The Journal of Rheumatology 2024;51:337–49
doi:10.3899/jrheum.2023-0334
First Release February 15 2024

The Journal of Rheumatology

Expert Review

Rheumatoid Arthritis: The Continuum of Disease and Strategies for Prediction, Early Intervention, and Prevention

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ABSTRACT. Rheumatoid arthritis (RA) is known to include a pre-RA stage that can be defined as the presence of familial or genetic risk factors, biomarker abnormalities (eg, anticitrullinated protein antibodies [ACPA]), symptoms, and even abnormal imaging findings prior to the development of the onset of clinical RA with inflammatory arthritis that is apparent on physical examination. Indeed, there are multiple completed or ongoing retrospective case-control as well as prospective observational studies to identify the key biologic drivers of disease. Further, building on the predictive ability of combinations of biomarkers, symptoms, and imaging for future RA, there are multiple clinical trials completed, underway, or in development to identify approaches that may prevent, delay, or ameliorate future clinical RA in at-risk individuals. Importantly, however, although an effective preventive intervention has not yet been identified, at-risk individuals are being increasingly identified in clinical care; this presents a challenge of how to manage these individuals in clinical practice. This review will discuss the current understanding of the biology and natural history of RA development, nomenclature, and current models for prediction of future RA, as well as evaluate the current and ongoing clinical prevention trials with the overall goal to provide insights into the challenges and opportunities in the field of RA prevention. Moreover, this review will provide up-to-date options for clinical management of individuals at risk for RA.

Key Indexing Terms: preclinical rheumatoid arthritis, prediction, prevention, rheumatoid arthritis

Rheumatoid arthritis: overview and current management

Rheumatoid arthritis (RA) is typically diagnosed in clinical care based on the presence of symptoms and signs of active joint inflammation (ie, a swollen joint on physical examination consistent with synovitis), as well as biomarkers such as autoantibodies and imaging findings that can demonstrate joint inflammation and/or damage. This diagnosis can be termed "clinical RA." In addition, there are established classification criteria for RA, which include the 1987 American College of Rheumatology (ACR) criteria[1] and the 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) criteria.[2] There are also 2 categories of clinical RA termed "seropositive" and "seronegative," defined as the presence or absence, respectively, of serum elevations of autoantibodies, which currently include rheumatoid factor (RF) and/or anticitrullinated protein antibodies (ACPA). After a diagnosis is made, treatment is typically initiated with disease-modifying antirheumatic drug (DMARD) therapies that have been established as effective in treating the primary disease manifestation of inflammatory arthritis (IA) in controlled clinical trials.[3] For the majority of individuals who are diagnosed with clinical RA, DMARD therapy results in improved well-being and function as well as reduced joint damage, with a subset of individuals reaching disease remission and an even smaller subset reaching DMARD-free remission.[4-6] However, for the majority of individuals who develop clinical RA, it is a disease that will require lifelong therapy, with ongoing adverse effects on their well-being and finances, and sustained remission is infrequent (< 50% of patients in some studies[6-10]). As such, ultimately, the prevention of RA may result in substantially less impact on personal and public health.

KDD's work on this manuscript was supported by the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH/NIAMS P30 AR079369).

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KDD has received consulting fees from Werfen and BMS, and grant funding from Janssen Research and Development and Gilead Sciences. DAR is a scientific advisor for GSK Mexico. LJO has received consulting fees from BMS.

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Accepted for publication November 23, 2023.

RA begins prior to the appearance of clinically apparent IA

There is established and growing evidence that RA develops in a series of stages, as outlined in the Figure. In general, it appears that the natural history of RA begins prior to clinical RA during a period that can be termed "pre-RA," where genetic and environmental factors interact to drive early breaks in immune tolerance that, to date, have been best identified through blood elevations of autoantibodies, including RF and ACPA,[11-16]

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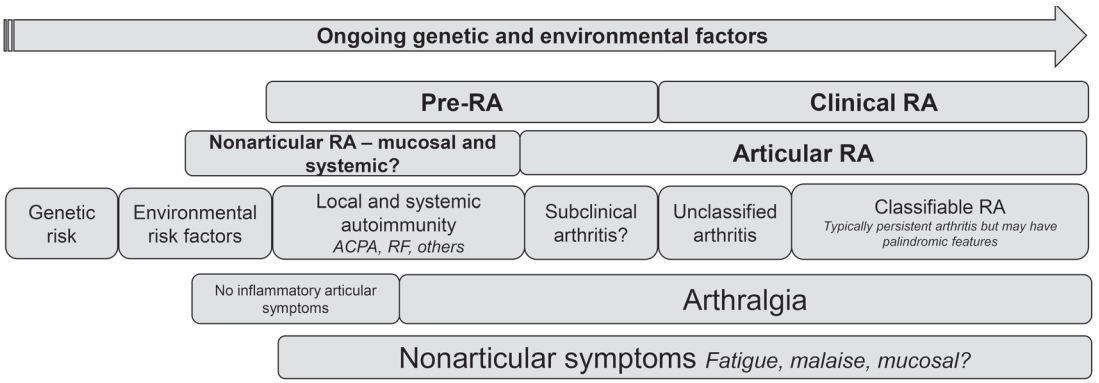

Figure. Model of seropositive RA development. Genetic and environmental risk factors combine to trigger initial autoimmunity, potentially at mucosal sites. This autoimmunity may then progress to clinically apparent IA, which can be termed "clinical RA." Notably, detectable autoimmunity and/or subclinical arthritis in absence of clinical RA may be termed "pre-RA." Some individuals may not progress through all stages. ACPA: anticitrullinated protein antibody; IA: inflammatory arthritis; RA: rheumatoid arthritis; RF: rheumatoid factor.

