Commentary

Nomenclature for the Phases of the Development of Rheumatoid Arthritis

Karim Raza, MD[1,2]; V. Michael Holers, MD[3]; and Danielle Gerlag, MD[4]

[1]*Institute of Inflammation and Ageing, Arthritis Research UK Rheumatoid Arthritis Centre of Excellence, Medical Research Council Arthritis Research UK Centre for Musculoskeletal Ageing, University of Birmingham, Birmingham, United Kingdom;* [2]*Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, United Kingdom;* [3]*Division of Rheumatology, University of Colorado—Denver, Aurora, CO, USA; and* [4]*RxCelerate, Cambridge, United Kingdom*

ABSTRACT

Rheumatoid arthritis (RA) is a common immune-mediated inflammatory disease. Research on RA is increasingly focused on the earliest stages of the disease, and has provided strong evidence that clinical signs and symptoms may be preceded by a preclinical phase during which evidence of systemic autoimmunity may be present. To facilitate research in this area, a number of international initiatives have proposed definitions of the phases of disease leading up to RA. The first of these initiatives was the European League Against Rheumatism's (EULAR) set of recommendations on terminology in persons at risk for RA, which suggested that the "at-risk phases" be described in terms of patients variably having: (A) genetic risk factors for RA; (B) environmental risk factors for RA; (C) systemic autoimmunity associated with RA; (D) symptoms without clinical arthritis; and (E) unclassified arthritis. The phrase *clinically suspect arthralgia* (CSA) is now widely used and can be regarded as describing a subgroup of patients in phase D. A definition of CSA was recently proposed by a EULAR taskforce, and primary research has begun to explore the full range of symptoms, as well as their sensitivity and specificity alone and in combination with other factors, that characterize this phase. Similarly, immune abnormalities at mucosal and others sites that precede and/or are associated with the onset of musculoskeletal symptoms are being increasingly studied and understood. Whether some of these at-risk phases, in particular CSA, represent entities meriting their own classification criteria is an essential area for consensus and will be discussed. (*Clin Ther*. 2019;41:1279–1285) © 2019 Published by Elsevier Inc.

Key words: clinically suspect arthralgia/CSA, nomenclature, preclinical, rheumatoid arthritis.

INTRODUCTION

Autoantibody-positive rheumatoid arthritis (RA) is one of the most common immune-mediated diseases, with joint inflammation and cartilage and bone destruction as its hallmarks. During recent years, research on this disease has focused on its earliest phases, revealing that the development of clinically evident arthritis may (in those with seropositive disease) be preceded by a phase of systemic autoimmunity that can be present for many years.[1–4] With a median duration of 5 years before arthritis becomes evident, circulating RA-related autoantibodies, increased acute-phase reactants, and proinflammatory cytokines and chemokines can be found in the peripheral blood of people at risk for RA.[3] The risk for arthritis within 2 years in patients with musculoskeletal symptoms who are positive for both anti-citrullinated protein/peptide antibodies and immunoglobulin M rheumatoid factor is ~40%,[5] and first-degree relatives of patients who have been

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diagnosed with RA have a ~4-fold increased risk for the disease. It is thus clear that both genetic and environmental factors play a role in disease pathogenesis.[6] Indeed, in a prospective cohort, environmental factors, such as smoking,[7] in addition to obesity,[7] and having a decreased vagal tone,[8] were shown to increase the risk for arthritis in people who demonstrated circulating RA-related autoantibodies in their peripheral blood, while other studies have highlighted the association of poor oral health[9,10] and low fish intake[11] with the development of RA in this population.

The recognition of the existence of preclinical phases offers the opportunity to intervene, targeting associated processes with the aim of preventing or delaying the development of clinically manifested arthritis.[12,13] Approaches to prevention include modifying behaviors to positively influence lifestyle-related risk factors, and/or the use of conventional synthetic disease-modifying antirheumatic drugs and statins, or more targeted therapies focused on disrupting pathogenetic immune abnormalities.[14] In the context of seropositive RA, primary prevention can be conceptualized as an intervention to avoid systemic autoimmunity (eg, the development of anticitrullinated protein/peptide antibodies), and secondary prevention, the avoidance of the transition from the presence of these autoantibodies to RA.[12,15] This suggested approach is analogous to the proposed secondary prevention of type 1 diabetes in autoantibody-positive persons without clinically manifested diabetes.[16] Understanding the exact role of each of the currently identified contributing factors would support the identification of potential interventions to prevent RA.

