the number of ACPAs stabilized in subjects before and after diagnosis [25]. Given the limited sample sets thus far used to identify this phenomenon, this area needs further exploration; however, if these findings hold true, the reasons for the stabilization of epitope spreading after the onset of clinically apparent RA are not clear. It could be a treatment effect leading to a decrease in epitope spreading; however, it could also be that there is some threshold of ACPA reactivity that is necessary to develop clinically apparent RA, and that expansion of autoimmunity beyond that does not occur.

Overall model of RA development based on current knowledge

To date, available data suggests that RA-related autoimmunity as detected by autoantibodies initially develops on average 3–5 years prior to the first joint symptoms, and up to 15 years in some studies [45]. This autoimmunity may arise in the setting of inflammation, but initially inflammation is minimal. Over time, autoimmunity progresses with epitope spreading and changes in the pathogenicity of autoantibodies, through changes such as alterations of glycosylation, and perhaps the effect of antibodies to hinge regions. In addition, autoantibody avidity is changing. The primary autoantibody responses are RF and ACPAs, but multiple other autoantibody systems are also present in preclinical RA, including anti-PAD antibodies and antibodies to CarP, although it is not yet clear what specific biological roles these autoantibody systems play in the early evolution of RA. The initial autoantibody system present in preclinical RA is not yet clear, with some studies suggesting that ACPAs precede RF and others suggesting that RF precedes ACPAs; regardless, the presence of both ACPAs and RF appear to be the most specific biomarker combination for predicting future disease; additionally, the presence of these autoantibodies together is a harbinger of more imminent onset of clinically apparent arthritis. This may be due to mechanistically related aspects of these antibodies, with RF perhaps leading to increased immune complexes containing ACPAs [46]. Over time, these autoimmune and inflammatory processes expand and evolve culminating in the development of clinically apparent IA, that may then progress to classifiable RA.

Of note, the preclinical period of seropositive RA is much better defined than seronegative disease. This is largely due to an absence of specific biomarkers for seronegative RA. However, there have been some findings that suggest inflammatory markers such as cytokines and chemokines are abnormal in preclinical seronegative disease, in particular using the DoDSR sample set mentioned above, Deane and colleagues identified that multiple cytokines and chemokines were elevated in the preclinical period in subjects who went on to develop RF and CCP negative RA, although the inflammatory response was less than that seen in preclinical seropositive RA [17]. Furthermore, a number of novel autoantibodies have been identified in patients with ‘seronegative’ RA by RF and ACPA testing; for example, using a Dutch preclinical sample set from 79 subjects who later developed RA, Shi and colleagues demonstrated that anti-CarP antibodies were elevated in 5/79 of subjects who were otherwise negative for anti-CCP and RF-IgM in the preclinical period of RA [28]. Furthermore, as in more detail discussed in the next section, developing methods for detecting additional ACPAs can identify patients previously thought to be ‘seronegative’ through more standard testing. There are many issues surrounding both the biology as well as clinical classification of seronegative RA [47–49]; however, as many studies suggest that seronegative status for RF and ACPAs may encompass ~30 % of patients with RA [50], ultimately identifying new means to identify and study preclinical seronegative RA will be of benefit to understanding this important subset of RA.

ACPAs: beyond the current commercial tests

Current commercially available assays for ACPAs including various versions of the CCP assay have provided invaluable information regarding preclinical RA; however, as discussed

above, given these assays likely test a variety of antigens, the details of specific ACPA reactivities are unknown. As such, as mentioned above, testing for a range of autoantibodies to specific citrullinated proteins can improve our understanding of RA in terms of preclinical epitope spreading, and may improve on diagnostic accuracy.

