Rheumatoid Arthritis Classification Criteria
It’s Finally Time to Move On!

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Abstract
The diagnosis of rheumatoid arthritis (RA) is often challenging, due to a wide spectrum of presentations, progressive changes in disease course over time, and, perhaps, most importantly, lack of a clinical or laboratory gold standard to define the presence or absence of disease. Several attempts at the creation of RA classification criteria have been undertaken; however, each time, there have been significant limitations in applying these criteria to the clinical setting. Several components of the 1987 RA criteria require the presence of established joint damage; thus, they were limited in their ability to identify patients with early disease, potentially delaying initiation of early aggressive therapy until irreversible damage had occurred. With the recognition that early, aggressive therapy has the potential to decrease RA-associated morbidity and significantly alter disease course, there is clearly a need for criteria that also will facilitate early diagnosis and encourage initiation of therapy through disease modifying drugs (DMARDs). This mission recently has been taken on by a combined task force composed of membership from both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), the outcomes of which are discussed below.

Unlike other chronic diseases, such as hypertension and diabetes, there is no gold standard for the diagnosis of RA. Clinical diagnosis often relies on the overall opinion of the evaluating clinician, whose “gut” feeling or general “gestalt” of a disease pattern must be derived from clinical and personal experience. It is, thus, not surprising that attempts to create criteria that replicate the process of diagnostic evaluation must embrace multiple components, including patient history, symptom elicitation, physical examination, and selective supporting laboratory and radiographic data.

History of RA Classification Criteria
Classification criteria for RA were first proposed, in 1956, and ultimately adopted and published by the American Rheumatism Association (ARA) in 1958. This initial publication concluded with the statement, “The criteria should be reviewed in two to three years and revised as necessary.” As the 1958 criteria included a number of histological features that were not applicable in clinical practice, this domain was subsequently excluded, thus making the criteria more applicable for use in epidemiological studies. While the 1958 criteria separated patients into possible, probable, definite, and classic RA, the revision, known as the New York Criteria, was produced, in 1967, but the criteria were poorly received due to lack of a defined cut-point for definite cases of RA. The next set of criteria was initially assembled by a committee of the ARA, now the American College of Rheumatology (ACR), in 1987, and developed by a panel of leaders in the field of rheumatic disease. This group endeavored to create a list of criteria on which the first evidence-based validations were performed, as the advent of modern clinical trials required development of stringent classification criteria to assure patients enrolled in randomized controlled trials could be fairly compared.

Limitations to the Current RA Classification Criteria
A major challenge to the development of RA classification criteria has stemmed from the need to include information from varied domains, including patient history and health...
status, physical examination and physician assessment, appropriately supplemented by laboratory and imaging studies. Though honest attempts were made to develop evidence-based criteria derived from actual RA patient cohorts for the criteria set, in 1987, it soon became clear there were significant limitations to the use of these criteria with respect to both sensitivity and specificity. Sensitivity was potentially limited by the requirement that patients meet criteria from three of the four domains discussed above, thereby excluding those with very strong evidence in only one or two, such as the presence of severe bilateral synovitis in a seronegative patient who has not yet developed radiographic changes.

The data used to develop the 1987 ARA criteria relied upon a cohort of tertiary care referrals with, on average, 7 years’ disease duration; control cases from these clinics were generally subjects with established diagnoses other than RA,7 such as systemic lupus erythematosus or osteoarthritis.3 This resulted in decreased sensitivity for detection of early disease as well as overestimating specificity of the diagnostic criteria. Subsequent evaluation of the performance of the 1987 criteria, compared with the earlier 1957 criteria, demonstrated that, although the newer criteria were generally better at predicting those who would progress to more severe disease, their sensitivity, especially in earlier disease, was quite limited.6 These observations were confirmed in other studies, again demonstrating good performance of the 1987 criteria in established disease7 but limited sensitivity for detection of early RA.8-15

**Current RA Biomarkers**

For decades, rheumatoid factor (RF), IgG, IgA, and IgM auto-antibodies directed against the Fc portion of IgG have been considered the primary serologic marker for the diagnosis of inflammatory arthritis.5 Acute phase reactants, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are markers of inflammation that are not specific for RA; nonetheless, they have proven to be the best validated biomarkers to date. Though elevations in one or both can be helpful, their ubiquitous nature in many inflammatory states, as well as their absence in as many as 40% of patients with active RA,16 prevents them from becoming a gold standard for the diagnosis of RA.

