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ACR/EULAR 2010 rheumatoid arthritis classification criteria

Jonathan Kay[1] and Katherine S. Upchurch[1]

Abstract

Advances in our understanding of the pathogenesis of RA over the past two decades, particularly the identification of cytokines that promote synovial inflammation (e.g. TNF-α, IL-1 and IL-6), have led to treatment courses that affect the disease process itself, beyond alleviation of symptoms. In turn, emphasis has shifted to intervention early enough in the disease course to prevent the joint destruction that follows inflammation. Accordingly, in 2010 the ACR and the European League Against Rheumatism (EULAR) put forward revised classification criteria emphasizing RA characteristics that emerge early in the disease course, including ACPAs, a biomarker that predicts aggressive disease. These were in contrast with the 1987 ARA criteria, which distinguished established RA patients from those with other forms of arthritis, and identified patients with later disease. The categories of the 2010 ACR/EULAR criteria are grouped into four classifications, with point scores for each: joint symptoms; serology (including RF and/or ACPA); symptom duration, whether $<$6 weeks or $>$6 weeks; and acute-phase reactants (CRP and/or ESR). The criteria were developed in a three-phase process, beginning with an analysis of patient cohorts to determine what disease characteristics had persuaded clinicians to initiate MTX therapy, followed by consensus-based decisions and the creation of a scoring system that would predict which patients would go on to develop persistent and/or erosive disease.

Key words: rheumatoid arthritis, ACR/EULAR classification criteria, synovial inflammation, joint destruction, anti-citrullinated protein antibodies, ACPA.

Introduction

RA is a chronic systemic disease in which immunologically mediated inflammation of synovia-lined joints can result in marked disruption of joint structure and function. Over the past two decades, significant advances in basic science research have elucidated the biology of this inflammatory process, including the identification of some of the cytokines that drive chronic synovial inflammation (e.g. TNF-α, IL-1 and IL-6). This has resulted in an explosion of targeted biologic therapies for RA that have proved significantly more effective than previously available treatments in improving disease activity, preventing joint destruction and preserving physical function. Using these new therapeutic agents, remission of disease activity is now a realistic possibility [1].

Patients with established RA typically require continued drug administration to control disease activity. The observation that delays in treatment with conventional DMARDs resulted in worse outcomes led to the finding that effective therapeutic intervention to reduce synovitis during a window of opportunity earlier in the course of disease effectively reduced structural damage [2]. The appropriate intensive use of conventional DMARDs has resulted in patients achieving better structural and functional outcomes than with routine treatment strategies [3]. Over the past decade, new biomarkers such as ACPAs have been shown to predict an aggressive disease course that often is accompanied by joint destruction. ACPAs may be present in patients with RA for many years before the onset of clinical disease.

The 1987 ARA revised criteria for the classification of RA, which have been used to define this disease in clinical trials of novel therapies, fail to diagnose some patients with early RA who might benefit most from the initiation of early, aggressive treatment. These criteria were formulated by comparing patients with established RA to

[1]Division of Rheumatology, Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA.

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Correspondence to: Jonathan Kay, Division of Rheumatology, Department of Medicine, University of Massachusetts Medical School, Worcester, MA 01605, USA.
E-mail: jonathan.kay@umassmemorial.org

patients with other conditions who present with joint pain, including OA, SLE, FM, AS and PsA. The main purpose of these criteria was to distinguish RA from other forms of arthritis, rather than to identify and diagnose patients with RA in the earlier stages of disease when they might benefit most from intervention [4]. These classification criteria were developed before the diagnostic and prognostic importance of ACPAs were recognized; thus, only serum RF was included as a serological marker. The inclusion of radiographic changes (bony erosions or periarticular decalcification) as a diagnostic criterion was clearly consistent with the goal of avoiding the overdiagnosis of RA, as opposed to identifying patients with disease who would respond to treatment. Thus, the window of opportunity to receive treatment that could control disease activity and prevent structural damage might already have passed for many of the patients classified as having RA using the 1987 ARA criteria [5].

The 2010 RA classification criteria

In 2007, a group of American and European rheumatologists who were experts in the diagnosis and treatment of RA met in Zürich to discuss the limitations of the existing 1987 ARA criteria and to plan the development of a new set of criteria to diagnose and classify patients with RA early in the course of disease. This meeting resulted in the formation of a joint ACR/European League Against Rheumatism (EULAR) working group that was charged to create these new criteria using an approach that combined analysis of data with a Delphi consensus method. Such criteria would facilitate early therapeutic intervention to prevent structural damage and permanent functional limitation [5].