although multiple other autoantibodies including anticarbamylated protein (anti-CarP),[17] antimalondialdehyde-acetaldehyde (anti-MAA) antibodies,[18] and antipeptidyl arginine deiminase (anti-PAD) antibodies[19] have been identified. These antibodies are elevated, on average, approximately 3 to 5 years prior to a diagnosis of clinical RA (although up to years, or longer, in some cases).[11,12,20] Further, array-based technologies have also identified that ACPA undergo epitope spreading in pre-RA.[21] ACPA have been shown to undergo variable domain (Fab) N-linked glycosylation,[22] and glycosylation changes in ACPA have been shown to independently associate with the development of future IA in ACPA-positive individuals.[23] Studies have also demonstrated that autoantibody elevations can be present in conjunction with altered T cell subsets, [24] B cell and interferon signatures,[25,26] and a general increase in inflammation (eg, elevated C-reactive protein, calprotectin,[27] and cytokines and chemokines[13,28,29]).

Along with the expansion in autoimmunity and inflammation, symptoms (eg, joint pain, stiffness and swelling, and fatigue) may evolve. There is growing evidence that although IA may not be identifiable on physical examination, features of synovitis or even joint damage may be seen on imaging and can therefore be termed "subclinical IA"; further, tenosynovitis may be one of the first manifestations of RA musculoskeletal (MSK)-related tissue injury.[21,22,30,31] Disease can then progress to overt clinically apparent IA that is clinically diagnosed as RA (ie, clinical RA) and may further meet established classification criteria.[1,2] Notably, the features and nomenclature to define and label each of these stages of RA development are somewhat variable (Figure and Table 1), and are best understood in seropositive RA. Notably, when referring to individuals who may be in a pre-RA state, a EULAR task force determined that the term "pre-RA" should only be applied retrospectively once it was known that an individual had developed clinical RA.[32] As such, the term "at-risk individual" is often used to describe individuals who exhibit some risk factors for future RA but whose future development of clinical RA is unknown.

There are multiple genetic and environmental factors that have been associated with an increased risk for clinical RA,[23] although most studies that have associated genetic and environmental risk factors with RA have been performed in a case-control fashion in individuals with established clinical RA. As such, these factors may not be truly associated with the initial generation of autoimmunity that may have occurred years prior to clinical RA. However, there are a growing number of prospective studies in at-risk populations that have identified factors that are associated with increased risk for future clinical RA (Box 1). For genetic factors, the strongest identified is a set of alleles coding certain sequences in the HLA region that in aggregate are called the shared epitope (SE)[33]; although findings are mixed, several studies demonstrate that SE is associated with ACPA positivity as well as a transition to future clinical RA in ACPA-positive individuals.[34-36] Further, in a nested case-control study within the Nurses' Health Study, a score derived from 22 genetic variants predicted RA risk, suggesting genes beyond the SE are related to progression to clinical RA.[37] For environmental factors, smoking is the most reproducibly associated with a higher future risk of RA.[38,39] In addition, a number of studies have identified obesity as a risk factor for clinical RA,[40,41] and that an antiinflammatory diet and higher levels of exercise may be protective.[42] Moderate alcohol intake has also consistently been identified as protective against future RA development, although the mechanisms behind this are not yet clear.[42-45] Multiple metabolic and/or immunologic processes have been purported to play a role in RA development, including fatty acid pathways that may be influenced by dietary intake.[46] As RA is more prevalent in women, reproductive and menopausal factors have been extensively studied. Postmenopause, postpartum period, and use of antiestrogen agents have been consistently associated with RA onset[47,48]; however, although a study in an at-risk population has demonstrated an association between the use of oral contraceptives and decreased risk for RF positivity,[49] the role of hormonal factors, including hormonal therapy, in the pre-RA period remains controversial.

Importantly, it is hypothesized that the early generation of autoimmunity occurs outside of the joints during a period that can be termed a "nonarticular" stage of RA development

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Table 1. Terminology used to describe the natural history of RA.