EULAR Recommendations on Terminology To Describe the At-Risk Phases of RA

To facilitate research that will unravel the interplay between factors known to be related to the progression from a state of health to RA (both seropositive and seronegative), the need for clear nomenclature has been recognized. A number of international initiatives have proposed definitions of the phases of disease leading to RA. The first of these was the European League Against Rheumatism (EULAR) set of recommendations on terminology in persons at risk for RA, proposed by the Study Group for Risk Factors for Rheumatoid Arthritis in 2012.[17] This multidisciplinary group, consisting of rheumatologists, scientists, and a patient representative, provided descriptive terms for the phases that patients may pass through before the diagnosis of RA. It was recommended that, in prospective studies, patients at risk for RA would be described as having: (A) genetic risk factors for RA; (B) environmental risk factors for RA; (C) systemic autoimmunity associated with RA; (D) symptoms without clinical arthritis; and (E) unclassified arthritis, before being diagnosed with RA (F) (Table).[17] Combinations of these suggested terminologies can be used to provide more clarity on the definition of the cohort and phase of the patients studied. Furthermore, these terminolgies also highlight the notion that patients do not necessarily move through all of the phases identified and do not necessarily pass through the various phases in a linear fashion.[18] In particular, patients with seronegative RA are likely to have never passed through phase C, although it is in theory possible that there may have been a transient presence of autoantibodies or other evidence of systemic autoimmunity associated with a breach of tolerance that is no longer detectable (with current approaches to autoantibody and other biomarker testing) once RA has manifested.

While the proposed terminology is intentionally broad, it is recognized that deeper insight into the contribution of the various risk factors, as well as the identification of additional novel risk factors, would help to create more granularity of the risk for arthritis

Table. European League Against Rheumatism recommendations on terminology to be used to define specific phases up to the development of rheumatoid arthritis (RA).*

Phase	Descriptor
A	Genetic risk factors for RA
B	Environmental risk factors for RA
C	Systemic autoimmunity associated with RA
D	Symptoms without clinical arthritis
E	Unclassified arthritis
F	RA

*The term *arthritis* is used to denote clinically apparent soft tissue swelling or fluid (not bony overgrowth alone). *A* to *E* can be used in a combinatorial manner; for example, an individual may have *A* + *B*, or *A* + *B* + *C* or *A* + *B* + *D*, etc.

in each phase. In addition, it is recognized that clustering of more specific risk factors and features within these at-risk phases may identify additional phases, or subcategories within the existing phases, which would benefit from definition in their own right. A recent example is the recognition of a more specific combination of features that might help physicians to identify patients who are at risk for RA on the basis of their symptomatology, which has been named *clinically suspected arthritis* (CSA).[19] Those with CSA represent a subgroup of patients in phase D of the EULAR nomenclature and will be discussed in more detail subsequently. Similarly, it is recognized that patients at risk for RA may have evidence of systemic inflammation, for example with elevated levels of C-reactive protein or of proinflammatory cytokines and chemokines in the blood, without necessarily having detectable RA-related autoantibodies. Whether *systemic inflammation*, as distinct from *systemic autoimmunity*, represents another biological characteristic that can be used to subclassify at-risk phases deserves further attention.