In this regard, Wagner and colleagues demonstrated that a bead-based ACPA array that included 16 antigens was more sensitive for RA than a commercial assay for anti-CCP2; specifically, autoantibody positivity for 4 or more specific antigens was 57 % sensitive for RA, and 96 % specific, compared to a sensitivity of 47 % for the anti-CCP2 assay (the specificity of the anti-CCP2 was not reported) [51]. Young and colleagues found similar findings in a cohort of FDRs without RA; in particular, using a similar ACPA array testing autoantibodies to 16 antigens, they found that 8 % of 99 FDRs who were negative for anti-CCP2 were positive for 9 ACPAs, with this number of ACPAs being 67 % sensitive and 92 % specific for established RA. Overall, these findings suggest that newer ACPA arrays may prove more sensitivity to detecting RA-related autoimmunity than currently available commercial assays such as anti-CCP, although this will need further study. In particular, while many studies support that, for the majority of subjects, the appearance of circulating autoantibodies occurs prior to the onset of clinically apparent arthritis. However, some studies suggest that, in some cases, clinically-apparent IA precedes the appearance of autoantibodies. Specifically, Barra and colleagues have found in a cohort of patients with early clinically apparent IA, who were initially autoantibody negative, that 13/123 (11 %) became positive for ACPA, and 21/136 (18 %) for RF [52]. These findings may be explained by fluctuating levels, or autoantibodies that were missed by commercially available tests, but these findings also raise the issue that not all subjects may have detectable autoimmunity by conventional means at the time of onset of IA.

Notably, ACPA arrays have also been able to provide insight into predicting the timing of onset of future RA. In particular, using 81 subjects who developed RA, and controls, from the aforementioned DoDSR cohort, Sokolove and colleagues found that elevations of 3 specific ACPAs (citrullinated enolase, vimentin, and fibrinogen) along with elevations of 6 cytokines was ~58 % sensitive and ~87 % specific for onset of RA within 2 years. In addition, using data from the NHS and 192 women who developed incident RA, and controls, Arkema and colleagues found that increasing numbers of positive ACPAs were strongly associated with the onset of RA within 5 years (relative risk 17, 95 % CI 5.8–53.7) [53]. These findings are of particular importance in ‘personalized’ medicine approaches to RA, where identification of not only an individual’s overall risk for future RA, but the time frame in which they may develop disease is important for clinical care and advising them of their risk, as well as potentially for the design of clinical prevention trials where the estimated incidence of RA within a given time frame is crucial to trial design.

Areas for future exploration

While the above data have provided us with substantial knowledge about the early development of RA, there are still multiple areas that need to be explored. Several of these are listed in Table 2, but perhaps the most important question to be answered is what are the factors, genetic, environmental or otherwise, that trigger and propagate RA-related

autoimmunity in the preclinical phase. This question is crucial to understanding the pathogenesis of disease, as well as to develop effective preventive strategies for RA. In particular, there has been a great expansion of our knowledge of the genes that are associated with increased risk for RA; however, it is still unclear where in the natural history of RA these genes may play a role—are they related to the development of initial autoimmunity, or do they allow for autoimmunity to propagate and expand to the point of tissue injury and clinically apparent disease? In addition, there are multiple environmental risk factors for RA including tobacco smoke [54], and established and emerging data that infections may play a role in triggering RA [55–59]. However, the long period of autoimmunity prior to the onset of clinically-apparent RA suggests that the genes and environmental factors that influence RA are acting years prior to the first swollen joint, and since these factors have not been well studied in preclinical RA, it is as of yet unclear if these environmental factors trigger RA-related autoimmunity, or propagate it.

Of particular interest is the anatomic site of initiation of RA. While RA-related autoantibodies may be generated in the joints in individuals with established disease [60], several imaging and one biopsy study of preclinical RA suggests that the joints are truly ‘normal’ in most subjects with RA-related autoantibodies [61–63]. If the joints are indeed normal in preclinical RA, where in the body are the RA-related autoantibodies being generated? Emerging data suggest that mucosal sites may be where RA is initiated, and Demoruelle and colleagues have demonstrated the generation of RA-related autoantibodies in the lungs in some subjects who are at-risk for future RA [35, 64]. Other data suggest that the periodontal region and organisms such as *Porphyromonas gingivalis* [65–67], or the gut may be involved in early RA [68]. The potential that RA starts outside the joints is highly intriguing, and raises the issue: are we asking the appropriate genetic, environmental, and biologic questions if we wish to understand how RA is generated outside the joints?