Term	Definition
Pre-RA, preclinical RA	The stage prior to the development of clinical RA. May be defined in several ways, including presence of autoantibodies, abnormal symptoms, and imaging findings.
At-risk	Any state in which an individual has a higher-than-average risk of developing RA but does not have current IA (ie, being an FDR of a patient with RA, presence of autoantibodies). Notably, a EULAR task force that included individuals with clinical RA, as well as individuals who are at-risk for future RA, determined that the term "pre-RA" should only be used retrospectively once it was known that an individual developed clinical RA.[32] As such, the term "at-risk individual" is often used to describe individuals who exhibit some risk factors for future RA but whose future status of clinical RA is unknown.
First-degree relative (FDR)	An individual who is related in the first degree (ie, parent, full sibling, offspring) to an individual with a specific disease. An FDR shares genetic and often environmental risk factors for developing the disease of interest.
Clinically suspect arthralgia (CSA)	A combination of signs and symptoms that is suggestive of the presence and/or risk for IA. This includes, but is not limited to, morning stiffness and pain in the small joints. The pain may or may not be elicited on physical examination.
Clinically apparent IA	A clinical finding of joint synovitis in the absence of trauma that is suggestive of the earliest stage of RA. A joint with synovitis is typically tender on range of motion/palpation, swollen with a palpable effusion, and warmer than noninflamed joints.
Palindromic rheumatism (PR)	Recurrent episodes of IA, typically involving the small joints of the hands and feet, that resolves spontaneously with limited or no symptoms between events. A subset of patients with PR will develop classifiable RA.
Subclinical IA	The presence of inflammation in a joint detected by imaging, typically by MRI or US, that is suggestive of IA, and a physical examination of the involved joint that is not suggestive of synovitis (ie, there is an absence of joint swelling).
Undifferentiated arthritis	IA that does not fulfill established classification criteria for RA or any other disease.
Clinical RA	Clinically apparent IA, with or without autoantibodies, that a clinician diagnoses and treats as RA. This includes individuals who have classifiable RA and those who do not. For example, a patient with low positive ACPA/RF and 3 swollen small joints may not have classifiable RA but still be diagnosed and treated as having RA.
Classifiable RA	A patient who meets established classification criteria for RA, either the 1987 ACR or 2010 ACR/EULAR criteria.[1,2]
Seropositive RA	Clinical RA with serum elevations of RA-associated antibodies, such as RF or ACPA.
Seronegative RA	Clinical RA without serum elevations of RA-associated antibodies, such as RF or ACPA.
Early RA	A patient who meets classification criteria for RA for a short duration, typically < 1 yr, although definitions vary in the literature.

ACPA: anticitrullinated protein antibody; ACR: American College of Rheumatology; CRP: C-reactive protein; EULAR: European Alliance of Associations for Rheumatology; IA: inflammatory arthritis; MRI: magnetic resonance imaging; RA: rheumatoid arthritis; RF: rheumatoid factor; US: ultrasound.

(Figure).[50,51] Further supporting a nonarticular stage of pre-RA, studies have shown an absence of synovitis on synovial biopsy in individuals who have circulating ACPA or RF.[52,53] As to where this autoimmunity is generated, there are some data supporting that it may be at mucosal sites, including the periodontium, lung, and gut.[54] In particular, there are several studies that have suggested that lung disease, including airways or interstitial lung disease, may precede the onset of articular RA,[55-57] and that RA-related autoantibodies may be generated in the lung in some individuals prior to clinical RA onset.[58] In addition, there is growing evidence that certain microbial factors that are present at mucosal surfaces may be associated with RA-related autoimmunity.[59-62]

Overall, an emerging concept is that the evolution of RA is characterized by a series of transitions, where an individual progresses from a stage of risk factors to detectable autoimmunity, then clinical RA, with each of these transitions likely related to genetic, environmental, and stochastic factors, as well as some failed immunoregulatory checkpoint.[63] However, there are several additional considerations regarding this model of RA development. First, these transitions are not necessarily consecutive or mutually exclusive. Second, not all individuals who develop detectable circulating RA-related autoimmunity develop clinical RA, indicating that the development of autoimmunity is not an indication of inevitable clinical RA. Third, the trajectories of autoimmunity, symptoms, and the onset of clinical RA differ among individuals. Multiple studies have shown that autoantibodies may be elevated, on average, 3 to 5 years prior to the onset of clinical RA; however, some studies also demonstrate elevations over 15 years prior to clinical RA onset.[11,20] For some,

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clinical RA may be explosive, with multiple joints developing IA in a short time. Others may have gradual accumulation of IA, and still others may have waxing and waning findings (which can be termed "palindromic rheumatism"[64,65]). The precise relationship between symptoms and autoimmunity is not clear; all these issues will need further study.

Predicting future clinical RA

Many prospective studies have sought to develop prediction strategies to identify individuals at high risk of developing clinical RA (Table 2). Autoantibodies are the best studied predictor of RA risk, and ACPA and RF status have been shown in multiple studies to predict future RA.[13,27-30] Importantly, increased ACPA levels clearly confer a higher risk of RA.[29,66] Notably, there may be differences in the predictive ability between the various commercially available assays for ACPA, although additional research is needed to clarify the specific differences.[67,68] Multiple other autoantibody systems have been identified in the pre-RA period, including anti-CarP,[69] anti-MAA, and anti-PAD,[14,18,19,70] but their overall additive predictive value needs further validation. Other blood-based biomarkers, including cytokines, chemokines, and cell subsets, have also been explored in RA prediction. Particularly in prospective studies, alterations of T cell subsets,[71] presence of B cell signatures,[25] and presence of a type 1 interferon signature[26] were associated with increased risk for incident clinical RA, although these findings have not yet been widely replicated. Preliminary studies on serum proteomics[35-37] and sputum abnormalities[38,39] suggest that additional biomarkers may be of utility in RA prediction, but further study and validation are needed.

Imaging has shown promise in RA prediction. Ultrasound (US) power Doppler, which can identify increased synovial blood flow indicative of inflammation in antibody-positive individuals with arthralgia[43,44] and early erosive disease, particularly in the feet,[45] are predictors of RA development. Magnetic resonance imaging (MRI) detection of joint inflammation (synovial and/or tenosynovial) is associated with future RA, particularly in those who are ACPA-positive.[22,51] Notably, imaging evidence of tenosynovitis in the hands is also independently associated with future RA development in individuals with clinically suspect arthralgia (CSA) and ACPA positivity, and may suggest that the tenosynovium is one of the first joint-related targets in RA development.[46]

