Is it Time to Label 'At Risk of Rheumatoid Arthritis' a Disease?

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Abstract

Rheumatoid arthritis (RA) is increasingly recognised as the final stage of a prolonged disease continuum that may begin years before the onset of clinically apparent synovitis. During this at-risk phase, individuals without clinical synovitis may present with autoantibodies, musculoskeletal symptoms, systemic inflammation, and subclinical synovitis detectable on imaging. Emerging evidence suggests that this phase is associated not only with an increased risk of progression to RA, but also with a substantial clinical, psychological, and socioeconomic burden.

This viewpoint examines evidence on at-risk individuals who frequently report fatigue, pain, impaired function, reduced quality of life, and psychological distress, often comparable to patients with early RA. Imaging studies also demonstrate frequent subclinical synovitis associated with progression risk and functional impairment. Qualitative studies further highlight the emotional burden related to uncertainty and risk awareness. Finally, economic analyses suggest substantial societal costs, largely driven by reduced work productivity. Recent interventional trials have shown that early therapeutic intervention can improve symptoms, imaging findings, and patient-reported outcomes, while reducing progression to inflammatory arthritis in selected populations. These findings support the concept that the at-risk phase represents a biologically and clinically meaningful condition.

Different approaches to defining and classifying the at-risk phase of RA, including stage-based models, are discussed alongside challenges related to terminology. Recognising the at-risk phase of RA as a disease entity could facilitate earlier intervention strategies, improve patient outcomes, and support the development of clearer clinical management pathways.

Key Points

1. Individuals may exhibit consistent predictive risk factors for future rheumatoid arthritis (RA), highlighting a continuum of disease development.

2. This feature article examines the concept of 'pre-RA disease', describing how at-risk individuals experience clinically meaningful symptoms and health burden prior to arthritis onset, alongside evidence of favourable responses to early intervention.

3. Patients at risk of RA represent a clinically relevant population with measurable disease burden that should be recognised by clinicians and regulatory authorities, with appropriate consideration given to timely monitoring and treatment strategies.

BACKGROUND

Rheumatoid arthritis (RA) is now recognised as the final stage of a dynamic disease continuum, which may evolve over several years prior to the development of clinical joint swelling, essential for the diagnosis/classification of RA.[1] This process typically starts in the context of genetic and environmental susceptibility, followed by the development of autoantibodies such as anti-cyclic citrullinated peptide antibody (anti-CCP) and/or rheumatoid factor, musculoskeletal symptoms, low-grade systemic inflammation, and subclinical synovitis detectable by imaging. This phase is referred to as 'at-risk of RA', and has traditionally also included 'clinically suspect arthralgia'.[1]

There is a growing body of evidence that this phase is characterised not only by an increased risk of progression to clinical arthritis but by a significant clinical burden, which complies with the formal definition of a disease as "a condition of the individual or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms."[2] In line with this, the WHO has created an International Classification of Disease code (ICD-10-CM code R76.81) for abnormal anti-CCP alone or with abnormal rheumatoid factor in the absence of RA.

CLINICAL IMPACT

Individuals in the at-risk phase of RA frequently report an evolving spectrum of clinical features and pain characteristics, despite not presenting with clinical joint swelling. Fatigue is a dominant and burdensome symptom in this phase, reported by up to 75% of individuals with seropositive arthralgia, often preceding clinical arthritis by months or years.[3] Psychological factors such as stress and

sleep disturbances further contribute to the overall symptom burden.[4] Prospective studies have shown that these individuals experience measurable impacts on function, mood, and health-related quality of life using tools such as the Health Assessment Questionnaire-Disability Index (HAQ-DI), often comparable to early RA, established RA, and other diseases like COPD.[3,5,6] Importantly, patient-reported pain and general health were similar in those who developed inflammatory arthritis and those who did not.[7]

THE PRESENCE OF SUBCLINICAL SYNOVITIS

Multiple studies have shown higher rates of subclinical synovitis in at-risk individuals compared with healthy controls, both on MRI and ultrasound, which are associated with progression to RA.[8,9] Higher MRI subclinical inflammation (including synovitis, tenosynovitis, and bone marrow oedema) are significantly correlated with higher HAQ-DI scores. Previous work has shown that subclinical inflammation may resolve if autoantibody levels are low and without other risk factors,[10] and that absence of ultrasound subclinical synovitis has a high negative predictive value for developing inflammatory arthritis.[11] Nonetheless, those who fail to progress also suffer a significant burden during the at-risk phase.