Furthermore, as discussed above, the development of clinically apparent IA/RA after expansion of autoimmunity suggests that there is some threshold that must be crossed to transition from asymptomatic autoimmunity to clinically apparent disease; however, it is not yet clear what this threshold is, or what triggers and drives the progression of autoimmunity. It may be that early ACPAs do not target the joint, and later ACPAs do, after epitope spreading has occurred, and that allows for the development of IA. It may also be that certain levels of autoantibodies need to be reached in order to form sufficient immune complexes to trigger arthritis, target enough tissue to lead to symptoms, or to trigger effector cells (e.g., synovial fibroblasts) [69]. This may have important implications for understanding mechanisms of RA development, as well as in ultimately developing preventive strategies for RA.

Novel advances in the means to assess autoimmunity also need to be applied to understanding preclinical RA. As mentioned above, testing for autoantibodies to multiple citrullinated antigens using ACPA arrays has extended our understanding of the evolution of autoimmunity in preclinical RA, and provided us with some ability to predict the timing of future onset of RA as well as perhaps increased sensitivity for autoimmunity to citrullinated proteins, although a caveat is that these ACPA assays have been developed largely using clinically-apparent RA, and it may be that the ‘true’ earliest autoreactivities have not yet

been identified in RA, especially if those reactivities are not specifically joint-related. Furthermore, developing new autoantibody systems may allow us a greater understanding of 'seronegative' RA. There are also emerging technologies to identify single B and T cells that are reactive to self-antigens, and these will need to be investigated in preclinical RA [70–72]. In addition, gene expression and epigenetic changes [73], the role of microparticles [74] and other immunologic responses will all need to be explored in preclinical RA.

Perhaps most importantly, studies of preclinical RA need human subjects! And while retrospective studies using fortuitously collected samples have yielded tremendous understanding thus far of preclinical RA, and may continue to do so, with rapidly advancing technologies that require specialized sample collection (e.g., live cells), and the growing understanding of the role of mucosal sites in the initiation and propagation, ultimately preclinical RA needs to be studied in prospectively developed cohorts who can be evaluated in real time.

Furthermore, in addition to using prospective studies to understand the mechanisms and natural history of RA development, such studies can also identify subjects who may be candidates for preventive interventions. Importantly, clinical prevention trials for future RA have already been tried, or are underway [75]. Notably, a Dutch study is underway that is treating subjects without IA who have RF and ACPA positivity and at least one other markers such as elevated CRP or imaging evidence of subclinical synovitis with rituximab 1,000 mg × 1 dose or placebo in an effort to determine if this single intervention can prevent or delay the onset of future onset of RA [76]. Notably, type 1 diabetes (T1DM) follows a model of development similar to RA in that disease-related autoantibodies precede the onset of clinically apparent disease [77]; investigators have already implemented several clinical trials to prevent future disease in at-risk individuals. These trials have not yet been successful in preventing T1DM, but the trials have established a strong infrastructure for the study of preclinical disease and, because of mechanistic studies that were coupled with the clinical trials, additional preventive trials are currently underway [78]. Such an approach may also greatly benefit the field of RA.

Conclusions

Key studies to date have established that there is a preclinical period of RA development. Going forward, we need to expand on this important foundation to use established and emerging approaches in well-characterized prospective studies to further the knowledge of preclinical RA that will hopefully lead us to preventive approaches to RA.