Joint or other MSK symptoms of pain, stiffness, and swelling, although nonspecific, are important predictors of the development of future clinical RA.[65,72-75] A set of symptoms and timing corresponding to CSA have been developed by a EULAR task force derived from patients with joint pain without evidence of arthritis.[72] The characteristics defining CSA include timing of joint symptoms, location of symptoms in the metacarpophalangeal (MCP) joints, morning stiffness > 60 minutes, more severe symptoms in the morning, first-degree relatives (FDR) with RA, difficulty making a fist, and positive squeeze test of the MCPs. This was evaluated in a separate prospective study of individuals with joint/MSK symptoms that demonstrated that if ≥ 3 variables were present based on a rheumatologist evaluation, there was a positive predictive value (PPV) of ~30% for future clinical RA; however, if this was applied in individuals prior to a rheumatology evaluation, the PPV was ~3%.[74]

Demographics, environmental exposures, and genetic factors

Box 1. Risk and protective factors for future RA development evaluated in prospective studies or cross-sectional studies of individuals at risk for or with pre-RA.

Genetic and familial risk factors
- Shared epitope associated with higher risk for transition to RA in ACPA+ individuals at baseline.[34]
- Genetic risk score using 22 variants associated with increased risk of RA.[37]
- FDR status increased risk of progression to articular RA in arthralgia cohort.[45] Certain populations have a high risk for RA, including populations indigenous to the Americas, who have ~5- to 7-fold increased risk for RA compared to non-Indigenous populations.[113]

Sex-related factors
- Female sex, given women have a 2- to 3-fold higher risk for RA compared to men.[23]
- Longer duration of breastfeeding and higher parity are protective.[114]
- Oral contraceptive use associated with decreased autoantibody positivity in individuals at risk for RA (eg, FDRs).[49]

Environmental factors (reviewed in Deane et al[23] and Zaccardelli et al 2019[42])

Increased risk for RA
- Cigarette smoking, especially long duration, and high-intensity smoking
- Obesity
- Inflammatory diet

Protective against RA
- Moderate alcohol consumption
- High intake of fatty fish and omega-3 fatty acids

Other factors

Mucosal and/or microbiome influences
- Lung disease (airways, parenchymal)[115]
- Periodontal inflammation[116]
- Multiple organisms including viruses and bacteria have been associated within increased risk for RA
- Stress and/or stress responses and potentially mental health (complex and unclear if stress/mental health could drive autoimmunity, or be influenced by autoimmunity, or both)[117,118]

ACPA: anticitrullinated protein antibody; FDR: first-degree relative; RA: rheumatoid arthritis.

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Table 2. Prediction of future IA and RA in prospective studies of at-risk populations.

Publication, Year	Country / Population	Study Type	No. of Subjects and Incident IA/RA	Key Findings
del Puente, 1988[15]	USA, Akimel O'Odham (Pima) people	Prospective cohort study	2712 subjects; 70 (2.6%) with incident IA/RA after up to 19 yrs of follow-up	The highest rate of development of RA (48/1000 PYs) was in subjects with baseline RF titer of > 1:256.
Silman, 1992[16]	UK	Prospective cohort study	370 unaffected FDRs from families with RA; 14 with incident RA	Incident RA was highest in subjects with RF positivity.
van de Stadt, 2013[45]	The Netherlands	Prospective study of individuals presenting to rheumatology clinics	347 subjects with RF and/or ACPA positivity but no IA at baseline; 131 with incident IA/RA after a median of 12 mos	A score was developed assigning 1 point for each of the following that were present: positive FDR status, no alcohol consumption (use of alcohol was protective), symptoms starting < 12 mos prior, intermittent symptoms, symptoms in upper and lower extremities, VAS of ≥ 50 mm, morning stiffness ≥ 60 mins, 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 yrs.
de Hair, 2013[39]	The Netherlands	Prospective study of ACPA+ and/or RF+ subjects	55 subjects; 15 (27%) with incident IA after a median of 13 mos	Nonsmokers and those with normal body weight had the lowest rates of progression to IA/RA.
Ramos-Remus, 2015[76]	Mexico	Prospective study of unaffected FDRs of patients with RA	819 FDRs; 17 (2.1%) with incident IA/RA over 5 yrs	ACPA positivity with or without concomitant RF positivity had PPVs of 58-64% for development of RA during follow-up.
Rakieh, 2015[34]	UK	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 mos	A score was developed assigning 1 point for each of the following: tender joints, morning stiffness > 30 mins, presence of the shared epitope, high levels of RF and/or ACPA, and the presence of US power Doppler findings in ≥ 1 joint. In individuals with the highest scores (≥ 2), > 41% developed IA/RA within 24 mos, and in individuals with scores of ≥ 4, 68% developed IA within 24 mos.
Burgers, 2017[74]	The Netherlands and Sweden	Prospective study of subjects with arthralgia	178 subjects with arthralgia meeting EULAR criteria for CSA at baseline; 44 (18%) developed incident IA/RA after a median of 16 wks	Study to validate the EULAR definition for clinically suspect arthralgia.[71] The presence of ≥ 3 of the following factors was ~84% sensitive and had a PPV of ~30% for IA/RA within 2 yrs: duration of onset of symptoms < 1 yr, symptoms in MCP joints, morning stiffness ≥ 60 mins, 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 nonrheumatologist practitioner (PPV ~3%).
Tanner, 2019[78]	Canada	Prospective cohort study of FDRs of patients with RA	374 subjects; 10.9% were ACPA+ at baseline; 18 (4.8%) developed IA/RA after ~5 yrs of follow up	ACPA+/RF+ individuals at baseline developed IA at a higher rate/1000 PYs (97.1) than ACPA+/RF– (36.4), ACPA–/RF+ (7.2), and ACPA–/RF– (4.1). ACPA+/RF+ were just as likely to become autoantibody negative as developing IA after 5 yrs.
Gilbert, 2021[79]	Switzerland	Prospective cohort study of FDRs of patients with RA	1458 subjects; ~5% were ACPA+ at baseline; ~17% were RF– IgM+	As of 2021, 16 individuals had developed incident IA and were predominately ACPA+.
Bemis, 2021[77]	USA	Prospective cohort study of FDRs of patients with RA	1780 subjects; 304 antibody + (17.1%) at baseline; 20 (15.3% of antibody +) developed IA after ~4.5 yrs of follow up	ACPA+/RF+ individuals at screening developed IA at a higher rate (38%) than ACPA+ alone (15%) and RF+ alone (9%). High level ACPA (ie, ≥ 2 × ULN) at screening was associated with the development of IA (HR 4.1).