The goal of this working group was to distinguish that subset of patients who were at high risk for developing persistent and/or erosive disease from the overall group of patients who present with new-onset undifferentiated inflammatory arthritis and to develop a set of rules to identify this subset. Such patients would be classified as having RA. These rules, or criteria, would be used not only to identify individuals at high risk for chronic disease activity and erosive damage but also as a basis for choosing patients in whom to initiate targeted DMARD treatment early in the disease course [5]. The criteria were developed in three phases.

Phase I: cohort analysis

The initial phase of this process consisted of an analysis of data from seven European cohorts and one North American cohort of patients who presented with early undifferentiated synovitis. Initiation of MTX therapy to prevent structural joint damage was considered to be a surrogate for the diagnosis of RA. Those common clinical and laboratory variables that had prompted experienced clinicians to initiate MTX therapy in these patients within 1 year of enrolment were identified. Anatomic location of swollen and tender joints, levels of acute-phase reactants and titres of serological biomarkers were identified as being those variables that contributed most to the decision to initiate MTX therapy among these patients. The relative contribution of each variable to this decision was estimated (Table 1) [5, 6].

Table 1 Criteria identified during phase 1 and the relative weight assigned to each [5, 6]

Variable	Comparison	Relative weight
Swollen MCP joint	Present *vs* absent	1.5
Swollen PIP joint	Present *vs* absent	1.5
Swollen wrist	Present *vs* absent	1.6
Hand tenderness	Present *vs* absent	1.8
Acute-phase response	Low-level normal *vs* normal	1.2
Acute-phase response	High normal *vs* normal	1.7
Serology	Low positive *vs* negative	2.2
Serology	High positive *vs* negative	3.9

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Phase II: consensus-based decisions

The second phase of this process was designed to assess the applicability of those criteria identified during the initial data-driven process to the classification of patients with early undifferentiated inflammatory arthritis, using a Delphi consensus method. A panel of 24 rheumatologists (12 from North America and 12 from Europe), each of whom had extensive experience in the diagnosis and treatment of RA, met in Chicago in 2009. The clinicians contributed case histories of actual patients with inflammatory arthritis at different stages of disease. The entire panel reviewed all of the case histories and agreed on a number of factors, or variables, that were important in determining the relative probability that each patient might develop persistent joint inflammation, which would prompt the initiation of MTX therapy with the intent to prevent development of structural damage. The panel members based their decisions on extensive clinical experience and knowledge of the clinical trial evidence on which RA therapeutic management strategies are based.

The individual factors were classified into domains, and, within the domains, key categories were identified. The relative weights of the individual variables were assessed using decision-science theory and employing decision-support computer software (www.1000minds.com). This computer program performed comparisons of all possible pairs of individual factors, allowing each panel member to vote on which pair was more likely to prompt a decision to initiate MTX therapy. Using this method, the relative contribution of each variable was assigned a score from 0 to 100, with 100 representing the greatest likelihood of an association between a given variable and the decision to initiate MTX therapy. Subsequently, factors that contributed equally were combined, and other variables that contributed little to this decision were eliminated. Comparison of pairs of the remaining factors was repeated, using the

decision-support computer software, and the resulting weighted scores of each of the final variables, which were grouped into four domains, were converted to a scale of 0–10 and rounded to a minimum point difference of 0.5 [5, 7].

Phase III: consolidating phases I and II

In the final phase of developing new classification criteria for RA, the results of phases I and II were consolidated. The goal of the entire process was to create a scoring system that could be applied reliably to patients with inflammatory arthritis, early in the course of disease, to predict which would go on to develop persistent and/or erosive disease. Thus, an optimal cut-off point at which a patient would be classified as having definite RA had to be determined. The scoring system and criteria must be able to be applied repeatedly, as some patients with inflammatory arthritis who may not yet be classifiable as having RA early in their disease course might subsequently be classified as having definite RA after their disease had progressed. The same criteria must also be appropriate for use in patients who present later in their disease course and are receiving treatment. However, although these new criteria were designed to classify patients as having RA, they were not intended to distinguish among patients with RA as to the severity of their disease [5].

To establish a cut-point above which a patient would be classified as having definite RA, a two-step approach was used. First, a consensus-based approach based on clinical experience was employed. Subsequently, this cut-point was validated using data from three additional cohorts of patients with undifferentiated inflammatory arthritis.