The recent advent of highly specific biomarkers for RA, not available at the time the 1987 criteria were developed, offers a significant opportunity to classify patients with RA early in the disease process. Anti-citrullinated protein antibodies (ACPA), most commonly measured by commercial assays for antibodies against cyclic citrullinated peptides (anti-CCP), have been identified as important for both the diagnosis17,18 and subsequent prognosis in RA.19 Although the presence of anti-CCP Abs (antibodies) offers better specificity than RF (95% to 97% vs 65% to 75%), the two tests have similar sensitivity for diagnosis, with minimal benefit gained from the combination of the two in established RA.20 However, there is evidence, especially in subjects with very early or undifferentiated arthritis, that use of both RF and anti-CCP testing can improve diagnostic specificity with a minimal loss of sensitivity.20 Nonetheless, up to 30% of RA patients do not have usual biomarkers of RF, anti-CCP, elevated ESR, or CRP.16,21 Thus, a significant population of patients with RA will be missed if too much attention is focused on current clinically available biomarkers.

**New RA Criteria: Why Now?**

As discussed above, the 1987 RA criteria perform poorly in early disease.6,15 At the time of their development, the accepted paradigm for treatment of RA was the “pyramid approach” or “start low and go slow,”22 and therapeutic options were limited. For standards of practice at the time, they were deemed appropriate.

Over the past two decades, the therapeutic “pyramid” for RA has been inverted. The benefits of early aggressive therapy have been confirmed to improve clinical outcomes as well as disease-associated morbidity23,24 and, potentially, mortality25 in several well-designed randomized controlled trials (RCTs). Similarly, because most RA patients in the United States are referred from primary care physicians, it is essential that diagnostic criteria facilitate early referral to rheumatologists.26

With the introduction of many new effective therapies over the past decade, it is imperative that subjects who will develop more severe disease be identified as early as possible to have the opportunity to receive aggressive therapy. The presence of anti-CCP Abs has been shown to identify a population at increased risk for aggressive, erosive disease27; thus, potentially identifying those most likely to benefit from this early aggressive therapy.

In addition to disease duration,28 markers that predict persistently active disease include involvement of small joints, presence of anti-CCP Abs,29 and a combination of markers.30 The presence31-34 and titer33,35-38 of anti-CCP Abs have been shown to predict higher disease activity and increased risk for radiographic progression. Importantly, the presence of anti-CCP Abs has been linked with an increased likelihood of disease remission following very early initiation of aggressive therapy, even in subjects with undifferentiated inflammatory arthritis.39

Although some may argue that early undifferentiated arthritis may remit in those subjects not yet meeting current RA criteria,40 an alternative view suggests that if a diagnosis of RA can be confirmed sufficiently early to allow institution of aggressive therapy, sustained remission may be attained in those who would have otherwise progressed to chronic disease. Our evolving understanding of RA pathobiology has suggested that we may be dealing with several different diseases, some more aggressive than others, with different genetic and environmental risk factors and perpetuating mechanisms.41 The role of novel biomarkers to facilitate identification of such individuals is likely to be a major component of future rheumatologic care.
In addition, there may be significant benefit in confirming a diagnosis of any inflammatory arthritis, even if not RA (i.e., psoriatic arthritis or seronegative arthritis, with predominantly peripheral joint involvement), as these subjects will also likely benefit from early aggressive therapy, if not just by assuring optimal care via early rheumatologic referral.