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Table 2. Continued.

Publication, Year	Country / Population	Study Type	No. of Subjects and Incident IA/RA	Key Findings
Bergstedt, 2022[35]	USA	Prospective cohort study of ACPA+ individuals found through health-fair screening	90 ACPA+ individuals; 26 (29%) developed IA after ~2 yrs of follow up	Those who developed IA had a higher prevalence of SE (69% vs 38%). High level ACPA (≥ 2 × ULN) was higher in those who developed IA (85% vs 60%). Dual RF-IgA and RF-IgM+ was associated with IA (HR 2.9).
Duquenne, 2023[66]	UK	Prospective cohort study of individuals found through clinical referrals for joint symptoms	455 ACPA+ (CCP2) subjects without baseline IA; 148 (~33%) developed clinical IA over a median follow-up of 223 wks	Developed scoring systems to predict IA within 1 yr: A simple score used to triage referrals to secondary care, which included morning stiffness > 30 min, ACPA level, RF+, and elevated ESR. A score above the threshold had a PPV of ~28% for IA development within 1 yr. A comprehensive score used in secondary care which included age > 50 yrs, ever smoker, morning stiffness, ACPA level, RF+, SE+, ESR high, VAS global pain, HAQ score, US PD signal, US tenosynovitis+, US erosion+. A score above the threshold had a PPV of ~70% for IA development within 1 yr.

ACPA: anticitrullinated protein antibodies; CCP2: cyclic citrullinated peptide 2; CSA: clinically suspect arthralgia; ESR: erythrocyte sedimentation rate; EULAR: European Alliance of Associations for Rheumatology; FDR: first-degree relative; HAQ: Health Assessment Questionnaire; HR: hazard ratio; IA: inflammatory arthritis; MCP: metacarpophalangeal joints; PD: power doppler; PPV: positive predictive value; PY: person-year; RA: rheumatoid arthritis; RF: rheumatoid factor; SE: shared epitope; ULN: upper limit of normal; US: ultrasound; VAS: visual analog score.

also contribute to the prediction of future RA. These potentially include age, sex, family history of RA, smoking, dietary factors, obesity, and the SE.[41,42,66]

Multiple studies have used combinations of factors to develop prediction models for future clinical RA. The models in general include combinations of demographic features, joint symptoms, examination findings, autoantibodies, and in some cases, imaging findings. The details of these studies are included in Table 2, and the rates of development of RA in clinical trials in Table 3. In general, the models impart PPVs of ~20% to 70% for clinical RA development within 1 to 5 years, with the higher PPVs found with the presence of multiple risk factors for RA. Further, in most models, high levels of ACPA impart the highest risk for future clinical RA. Importantly, the methods to identify individuals who are at risk for future RA differ across studies. In particular, most studies of pre-RA have focused on at-risk populations identified through referrals from primary care of individuals with joint/MSK symptoms, and therefore it may be reasonable to assume that prediction models are most applicable in those populations. However, several studies have identified at-risk individuals through methods such as testing high-risk populations (eg, Indigenous North Americans), FDRs of individuals with RA, or health fair participants for ACPA, and then following those individuals longitudinally.[15,35,76-78] In these studies, ACPA positivity is generally associated with rates of clinical IA development of ~20% to 30%, or higher, within 5 years, although 1 FDR cohort reported an incidence rate of RA of ~2 cases per 1000 person-years.[79] These rates are similar to general rates seen in populations of individuals at risk for RA identified through clinic referrals for joint/MSK symptoms. This could be because even individuals who participate in population-based studies may do so because of a higher degree of symptoms, although this has not been evaluated in depth in published work. Additional studies of how the mechanism by which individuals are identified as being at risk for RA should be performed to develop predictive models that are applicable in these settings.

RA prevention clinical trials

Given the growing understanding of the pre-RA state and prediction models for future RA, multiple clinical trials aimed at preventing the first onset of clinical RA have been implemented. These trials are further underpinned by the "window of opportunity" concept, where earlier treatment once an individual has clinical RA leads to improved long-term outcomes and therefore moving interventions into a pre-RA period may prevent or delay the onset of clinical RA.[80-83]

Of the completed RA prevention studies (Table 3), most have used medications that are already approved for use in the treatment of clinical RA. The rationale for this is that RA-approved drugs improve clinical RA in many patients[84]; thus, it is conceivable that the same medications might also delay or prevent the first onset of clinical RA. Further, the safety profile of DMARDs used to treat RA is well established and therefore regulatory agencies are more likely to approve their use in prevention trials. Moreover, many at-risk populations (eg, FDRs) who are likely to be recruited to prevention studies are familiar with their use.