As in phase II, the expert panel of rheumatologists was asked to assess a different set of case histories of patients with inflammatory arthritis at various stages of disease to address two questions: (i) would treatment with MTX or another DMARD be initiated because of concern for the patient's risk of developing persistent or erosive inflammatory RA? and (ii) would the patient be appropriate to enter into a clinical trial of a new investigational biologic therapy for RA? Each patient was scored using the scoring system developed in phase II. Based on ranking the case scenarios according to the answers to these two questions, the mean cut point at which the cases changed from probable to definite was determined by consensus to be 65.7 (based on the 0–100 scale; range 60.0–70.3). Thus, on the scale of 0–10, a score of $\geqslant 6$ was considered to be consistent with a definite diagnosis of RA.

This cut-off point was verified by applying the new scoring system to data collected from three cohorts of patients with undifferentiated inflammatory arthritis that had not been used in phase I: one each from France, Norway and the Netherlands. The data were sorted according to which patients had received treatment with MTX or another DMARD or with a targeted biologic agent. In these cohorts, the score that differentiated those patients who received treatment for the ultimate diagnosis of RA from those who did not was in the same range (between 60 and 70) as that determined by the expert panel [5].

The 2010 RA classification criteria: domains, categories and point scores

The 2010 ACR/EULAR RA classification criteria (Table 2) [5] are intended to be applied to patients who present with definite swelling of at least one joint on clinical examination, for whom another diagnosis (e.g. SLE, PsA, gout) does not better account for the synovitis.

Because the presence of a bony erosion indicates that structural damage already has occurred, appropriate patients in whom an erosion characteristic of RA is already evident on plain radiographs are classified as having RA without applying the scoring system. Patients with long-standing disease need not have actively swollen joints to be diagnosed as having RA. If retrospective data indicate that such patients previously fulfilled the 2010 RA classification criteria, those patients may be classified as having RA regardless of whether or not they are currently receiving treatment [5]. The process by which definite RA is classified can also be illustrated as a tree algorithm (Fig. 1) [5].

Key differences between 1987 ARA criteria and 2010 ACR/EULAR criteria

In the 1987 ARA RA classification criteria, seven discrete criteria are considered. This classification system specifies that patients satisfying at least four of the seven criteria should be considered as having RA. Radiographic changes, including bony erosion and periarticular osteopenia, that constitute one of the seven criteria are not present among patients with the earliest stages of disease that are most amenable to therapeutic intervention. The only laboratory abnormality included in these classification criteria is the presence of circulating RF. Thus, patients who have circulating ACPAs but no circulating RF may not satisfy the 1987 ARA criteria. These criteria place significant weight on the presence of arthritis involving hand joints, symmetrical joint involvement and the presence of rheumatoid nodules; these features may not be present at very early stages of RA disease activity.