**2010 Diagnostic Criteria: Moving On**

The recently proposed RA classification criteria are not a new idea. In the early 1990s, several groups suggested re-evaluation of the 1987 criteria, noting poor performance of pain and morning stiffness domains. Suggested modifications included using the number of swollen-painful joints as well as the presence or absence of pain associated with squeezing metatarsal or metacarpophalangeal joints. Even with these proposed changes, diagnostic specificity still derived mainly from radiograph and serologic data. Some suggested using the 1987 criteria in a decision-tree format to improve sensitivity. To take advantage of newer biomarkers, others proposed a simple modification to the 1987 criteria, addition of anti-CCP Abs as a criteria or their inclusion to replace the much less common, but also highly specific nodules-erosions criteria.

With the above limitations in mind, a combined task force of experts from the ACR and European League Against Rheumatism (EULAR) collaborated to develop the combined ACR/EULAR classification criteria for the diagnosis of RA. The task force specifically sought to avoid the term “diagnostic criteria,” as their goal was the development of criteria to identify or “classify” those patients with early RA, as well as those at highest risk for persistent or erosive disease, those most likely to benefit from early aggressive therapy.

Generation of these criteria occurred in a three-phase process. In phase one, a data-driven regression model was applied to variables derived from a database of over 3000 patients with early inflammatory arthritis from nine early arthritis cohorts, to identify a short list of parameters that defined patients with RA by progression to initiation of DMARD therapy. In the second phase, a short list of variables from phase one was provided to a panel of 22 RA experts (11 each from ACR and EULAR) and applied to 30 clinical cases to identify and rate which performed best in identifying early disease. Finally, in the third phase, results from phases 1 and 2 were applied to a validation set consisting of three cohorts independent of the original nine cohorts of subjects. These results were utilized to generate cut points and a final scoring system to identify “definite” RA.

The new scoring system of the 2010 ACR/EULAR criteria, similar to prior criteria, includes four domains: symptom duration, number of joints involved, types of joints involved, and laboratory biomarkers of inflammation and autoimmunity. Results of this process are presented in Table 1. Although the new criteria may be suitable for the diagnosis of established RA, they are specifically intended for use in early disease, before joint imaging can reveal synovitis and erosions typical of RA. The question arises as to which components of the new criteria impart improved performance over the prior 1987 criteria. The advent of anti-CCP Ab testing over the last decade has allowed addition of this marker to the current iteration, providing the opportunity to increase diagnostic specificity, especially in early RA.

Weighting for an increased number of involved joints was also added, a characteristic consistently shown to identify those at higher risk for the development of chronic, persistent inflammatory arthritis. Interestingly, the traditionally held and previously identified observation of a symmetric pattern of joint involvement did not bear out in the above

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**Table 1 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Joint Involvement</th>
<th>Serology</th>
<th>Duration</th>
<th>Acute Phase Reactants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Large joint (0 points)</td>
<td>Negative RF and CCP (0 points)</td>
<td>Less than 6 weeks (0 points)</td>
<td>Abnormal ESR or CRP (1 point)</td>
</tr>
<tr>
<td>2-10 Large joints (1 point)</td>
<td>Low titer positive CCP or RF (2 points)</td>
<td>6 or more weeks (1 point)</td>
<td></td>
</tr>
<tr>
<td>1-3 small joints (2 points)</td>
<td>High titer CCP or RF (3 points)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10 small joints (3 points)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 10 joints (with at least one small joint) (5 points)</td>
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</table>

**Total Possible Points**

5 3 1 1

Patients receive the highest point level for each domain: 6 points is defined as definite RA, though those with lower scores may obtain more points with time and subsequently be defined as having RA.
process and was not included in the current criteria, as it was not predictive.49 Similarly, morning stiffness also was not identified in the above process and was not included in the updated classification criteria.48

Old Before Their Time: Novel Diagnostic Modalities

Even as the new ACR/EULAR RA criteria are being published, the next generation of laboratory and imaging biomarkers is being developed. Diagnostic ultrasound and magnetic resonance imaging (MRI) have been shown to identify early synovitis, even before it can be detected by clinical exam,52 and erosions, well before they are evident by conventional radiography.53 Similarly, the next generation of RA biomarkers is aggressively being pursued. The identification of ACPA specificity (beyond anti-CCP Abs, including other citrullinated peptides) is expected, ultimately, to result in the ability to further sub-phenotype RA patients. As the newly proposed RA criteria are designed not only to identify subjects with RA but also those more likely to develop aggressive disease, there is a potential for novel biomarkers, including markers of bone and joint breakdown,54-58 circulating cytokines,59,60 and additional autoantibody specificities61,62 to impart further improved prediction of disease outcome.