A pioneering study of RA prevention was undertaken in a clinical trial using intramuscular dexamethasone.[85] The trial

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Table 3. Summary of published trials to prevent/delay incident clinical RA in high-risk populations[a].

Study, Year	Inclusion Criteria	Study Design and Intervention	Primary Outcome	Results
Bos, 2010[85]	RF and/or ACPA+; SE+; arthralgia	RCT; dexamethasone 100 mg IM × 2 doses vs PBO	Incident clinical IA	17/83 (21%) developed IA after a median follow-up of 26 mos; no difference between arms (dexamethasone 21% vs PBO 20%). Dexamethasone use associated with decreased autoantibody levels.
Gerlag, 2019 (PRAIRI)[86]	RF and ACPA+; CRP > 0.6 mg/L; arthralgia	RCT; RTX 1000 mg × 1 dose (and steroid) vs PBO	Incident clinical IA	30/81 (37%) developed IA after a mean follow-up of 29 mos; no significant difference in overall rates of IA between arms (RTX 14/41 [34%], PBO 14/40 [40%]); RTX associated with delay of IA onset.
van Boheemen, 2021 (STAPRA)[87]	RF and ACPA+ or ACPA > 3 × ULN; arthralgia	RCT; atorvastatin 40 mg/d × 3 yrs vs PBO	Incident clinical IA	15/62 (24%) developed IA after a median follow-up of 14 mos; no significant difference between arms (atorvastatin 9/31 [29%] vs PBO 6/31 [19%]).
Krijbolder, 2022 (TREAT EARLIER)[88]	Arthralgia and MRI evidence of joint inflammation in absence of clinical swollen joint; RF/ACPA not required for inclusion although 33% of participants were RF and/or ACPA+	RCT; methylprednisolone 120 mg × 1 dose and MTX up to 25 mg/wk × 1 yr vs PBO; 1-yr postdrug follow-up	RA by 2010 criteria present at 2 timepoints 2 wks apart	44/236 (19%) developed RA over the 2 yrs of the trial; no significant differences between arms (MTX 23/119 [19%], PBO 21/117 [18%]; decreased measures of physical function, pain, and MRI inflammation in MTX-treated group. The highest rate of RA development was within ACPA+ individuals (27/54 [50%]), although there was no significant difference in rates between arms at 2 yrs.
Rech, 2021, 2022 (ARIAA)[92,93,b]	ACPA+ and MRI evidence of joint inflammation	RCT; ABA 125 mg SC weekly × 6 mos vs PBO; 1-yr postdrug follow-up	MRI inflammatory parameter improvement; clinical RA	In preliminary analyses, at 18 mos there was significant MRI improvement in ABA arm compared to PBO (28/49 [57%] vs 14/49 [29%]). At 18 mos there was also significantly less progression to clinical RA in ABA arm compared to PBO (17/49 [35%] vs 28/49 [57%]).
Deane, 2022 (StopRA)[91,b]	ACPA ≥ 2 × ULN	RCT; HCQ 200-400 mg/d × 1 yr vs PBO; 2 yrs postdrug follow-up	RA by 2010 criteria	In preliminary analyses, 43/144 (30%) developed RA over the 3 yrs of the study; no significant differences between arms (24/71 [34%], PBO 26/73 [36%]); trial halted and final analyses pending.
Cope, 2023 (APIPPRA)[95,b]	ACPA+, RF+ or ACPA ≥ 3 × ULN; arthralgia	RCT; ABA 125 mg weekly injection × 1 yr vs PBO; 1-yr postdrug follow-up	RA by 2010 criteria	In preliminary analyses, at 2 yrs, 65/213 (~31%) of participants developed RA by 2010 criteria; 25% in ABA arm and 37% in PBO arm. This resulted in differences in mean arthritis-free survival time between arms of ~99 days ($P = 0.002$).

[a] Although the inclusion criteria varied across studies, in all studies, no subjects could have clinical RA at baseline, and the primary endpoint included the development of examination evidence of IA. [b] The results from ARIAA, StopRA, and APIPPRA have only been presented in abstract form. ABA: abatacept; ACPA: anticitrullinated protein antibodies; APIPPRA: Arthritis Prevention in the Pre-Clinical Phase of RA With Abatacept; ARIAA: Abatacept Reversing Subclinical Inflammation as Measured by MRI in ACPA Positive Arthralgia; CRP: C-reactive protein; HCQ: hydroxychloroquine; IA: inflammatory arthritis; IM: intramuscular; MRI: magnetic resonance imaging; MTX: methotrexate; PBO: placebo; PRAIRI: Prevention of Clinically Manifest Rheumatoid Arthritis by B Cell Directed Therapy in the Earliest Phase of the Disease; RA: rheumatoid arthritis; RCT: randomized controlled trial; RF: rheumatoid factor; RTX: rituximab; SE: shared epitope; SC: subcutaneous; STAPRA: Statins to Prevent Rheumatoid Arthritis; StopRA: Strategy to prevent the Onset of Clinically-Apparent Rheumatoid Arthritis; ULN: upper limit of normal.

