Preclinical Inflammatory Rheumatic Diseases

An Overview and Relevant Nomenclature

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KEYWORDS

• Rheumatoid arthritis • Preclinical • Early • Risk • Prediction • Prevention

KEY POINTS

- Terminologies have been developed to describe the preclinical and clinically apparent phases of disease leading to rheumatoid arthritis (RA).
- Disease duration in research studies should be timed from the points of onset of the clinically apparent phases: the onset of phase D (symptoms without clinical arthritis), the onset of phase E (clinical arthritis), and the onset of phase F (RA).
- The future research agenda should include identifying and understanding (1) additional environmental risk factors for RA, (2) gene-environment interactions, (3) the full extent of immune abnormalities that characterize the preclinical phase of disease and the site of initiation of these immune responses, (4) processes that lead to the localization of the disease to the joints, and (5) the range of symptoms that characterize the early clinical phases of disease.

BACKGROUND

Inflammatory rheumatic diseases are common and are associated with significant morbidity, as a consequence of articular and extra-articular manifestations, as well as reduced life expectancy.

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In patients with rheumatoid arthritis (RA), a considerable body of research has shown that early treatment leads to significantly improved outcomes. For example, the initiation of disease-modifying antirheumatic drug therapy within the first 12 weeks of the onset of symptoms significantly reduces the rate of radiological progression compared with treatments started later,[1] with patients with more aggressive disease benefiting most from early therapy.[2] Although data are most robust for RA, there are data for other inflammatory rheumatic diseases suggesting that early treatment may also improve long-term outcomes.[3] However, treatments in the established phases of disease, even if given early, are rarely curative.

A desire to cure and even prevent disease has led to increased interest in the earliest phases of the inflammatory rheumatic diseases, including both the earliest phases of clinically apparent disease (before patients have developed the full set of characteristics that allow them to be classified as having the disease in question), and the phases of disease before the onset of symptoms.

This article focuses on RA, although many of the concepts discussed are equally relevant to other inflammatory rheumatic (eg, systemic sclerosis and systemic lupus erythematosus) and nonrheumatic (eg, type 1 diabetes) diseases.

THE INITIAL IDENTIFICATION OF A PRECLINICAL PHASE OF RHEUMATOID ARTHRITIS

Although understanding of the preclinical phase of RA has increased considerably in the last few years, the existence of such a phase was first appreciated in the 1980s. Pioneering work from Finland made use of serum samples from individuals participating in a series of community-based cardiovascular studies, because it was possible to identify those who had developed RA after sample collection.[4] Of 30 subjects who developed seropositive RA (between a few months and 9 years after the collection of serum samples), 16 were positive for rheumatoid factor with the frequency of positivity being greater in those nearer the onset of clinically manifest arthritis.[4] The presence of antiperinuclear and antikeratin antibodies in individuals before the onset of RA was subsequently reported.[5,6] Research in this area grew rapidly through the 1990s and 2000s and was the subject of a recent review by van Steenbergen and colleagues.[7]

As research interest increased, so did the number of terms used by researchers to describe the earliest phases of RA, including pre-RA, preclinical RA, autoantibody-positive arthralgia, early RA, very early RA, and extremely early RA. A lack of consistency regarding terminology made it difficult to compare results between studies and a paucity of information regarding the terminologies used in original articles made it difficult to understand what phase of disease individual researchers were reporting on. In order to develop an agreed set of terminologies regarding the phases of disease leading up to the development of RA, the EULAR (European League Against Rheumatism) Standing Committee for Investigative Rheumatology established the Study Group for Risk Factors for RA. Many of the principles underlying the nomenclature developed by this Study Group are applicable to the earliest phases of other chronic autoimmune/chronic inflammatory diseases.

TERMINOLOGIES TO DESCRIBE INDIVIDUALS IN PHASES LEADING UP TO THE DEVELOPMENT OF RHEUMATOID ARTHRITIS

In order to develop a set of terminologies to describe individuals in phases leading up to the development of RA, a multidisciplinary group including rheumatologists, laboratory scientists, and a patient representative reviewed and provided descriptive terms for the phases that individuals may pass through before the development of RA and