Finally, questions remain as to when the pathophysiologic process underlying RA begins, and at what point it can be stopped.63 Can we use novel imaging or laboratory biomarkers to diagnose RA in the earliest or even preclinical phase of autoimmunity? Both the presence of anti-citrulline autoimmunity64-66 and upregulation of serum cytokines67 occur well before onset of clinical disease. This suggests a preclinical phase of disease potentially amenable to intervention, as has been demonstrated in very early inflammatory arthritis,37,66-71 including subjects not yet meeting 1987 diagnostic criteria for RA.

A New Era in Treatment Approach to RA?

Do the new criteria usher in a new era in the approach to the diagnosis and treatment of RA? Clearly one of the explicit goals of the ACR/EULAR task force was to facilitate early identification, referral, and treatments, but is this just the first step towards a new paradigm, whereby very early aggressive therapy becomes a true standard of care? Observational trials of community rheumatologists have demonstrated that nearly 50% of practicing rheumatologists initiate therapy only after fulfillment of the 1987 ACR criteria.72 Similarly, in a study of over 10,000 persons coded as having RA by a non-rheumatologist, only 27.3% consulted a rheumatologist within the next 3.5 years. The median time to rheumatology consultation was 79 days,73 perhaps due to physician expectations of established diagnosis before considering referral for initiation of aggressive therapy. It is hoped that the new criteria will encourage earlier identification and referrals to rheumatologists, so that subjects may obtain treatment within the “window of opportunity” for early intervention.

Though the new criteria are clearly a major step forward in identification of early RA, they also may be a first step towards even more aggressive screening of community populations for preclinical RA, especially in settings such as first degree relatives of patients74 and subjects with persistent musculoskeletal complaints at community health fairs.75 Given the specific prognostic value of anti-CCP testing, a paradigm can be envisioned in which those at very high genetic risk or with early or very mild joint complaints could be screened by anti-CCP Abs or the next generation of biomarkers at a primary care or community level. The hope would be that such interventions could produce sustained and even treatment-free remissions, as well as potentially open a new window for preventative rheumatology, either with conventional immune modulation or novel tolerizing immunotherapies.76,77

Of course, no actions in medicine are without potential limitations. As is the case with any dramatic improvement in diagnostic sensitivity, there is a potential for a corresponding loss of specificity. In the case of the new RA criteria, there is a risk that those who would never progress to persistent or destructive RA may be prematurely classified and, thus, exposed to unnecessary and potentially toxic therapies. Though, clearly, the data-driven process carried out by the ACR/EULAR task force has attempted to avoid this scenario, there will inevitably be the potential for over diagnosis. Finally, though there are clear data that the presence of Anti-CCP Abs are associated with development of severe, persistent, and destructive RA,29,78 it would be a shame to overvalue the presence of anti-CCP or RF Abs and miss the seronegative population, a group demonstrated much more likely to achieve treatment-free remission following early DMARD therapy.78

Conclusions

It is clear that the 1987 ACR RA classification criteria, while highly specific for established RA, are limited in their sensitivity to identify early disease. With current understanding of the importance of early aggressive therapy for prevention of disease-associated morbidity and new tools that may allow stratification of risks for severe persistent disease, the time has come for development of new criteria to facilitate major advances in RA management. The recently published ACR/EULAR criteria48 are a major step forward in this direction. Given the pace of scientific investigation in the field of RA, it is hopeful that the next revision of these guidelines will occur well before another 23 years of scientific advances have passed.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.
References