enrolled at-risk individuals with elevated autoantibodies (ACPA or RF), joint symptoms, as well as the SE. The development of IA was no different between placebo and treatment groups after 2 years of follow-up,[85] although antibody levels were significantly lower in the dexamethasone group. In the Prevention of Clinically Manifest Rheumatoid Arthritis by B Cell Directed Therapy in the Earliest Phase of the Disease (PRAIRI) study, 81 ACPA- and RF-positive individuals with C-reactive protein elevation and/or imaging evidence of inflammation and without clinical IA were randomized 1:1 in a masked, placebo-controlled fashion to receive a single dose of intravenous (IV) rituximab (RTX; 1000 mg) vs placebo,[86] and all subjects also received 100 mg of IV methylprednisolone. There were no significant differences in overall rates of clinical IA after 29 months of follow-up between arms (RTX 34%, placebo 40%; $P = 0.448$); however, RTX delayed arthritis onset by approximately 5 months (16.5 vs 11.5 months) compared to placebo. In the Statins to Prevent Rheumatoid Arthritis (STAPRA) study, atorvastatin 40 mg daily for 3 years in ACPA-positive individuals failed to show any difference in arthritis onset after 3 years of

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follow-up,[87] though the study suffered from slow recruitment and was possibly underpowered.

In the TREAT EARLIER study, 236 individuals with CSA and MRI-detectable synovitis, tenosynovitis, and/or osteitis, yet without clinical IA, were randomized 1:1 in a masked, placebo-controlled fashion to receive methotrexate (MTX; dosed orally up to 25 mg/week) for 1 year.[88] Both autoantibody-positive and -negative participants were enrolled (~30% were ACPA-positive). Individuals randomized to the treatment arm were also given a single dose of intramuscular methylprednisolone (120 mg). After 2 years of follow-up, there was no difference in the development of clinical arthritis between the groups (MTX 19%, placebo 19%). However, MRI-detected joint inflammation, functional scores, pain, and morning stiffness all favored the MTX arm at the study endpoint of 2 years.

Notably, although the Vitamin D and Omega-3 Trial (VITAL) study was designed to determine the effects of vitamin D and omega-3 fatty acid supplementation on oncologic and cardiovascular outcomes[89] and did not recruit individuals based on risk factors for RA, it also examined autoimmune disease onset as an exploratory outcome. The combination of supplements showed a significant reduction in incident RA after 5 years of follow-up,[90] albeit in a subgroup analysis (probable incident RA, hazard ratio 0.27, 95% CI 0.09-0.80, $P = 0.02$).

Several other prevention studies have yet to publish formal peer-reviewed results. However, preliminary results from the Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis (StopRA) study in 144 ACPA-positive participants (> 2 × upper limit of normal [ULN]) randomized to receive hydroxychloroquine (HCQ) for 1 year (≤ 6.5 mg/kg/day) vs placebo show that HCQ does not delay or prevent RA onset compared to placebo.[91] In contrast, preliminary data from the randomized, masked, placebo-controlled Abatacept Reversing Subclinical Inflammation as Measured by MRI in ACPA Positive Arthralgia (ARIAA) trial demonstrated that abatacept (125 mg subcutaneous [SC] weekly) for 6 months in ACPA-positive individuals who also had hand MRI synovitis/tenosynovitis resulted in reduced joint inflammation by MRI as well as reduced progression to clinical RA up to 1 year after drug cessation.[92,93] In addition, preliminary data from the Arthritis Prevention in the Pre-Clinical Phase of RA With Abatacept (APIPPRA) study (randomized, masked, placebo-controlled) demonstrated that 1 year of abatacept (125 mg SC weekly) reduced rates of progression to clinical RA (by 2010 criteria) at 2 years.[94,95]

Challenges and opportunities in pre-RA research

There are multiple challenges in the design, implementation, and interpretation of clinical trials and observational studies in pre-RA, and there are efforts underway to harmonize such studies in order to optimize the scientific results.[96] First, in terms of the prevention trials, it is noteworthy that the inclusion criteria from these trials are quite different, leading to a heterogeneity of findings. This is likely primarily a result of a current lack of consensus on what constitutes a high-risk state for future RA. Second, it is generally agreed that ACPA positivity is a risk factor for future RA and as such, many observational and clinical trials have focused on ACPA-positive individuals (with or without additional risk factors). However, the prevalence of autoantibody positivity is typically < 5% and likely closer to 1% in the general population,[97] requiring large-scale efforts to identify autoantibody-positive individuals. Third, RA autoantibodies have been shown to undergo seroconversion, or reversion to a seronegative state.[78] Further, the fluctuation of autoantibody positivity may indicate evolving biologic processes and ultimately affect risk for RA, although more studies are needed to fully understand the implications on risk of autoantibody reversion to a negative state. Fourth, ultimately, the preferences and participation of individuals at high risk for RA will drive the performance of clinical trials as well as the actual use of preventive treatments. Indeed, many individuals, despite having relatively high risk of developing RA (ie, ACPA-positive), are not interested in participating in clinical trials.[98] As such, future research is needed to better understand recruitment strategies and participants' motivations and perspectives to enhance the efficiency of RA prevention trials.[96] This is critically important for populations that are at potentially the highest risk for RA development and who may benefit most from preventive interventions. This includes FDRs of patients with RA who may have up to a 5% to 7% lifetime risk of developing RA,[99] as well as Indigenous communities in North America who have a 2- to 3-fold higher prevalence of RA compared to White individuals.[78,100] Finally, choosing the right intervention or study drug—and the right individual and the right time to give it during pre-RA—is a crucial consideration for RA prevention trials. This is a balancing act between several competing factors: (1) targeting the appropriate biologic process for effective prevention, (2) an individual's actual risk of developing RA, (3) the side effects and/or tolerability of the study drug, and (4) ultimately, the cost-effectiveness of an intervention. Identifying a targeted therapeutic that specifically inhibits an immunological process that is active in the pre-RA stage would be ideal, and studies will need to identify which biologic pathways are most important and feasible to address to affect prevention.[101] It is also worth considering the results from the TREAT EARLIER study, as above, suggesting that MTX may not prevent RA, but modify its natural course. It is well known that treating RA in the above-mentioned window of opportunity improves disease control and remission rates.[102] It remains possible that at-risk individuals who start standard DMARDs such as MTX may derive benefits outside of disease prevention/delay, which may still be clinically important. For those at lower risk (eg, ACPA-positive without symptoms, low-level ACPA, normal imaging), interventions with a tolerable safety profile, or lifestyle modifications such as dietary interventions, warrant future study to determine their efficacy in delaying or preventing RA. There may also be certain biologic pathways that are important in certain stages of RA (eg, potential mucosal inflammation in a nonarticular stage of RA development) requiring interventions that are different from agents that may be more effective once articular inflammation has developed.[63] These areas will need further investigation.