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Table 1

Key early studies of preclinical RA

Study reference	Summary
del Puente et al. 1988 [7]	2,712 Pima Indians followed up to 19 years with biennial examinations; 70 subjects (~2.6 %) developed incident RA; highest rate of 48 per 1 000 person years in subjects with baseline RF titer of >1:256.
Aho et al. 1991 to 2000 [4–6,74]	19,072 adults initially evaluated from 1973 to 1977 in a Finnish study; by 1989, 124 developed RA, 89 with RF(+) RA and had pre-RA diagnosis serum available; findings from these subjects 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 [8]	370 unaffected first-degree relatives from families with multiple cases of RA were followed; 14 subjects developed incident RA, for an overall rate of 8 per 1,000 person-years; incidence was highest in subjects with RF positivity.
Rantapaa-Dahlqvist et al. 2003 [9]	Swedish biobank study of 83 cases with RA and 382 controls, most with one stored serum sample available from prior to RA diagnosis. 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 [10]	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 tested. Overall, 49 % of RA subjects positive for anti-CCP1 or RF-IgM a median of 4.5 years prior to diagnosis. Using a 0–5-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 prediagnosis period. Anti-CCP1 appeared to be positive prior to RF-IgM.
Majka et al. 2008 [11]	The United States Department of Defense Serum Repository was used to identify stored serum samples from 83 subjects who developed RA, and 83 matched controls. RF and anti-CCP2 elevated in 57 and 61 % of subjects prior to 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 subjects (<40) appeared to have a shorter duration of preclinical autoantibody positivity compared to older subjects (>40).
Chibnick et al. 2009 [12]	The prospective Nurses' Health Study was used to identified 93 cases of incident RA were identified, along with 3:1 matched controls; a single pre-RA diagnosis serum sample was tested for CCP2. At its standard cut-off 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. 2010 [22]	147 Dutch clinic patients with 'arthralgia' defined as joint symptoms in absence of inflammatory arthritis at baseline based on a 44-count joint examination by 2 physicians were followed 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 [32].

RA rheumatoid arthritis; Ig immunoglobulin; RF rheumatoid factor; CCP cyclic citrullinated peptide

Table 2

Future directions in the study of the early natural history of RA

Further understanding of the natural history of RA should be performed using fortuitously available samples from preclinical RA when available, but ideally from prospective studies designed specifically to investigate RA
Broad agreement on terminology applicable to the natural history of RA
Detailed understanding of the genetic, environmental (including microorganisms) and other (e.g., stochastic) factors that initiate as well as propagate RA. These should take into account that RA may be generated outside of the joints.
Application of established and emerging technologies to understand the initiation and evolution of autoimmunity and inflammation (e.g., ACPA arrays vs. current commercial ELISA assays such as anti-CCP; single cell B and T reactivity; epigenetic changes). In particular, it may be that antigens that are relevant in clinically apparent RA are not the same as those which are related to the initiation and propagation of early RA-related autoimmunity
Develop highly accurate prediction models for future RA; these models can use established biomarkers and other factors.
Development of markers to identify the preclinical period of seronegative RA (i.e. RF and ACPA negative) which is as of yet much less well defined than seropositive RA
Evaluation of subjects who resolve autoimmunity without pharmacologic intervention; in most studies, in subjects with autoantibody positivity who later develop RA have stable positivity, and rising levels of autoantibodies prior to diagnosis; however, while less studied, many controls have transient positivity for RA related autoantibodies – understanding mechanisms of this transient autoimmunity may lead to preventive approaches for disease.
Prevention trials that following on models in other diseases such as type 1 diabetes are coupled with detailed mechanistic studies of RA development. In particular, targets need to be identified that can lead to prevention of initial autoimmunity, as well as prevent the evolution from early 'asymptomatic' autoimmunity to more pathogenic and clinically apparent disease. Ultimately, findings from prevention trials can be used to evaluate public health efficacy and cost-effectiveness of preventive approaches for RA

RA rheumatoid arthritis; ACPA antibodies to citrullinated protein antigen; ELISA enzyme linked immunoabsorbent assay; CCP cyclic citrullinated peptide; RF rheumatoid factor