Recent Developments Related to CSA

The EULAR recommendations described earlier recognize a phase of disease in the transition to RA in which a patient has musculoskeletal symptoms without the development of clinically apparent synovial swelling (EULAR phase D). Patients in phase D who eventually develop RA may already have RA-related autoantibodies in their blood[20,21] and at mucosal sites (eg, the respiratory tract[22]) and may also have other evidence of immune perturbation.[23,24] However, they may have no evidence of joint-based immune dysfunction, as evidenced by imaging modalities such as ultrasound or magnetic resonance imaging[25] as well as detailed analysis of the synovial tissue.[26] This stage of symptoms without clinical arthritis is important as it represents a key stage in the journey toward RA during which patients first become aware of relevant symptoms—which may prompt them to seek medical help. It thus represents an important entry point into preventive clinical trials—many of which include the presence of symptoms as an inclusion criterion.[14,27]

Following the development of the EULAR recommendations on nomenclature, the term *CSA* was introduced to describe a condition in which, on the basis of symptoms, a physician would be suspicious for the risk for RA and distinguish these patients from patients with arthralgia not at risk for RA. In order to help to define this term, a EULAR task force used a combination of data-driven and expert consensus–based approaches to identify 7 key features of patients with CSA.[19] Five of these features are related to a patient's history (joint symptoms of recent onset [duration, <1 year]; symptoms located in the metacarpophalangeal joints; duration of morning stiffness of ≥60 min; symptoms that are most severe in the early morning; and having a first-degree relative with RA), and 2 are related to physical examination (difficulty with making a fist; and positive result on squeeze test of the metacarpophalangeal joints).[19] The task force avoided identifying a single cutoff point to define CSA but provided the test characteristics of a range of cutoff points. Thus a high sensitivity (>90%) is obtained if at least 3 of the 7 parameters are present, while a high specificity (>90%) requires the presence of at least 4 of the 7 parameters. The categorization of a patient as having CSA has the physician's opinion as the starting point, and this EULAR definition will be useful for identifying the clinical features of patients to include in longitudinal observational studies and intervention trials in patients with CSA, to ensure that results between studies that include patients with CSA can be compared in a robust way.

However, it should be recognized that this definition is not appropriate for use in patients with arthralgia to identify a group of patients at high risk for RA prior to evaluation by a physician or other health care provider specifically experienced in the assessment of patients with inflammatory arthritis.[28] Furthermore, a patient may be in EULAR phase C or D but have musculoskeletal symptoms (eg, shoulder pain, metatarsophalangeal joint pain) that meet very few of the EULAR parameters that define patients as having CSA. It is thus clear that further work is necessary to understand the earliest symptoms in patients who may develop RA in order to: (1) identify those with the highest positive predictive values, with the aim of intervening in those with these symptoms to prevent RA; and (2) inform studies aimed at elucidating underlying mechanisms—since it is clear that subclinical synovitis does not explain all such symptoms.[29] Informed by qualitative work aimed at understanding early symptoms in those at high risk for RA,[30–32] a EULAR-supported initiative has developed, and performed initial validation of, a

questionnaire that captures data related to the frequency, severity, and impact of a range of these symptoms.[33] The application of this questionnaire in the context of longitudinal observational studies in cohorts of people at risk from many different countries and cultural/ethnic backgrounds will provide important data on the prevalence and predictive value of individual symptoms and symptom complexes related to the development of RA.

Mechanisms Driving the Transitions Between At-risk Phases

An important area for the integration of data from clinical and translational studies is how CSA itself, or the clinical subcomponents that in aggregate define it, are related to the emerging evidence of the presence of inflammation at nonarticular sites and immune perturbations in subsets of RA-related autoantibody-positive patients. For instance, recent work has demonstrated that first-degree relatives of patients with RA (EULAR phase A) or subgroups of patients who demonstrate RA-related autoimmunity (EULAR phase C) demonstrate not only mucosal inflammation (reviewed in reference 34) but also abnormalities of signaling and metabolomic pathways in circulating $CD4^+$ T lymphocytes,[24] clonal changes in the peripheral blood B-cell receptor repertoire,[23] as well as skewing of plasmablasts to the immunoglobulin A isotype,[35] increasing epitope spreading against citrullinated peptide targets,[36,37] and, in the lungs of at-risk persons, evidence of excessive neutrophil extracellular trap formation.[38] These results suggest that some aspects of CSA may be driven by, or are associated with, these immune diatheses, perhaps through the remote effects of elevated chemokines and cytokines associated with the development of pain.