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Current clinical care in pre-RA

Research into RA prevention is ongoing, yet clinicians continue to evaluate individuals in various states of pre-RA in their clinics; these can include individuals who have ACPA and/or RF testing for MSK complaints or other organ injury (ie, lung disease), yet do not have clinical RA on examination. There is no standard of care for the management of these individuals; however, some suggestions are listed in Box 2. In general, these approaches involve careful evaluation of the patient to determine if there is active clinical RA, as well as counseling on the natural history and personal risk of clinical RA, signs and symptoms of clinical RA, and shared decision making around the optimal approach for management.

A major emerging consideration is the use of imaging to identify active clinical RA in the event that IA is not seen on physical examination. Indeed, US and MRI are increasingly being used in rheumatology clinics worldwide to aid in the diagnosis and management of IA, and several of the clinical trials have used the presence of articular inflammation on MRI findings as inclusion criteria (Table 2). In addition, a study by Mankia and colleagues has identified that ~70% of rheumatology clinicians would likely use a DMARD in an individual who was ACPA-positive without clinically apparent IA yet had an abnormal imaging finding.[103] Further, a study by Krijbolder and colleagues found that individuals who participated in the TREAT EARLIER study who had CSA plus MRI findings of joint inflammation were willing to be treated with DMARDs, even acknowledging such treatment may only improve symptoms and not reduce progression to clinical RA.[104] However, although research in this area is progressing, the diagnostic accuracy of imaging for true IA has not been well established and there are known false-positive as well as false-negative findings that are related to inherent technologic issues as well as user/interpreter factors.[105-107] Further, although there are several synovial biopsy studies that have included at-risk individuals,[52,108] there is not yet a broad conclusion on how imaging corresponds with biopsy findings in pre-RA. In addition, there are currently no consensus guidelines on the use and interpretation of imaging to diagnose IA in absence of physical examination findings of IA. It is also important to note that even in the TREAT EARLIER trial, only ~20% of overall participants with MRI evidence of inflammation at baseline went on to develop clinical RA. As such, until more data and guidelines are available, it will be left to individual practitioners to use imaging findings cautiously in the diagnosis and management of IA in the absence of physical examination findings of clinical RA, with the emphasis that clinicians should be wary of overtreating individuals in whom we do not have clear evidence-based guidelines that support they would benefit from DMARD therapy.[109]

Conclusion

There is increasing understanding of the pre-RA stage of disease development, which has already driven the completion or development of multiple clinical prevention trials. Importantly, growing interest in this area and the huge potential for improvements in the public health impact of this disease is driving even more studies in understanding the biology of disease development and developing effective preventive interventions; efforts are also underway in other rheumatic autoimmune diseases such as systemic lupus erythematosus and psoriatic arthritis.[110,111] Further, there is now an approved preventive intervention in type 1 diabetes, which is a disease that has a model of development similar to RA.[112] It is exciting to see the field moving forward to a point where rheumatologists can include in clinical care the discussions around prediction of the clinical onset of RA, and potentially of other rheumatic diseases, as well as the use of potentially soon-to-be-approved preventive interventions.

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Box 2. Clinical care of an individual who exhibits RA-related autoimmunity or clinical features in the absence of clinical RA.

(1) Careful assessment to ensure that clinical RA is not present (may include imaging, with careful interpretation of findings). Consider evaluation for other conditions that may be related to autoantibody positivity. For example, given some association of ACPA with lung disease, consider symptom-driven evaluation for lung disease; if RF+, consider additional studies to ensure that autoantibody is not related to another condition (eg, hepatitis C, hematologic malignancy).
(2) Discussion of rates of progression to clinical RA. In general, studies suggest that positivity for ACPA has ~20-30% PPV for the onset of clinical RA within 3-5 yrs, although actual risk may be higher or lower depending on many factors.
(3) Consideration of lifestyle interventions that may reduce risk (eg, smoking cessation, exercise, optimal body weight, oral health). A caveat is that these interventions have not been proven to reduce RA risk in controlled trials, but they may have general health benefits.
(4) Counseling regarding signs and symptoms of evolving RA, and consideration for routine follow-up (perhaps annually).
(5) Treatment once clinical RA develops (caution regarding overtreatment if IA is identified only by imaging and not by clinical examination).
(6) Monitoring for advances in prevention that will affect clinical care.

ACPA: anticitrullinated protein antibody; IA: inflammatory arthritis; PPV: positive predictive value; RA: rheumatoid arthritis; RF: rheumatoid factor.

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