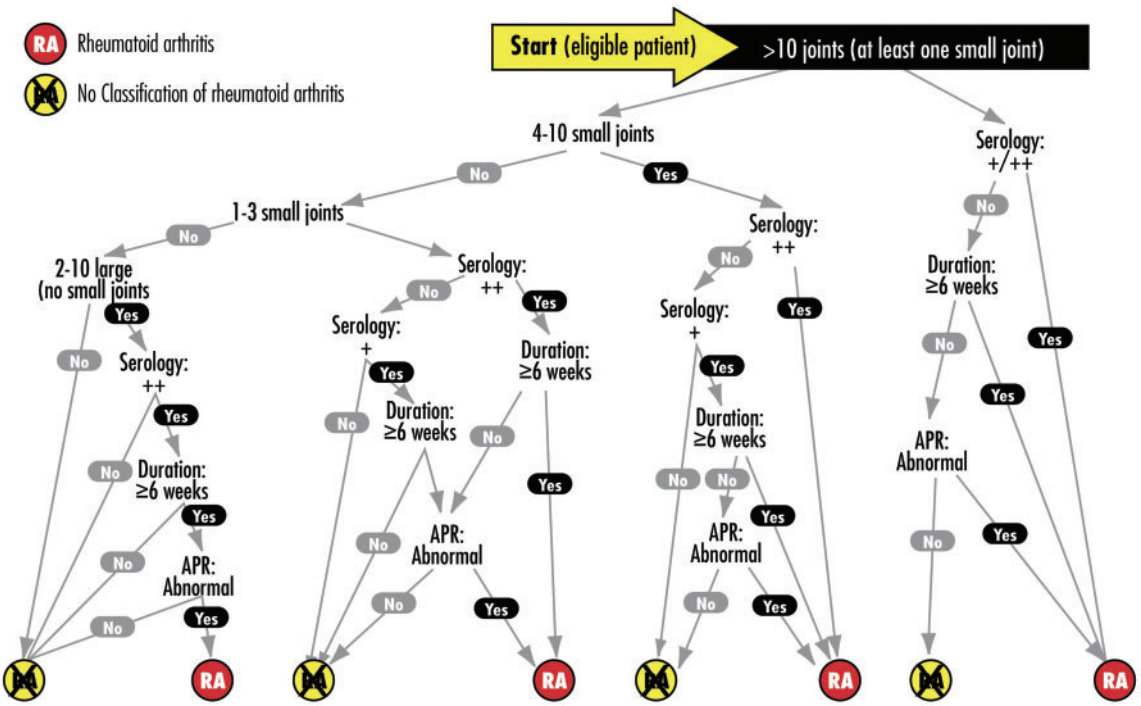
Because multiple potential variables were considered and weighted using decision-science theory during the formulation of the 2010 ACR/EULAR RA classification criteria, these new criteria place more emphasis on laboratory values, including serological biomarkers and acute-phase reactants. In contrast to the 1987 ARA classification criteria, circulating ACPAs are considered in addition to circulating RF; the presence of either of these serological biomarkers in high titre (more than three times the upper limit of normal) contributes additionally to the scoring system. Elevated concentrations of acute-phase reactants, either ESR or CRP, are also included as a separate domain. Although symmetry of joint involvement, duration of morning stiffness and the presence of rheumatoid nodules were initially considered

Table 2 2010 RA classification criteria: domains, categories and point scores [5]

Domain	Category	Point score
A	Joint involvement (0–5 points)[a]	
	1 large joint	0
	2–10 large joints	1
	1–3 small joints (large joints not counted)	2
	4–10 small joints (large joints not counted)	3
	>10 joints including at least one small joint	5
B	Serology (at least one test needed for classification; 0–3 points)[b]	
	Negative RF and negative ACPA	0
	Low positive RF or low positive ACPA	2
	High positive RF or high positive ACPA	3
C	Acute-phase reactants (at least one test needed for classification; 0–1 point)[c]	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D	Duration of symptoms[d]	
	<6 weeks	0
	⩾6 weeks	1

The points from each of domains A through D are added and the sum is considered to be the total score. A total score of ⩾6 is needed to classify a patient as having definite RA. [a]Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. DIP joints, first CMC joints and first MTP joints are excluded from assessment. Large joints refers to shoulders, elbows, hips, knees and ankles. Small joints refers to MCP joints, PIP joints, second through fifth MTP joints, thumb IP joints and wrists. [b]Negative means less than or equal to the upper limit of normal (ULN); low positive means >ULN; high positive means >3× ULN. [c]Normal and abnormal are determined by local laboratory standards. [d]Duration of symptoms as per patient's self-report. Table adapted from Ref. [5] with permission of John Wiley and Sons Ltd.

Fig. 1 Tree algorithm for classifying definite RA (red circles) or for excluding its current presence (yellow circles) [5].



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by the expert panel of rheumatologists during the consensus-driven process, none of these factors (which were included among the 1987 criteria) had positive predictive value of enough weight to be included in the 2010 ACR/EULAR RA classification criteria.

The initial impetus to create new RA classification criteria was to be able to include patients at the earliest stages of disease who might benefit the most from the initiation of effective therapy to prevent development of structural damage. Thus, the 2010 ACR/EULAR RA classification criteria do not include evidence of structural damage as one of the diagnostic criteria and expand the applicability of these criteria to patients with disease of <6 weeks duration. However, the ultimate assessment of these new RA classification criteria remains to be determined by applying them prospectively to cohorts of patients with early inflammatory arthritis and observing whether initiating effective treatment in patients meeting these criteria successfully reduces disease activity, prevents joint destruction and preserves physical function.

Rheumatology key messages

- A joint ACR/EULAR working group developed new criteria to facilitate diagnosing RA earlier.
- Structural damage is not part of the ACR/EULAR RA classification criteria.
- The RA classification criteria are applicable to patients with disease of <6 weeks' duration.

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