Furthermore, an understanding of how the environmental risk factors that are postulated drivers of EULAR phase B influence the development of CSA or unclassified arthritis, or are interlinked with the immune changes noted earlier in subgroups of patients in phases A and C, deserves substantive attention. Two examples of potential environmental determinants of RA, both of which have substantial potential for modulation as part of the management of CSA, are smoking and ω-3 fatty acid intake (reviewed in references 34 and 39). Although ω-3 fatty acid and fatty fish intake are interlinked, not all studies have shown that fatty fish intake is similarly protective against the development of RA.[40]

Smoking has been associated with the development of preclinical autoantibodies as well as the transition to classified RA, and its role in triggering RA is proposed to be related to the generation of citrullinated protein antigenic targets in the lung.[41] Whether smoking influences the development of symptoms indirectly through lung inflammation promoted by such local citrullinated antigen generation, or alternatively through other mechanisms that are operative even outside of the at-risk state, requires additional exploration. In at-risk populations, the ω-3 fatty acid level, regardless of the relationship to fish intake, is inversely associated with the risks for being rheumatoid factor and anti-CCP positive,[42] and for the development inflammatory arthritis.[43] Notably, ω-3 fatty acid pathway molecules are precursors of antiinflammatory molecules of the resolvin and maresin classes of biologically active lipids,[44] relative deficiencies of which are found in later at-risk phases and may promote the development of the CSA features that are influenced by inflammation.

CONCLUSIONS

The identification of the at-risk phases for future RA development has opened many new lines of investigation into the clinical and pathophysiologic aspects of this condition. The development of an initial terminology and the exploration of the concept of CSA are important steps forward, and likewise an understanding of the relationships between the clinical features and the immune diatheses that are increasingly identified will be necessary for a more comprehensive understanding of these fascinating phases of RA. Internationally accepted nomenclature to define at-risk phases is clearly helpful in a research context to ensure the comparability of data. As research advances, we may be able to identify particular at-risk phases that merit recognition as disease states in their own right; recognition of such disaese states may help communication between health care professionals and patients and may facilitate engagement with regulatory agencies in the context of the development of preventive treatments. Currently, many patients identified as being at risk for RA experience a range of emotions including fear, frustration, and uncertainty.[32] In part this may relate to the absence of an easily applied diagnostic

label. As our understanding of the relationships between immunobiological and clinical features develops, we may be able to define specific pre-RA phases for which it is appropriate to ascribe a diagnostic label, analogous to the way in which osteoporosis is defined as (an entirely asymptomatic) disease state that may precede a fracture. The identification of such disease states that have meaning in clinical care and that can be described in patients may help the process of shared decision making as clinicians and patients reach consensus regarding treatment—both to prevent RA development and to manage current symptoms (in the symptomatic at-risk phase). Decision making around intervention will be influenced by the extent of current symptoms (if any) and when RA might begin—for example a person with an 80% risk for RA development within the next 2 years may approach the concept of preventive treatment very differently from someone with an 80% risk for RA development within the next 20 years. For that reason, some authors have suggested the term *imminent RA* for persons who are at risk for the development of RA in the near future. An alternative would be to define the at-risk phase of a patient and then to provide an estimate of his or her risk for RA and the most likely time to its development (with associated measures of uncertainty around that estimate). We would suggest that a patient's perspectives are sought regarding whether he or she would value the inclusion of the term *imminent* in relevant nomenclature. As this field advances, we should remain cognizant of the risks associated with diagnostic labeling, which are multiple and range from those related to the psychological well-being of the at-risk person to insurance-related implications. Ensuring that patient voice is represented in developments in this area will help to ensure that outcomes are acceptable for them—as the most relevant stakeholder.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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Address correspondence to: Karim Raza, BMBCh, FRCP, PhD, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, B15 2TT, United Kingdom. E-mail: k.raza@bham.ac.uk