PATIENT PERSPECTIVES

Qualitative studies reveal that at-risk individuals experience distress related to persistent symptoms, uncertainty about disease progression, and emotional strain tied to risk awareness.[12,13] Their perspectives are shaped by personal factors such as prior exposure to RA within the family, differing levels of health literacy, and access to information.[13,14] Preventive interventions are met with mixed responses. Importantly, individuals were more inclined to accept preventive treatments or predictive testing when experiencing symptoms or when test results could offer precise risk estimates and timelines.[13,15]

ECONOMIC BURDEN

The economic impact of the at-risk phase of RA is a relevant issue, with increased healthcare use, early disability, and reduced productivity. The cost-effectiveness analysis in individuals with clinically suspect arthralgia and MRI-detected subclinical inflammation estimated total costs from both societal and healthcare perspectives between 43,035 EUR and 45,647 EUR over 2 years, predominantly related to impaired work capacity.[16] These findings support early intervention in the at-risk phase of RA and reinforce the argument it is a clinically and economically relevant disease state.

INTERVENTIONAL TRIALS

At present, multiple clinical trials have evaluated medical interventions in individuals at risk of RA.[9] The TREAT EARLIER trial showed that methotrexate significantly improved MRI scores, patient reported outcomes including function, and sustained these effects post-treatment, especially in anti-CCP positive individuals.[16,17] The APIPPRA trial showed an improvement in all these parameters, including quality of life measures during abatacept treatment period. A significant reduction in RA progression was seen in the treatment group, even after treatment cessation.[9,18] The ARIAA trial, also using abatacept, showed a significant improvement in MRI scores (57% versus 31%; p=0.014) and reduced RA progression (35% versus 57%).[9]

Whilst primary outcomes focused on disease progression such as imaging or clinical changes, intervention studies also demonstrated that symptoms and imaging findings can improve with treatment. Furthermore, when questioned, at-risk individuals reported symptom improvement, inflammation control, and function preservation as valuable targets, increasing the chances of participation.[9] The use of composite outcomes including symptom reduction and imaging remission may offer better measures of benefit than a binary ‘progression to RA.’

DISCUSSION

How should the at-risk phase of RA be defined and classified? A key question is whether it should be restricted to those at the highest risk of developing RA, such as autoantibody-positive symptomatic individuals, or whether it should be broader, encompassing all individuals with symptoms and a measurable clinical burden, irrespective of their risk of progression.

One possible approach is to consider stages within the at-risk phase of RA, ranging in ascending risk along the RA disease continuum. Stage 1: asymptomatic autoantibody positivity. Stage 2: symptomatic individuals with or without autoantibodies. Finally, Stage 3: those at the highest risk of progression to RA: those who, in addition to arthralgia, have high level autoantibodies and/or sub-clinical synovitis. This categorisation may help to capture the heterogeneity of this phase while allowing more tailored clinical and research approaches.

A final contentious issue is the terminology. Similarly to 'pre-diabetes' being defined by thresholds in haemoglobin A1c and/or blood glucose values, 'pre-RA' or 'pre-RA disease' could be defined by a certain level of risk. This would constitute a shift from the current denomination of 'at-risk of RA', initially used to avoid implying progression to RA. This would have the disadvantage of not including lower risk patients with clinical burden who are unlikely to progress.

Clearly, these suggestions will need to be refined as further evidence emerges regarding disease burden and progression. Nevertheless, they would allow clinicians to work with more homogeneous groups and facilitate studies aimed at improving quality of life for affected individuals. The absence of clear therapeutic guidance in this phase, despite evidence of disease burden and response to treatment, highlights the need for a shift in both classification and clinical management. The fact that the at-risk phase of RA, despite demonstrating a clear disease burden and response to therapy, currently lacks guidance for management suggests that changes are urgently needed.

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