Insights from Populations at Risk for the Future Development of Classified Rheumatoid Arthritis

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KEYWORDS

• Preclinical rheumatoid arthritis • Epidemiology • Biomarkers • Autoantibodies
• Dietary factors • Prediction • Prevention • Imaging

KEY POINTS

- Seropositive rheumatoid arthritis (RA) typically begins with a prolonged preclinical period characterized by circulating autoantibodies in the absence of clinically apparent inflammatory arthritis.
- As the point of clinically apparent disease approaches, preclinical RA is characterized by increasing epitope spreading of new antibodies to citrullinated protein antigens peptide specificities, elevated cytokines and chemokines, alterations in autoantibody avidity, and G0 carbohydrate content.
- Subjects at increased risk for developing classified RA based on the presence of RA-related autoantibodies demonstrate autoimmune and inflammatory characteristics similar to individuals with existing RA and those known by retrospective analyses to have been in the preclinical RA period.
- At-risk individuals are characterized by the increased prevalence of asymptomatic small airways disease that may play a key role in initiation of the disease.
- Further studies of at-risk individuals have the potential to deepen the understanding of the initiation and propagation of RA.

INTRODUCTION

Stages in the Evolution of Rheumatoid Arthritis

Rheumatoid arthritis (RA) encompasses 2 major subsets of disease, seropositive and seronegative.[1,2] Seropositive individuals exhibit RA-related autoantibodies, which

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include antibodies to citrullinated protein antigens (ACPAs), with this posttranslational modification most commonly found in an antigenic form on fibrinogen, vimentin, type II collagen, and enolase.[3,4] In addition, antibodies to the Fc domains of self-immunoglobulin (Ig) molecules that are designated rheumatoid factors (RF) are also found.[5] Based on clinical comparisons as well as studies of environmental and genetic associations, it is considered that seropositive and seronegative forms of RA likely exhibit overlapping but distinct pathogenic mechanisms.[6,7]

The current understanding of the natural history of seropositive RA is summarized in Fig. 1. In this regard, one might consider that the onset of RA occurs around the time that clinically apparent arthritis appears. However, there is a prolonged period characterized by the presence of highly specific RA-related autoimmunity, including both ACPA and RF, in patients that typically begins 3 to 5 years[8–16] before the onset of clinically apparent disease (reviewed by Deane and colleagues[17]). Although this period is defined retrospectively as the "preclinical" period of RA in subjects who eventually develop the disease, it is perhaps best designated an "ACPA and/or RF+ at-risk" status in the populations being studied in cross-sectional or prospective studies, because the eventual outcome in individual subjects is yet unknown.[18] Subjects may progressively develop further immune alterations and then clinically apparent arthritis. It is considered possible to "reverse" the disease course at these early points,[18,19] although it is uncertain as to the proportion of subjects who do so and the primary determinants of such a change.

Herein, evidence is presented addressing the question of whether intensive studies and deep phenotyping of individuals in the ACPA+ and/or RA-related autoantibody positive at-risk status can inform the field with regard to the mechanisms by which the earliest immunologic abnormalities develop and what biologic processes may be the early "drivers" of disease. As outlined herein, the results in aggregate of these studies of at-risk individuals do provide such insights and strongly suggest that the initiation RA likely involves an extraarticular, and most likely a mucosal, inflammatory process and/or dysbiosis.

Early Stage Studies of Rheumatoid Arthritis Natural History Utilize Several Approaches to Define the "At-Risk" Population

At-risk populations have been defined based on several characteristics, with the most commonly utilized being a close familial relationship, usually at the first-degree relative

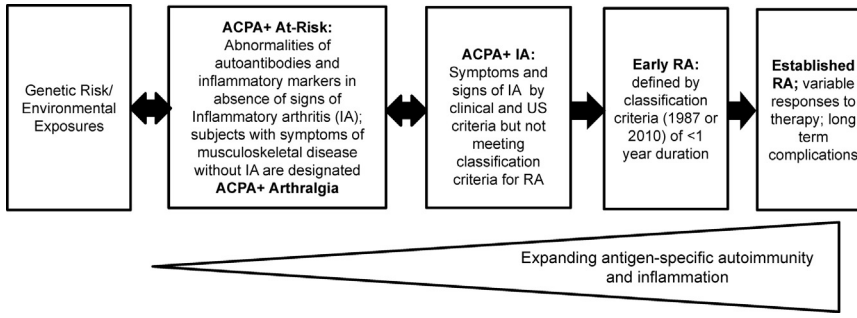

Fig. 1. Natural history of RA development. RA progresses through a series of stages first identified and characterized by detectable circulating RA-specific autoimmunity (ACPA+ At-Risk), with or without "arthralgia," followed by progression through symptoms, signs and clinically apparent and classifiable disease. The presence of bidirectional arrows at early stages indicates that subjects with early disease may resolve the findings and return to an earlier state.