

The Need to Better Classify and Diagnose Early and Very Early Rheumatoid Arthritis

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ABSTRACT. Early rheumatoid arthritis (RA) and very early RA are major targets of research and clinical practice. Remission has become a realistic goal in the management of RA, particularly in early disease. The 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA classification criteria, the EULAR treatment recommendations for RA, and the EULAR recommendations for the management of early arthritis focus on early disease and translate the knowledge related to early RA into classification and management. Nevertheless, there is a need for further improvement and progress. Results from 6 recent studies are summarized, evaluating the performance of the 2010 ACR/EULAR RA classification criteria. The data show a significant risk of misclassification, and highlight that overdiagnosis and underdiagnosis may become important issues if the criteria recommend synthetic and biological disease-modifying antirheumatic drugs. Therefore, some considerations are presented on how the current problems and limitations could be overcome in clinical practice and future research. A consensus is needed to better define the early phase of RA and differentiate from other early arthritis. The possible effect of misclassification on spontaneous and drug-induced remission of early and very early RA awaits further elucidation. Such research will eventually lead to more reliable diagnostic and classification criteria for new-onset RA. (J Rheumatol First Release Dec 15 2011; doi:10.3899/jrheum.110967)

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EARLY RHEUMATOID ARTHRITIS
UNDIFFERENTIATED ARTHRITIS
2010 ACR/EULAR RHEUMATOID ARTHRITIS CLASSIFICATION CRITERIA

VERY EARLY RHEUMATOID ARTHRITIS
MISCLASSIFICATION

With the advent of more effective treatment strategies — early treatment, disease-modifying antirheumatic drug (DMARD) combinations, tumor necrosis factor- α inhibitors, and tight control — remission has become a realistic goal in the management of rheumatoid arthritis (RA), particularly in early disease. Thus, for some time diagnosis and treatment of early RA (ERA) and very early RA (VERA) have been major targets of research and clinical practice. The goal of the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria is to identify RA among newly presenting patients with undifferentiated inflammatory synovitis. The criteria focus on features at earlier stages that are associated with persistent and/or erosive disease¹. The EULAR treatment recommendations for RA similarly state that treatment with DMARD should be started as soon as the diagnosis of RA is made and should aim for remission or low disease activity². Further, EULAR recommendations were formulated to improve the management of early arthritis (EA)³. The recommendations represent advances in turning the present knowledge related to early RA

into scientific and practical reality. Nevertheless, there is a need for further improvement and progress. The questions: Is there a risk of misclassification and consequently overtreatment with aggressive therapy in ERA? Which future practices may overcome current problems and limitations?

ERA. Interest in the early symptoms of RA goes back to the 1940s, when several authors made the distinction between the “typical” form of disease characterized by a slow and insidious onset and progressing course, and several “atypical” forms, which are further distinguished according to the mode of onset: acute start in small joints, acute start in large joints, asymmetrical joint symptoms, low sedimentation rate, arthralgic symptoms, and uncharacteristic symptoms⁴. At that time, RA was considered a nonspecific syndrome that could be triggered by many diverse etiological factors such as psoriasis, urethritis, and ulcerative colitis⁵. Prompted by the discovery of the association of RA with the rheumatoid factor (RF), it was apparent that many seronegative patients are clinically and radiographically quite different from patients with seropositive RA. The idea that these seronegative arthritides were, in fact, entirely separate entities was mirrored by the Nomenclature and Classification of the Rheumatic Diseases proposed by the American Rheumatism Association in 1963⁶. In that classification, RA, juvenile Still’s disease, ankylosing spondylitis, psoriatic arthritis (PsA), and Reiter’s syndrome

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were classified under separate headings with the common denominator “polyarthritis of unknown origin.”

The introduction of early arthritis clinics since the 1980s provided much information regarding EA, described factors predicting persistence and prognosis in ERA, and continued to show that the diagnosis of RA is often challenging, most importantly due to lack of a clinical or laboratory gold standard^{7,8,9}. The construct of ERA and each component of the definition (i.e., “early” and “RA”) has an indeterminate aspect, especially as the criteria for diagnosing RA are based on established disease¹⁰. The duration for ERA and VERA in the literature varies widely: for ERA, 2–3 years, and for VERA, 6 weeks to 3 months. The working group of the 2010 RA classification scheme, although not developed as criteria for ERA, used data from early arthritis clinics and designed the study to earlier identify that subset of patients who are at sufficiently high risk of persistent and/or erosive disease as to be considered for intervention with DMARD and classified as having RA¹. Conversely, following this current model underlying the disease construct “RA,” one may conclude that self-limiting and nonerosive arthritis is not RA. Undifferentiated arthritis (UA) and EA fall mostly into this category, but with variability in the extent of joint involvement and disease duration overlapping with RA. Most importantly, as known for some time and shown again recently, early and very early UA is usually RF-negative (49% to 75% and 91%, respectively) and anticitrullinated protein antibody (ACPA)-negative (71% to 76% and 90%)¹¹. Most of the patients with seronegative EA will never develop RA, although no doubt there are patients with otherwise typical RA who are seronegative. On the other hand, numerous studies have shown that positive RF and ACPA have a very high prognostic value for the development from EA and very early arthritis to RA¹².

Risk of misclassification and overuse of aggressive therapy. Six recent studies reported the performance of the 2010 RA classification criteria in prospective EA cohorts (symptom duration < 1 year to < 2 years), in a very early arthritis cohort (seen within 3 months of the onset of any symptom), and in undiagnosed subjects with joint symptoms (median duration of symptoms 18 weeks)^{13,14,15,16,17,18}. The characteristics of these studies vary considerably as do the reported evaluation measures (Table 1). Only the sensitivities and specificities are available from all studies and may give a comparative overview of the performance of the 2010 RA classification criteria. Overall, patients with ERA and VERA are identified in 58%–91% and 62%–74%, respectively, a rather unsatisfactory result in view of the fact that the new criteria were developed to facilitate the early recognition of RA. Most importantly, because of the low specificities (47%–60% and 66%–78%, respectively), up to half and one-third of the patients may be misclassified as having ERA and VERA, respectively. These data highlight that overdiagnosis and underdiagnosis may become important issues if the criteria recommend use of synthetic and biological DMARD. Cader,

et al in their study of patients with VERA suggested that the 2010 RA classification criteria will allow more rapid identification of patients requiring methotrexate (MTX) compared with the 1987 criteria if applied at baseline, but that misdiagnosis may become significant if these criteria are used to direct treatment within the phase when treatment makes the greatest difference — the first 3 months after symptom onset¹⁴. Recently Britsemmer, *et al* reported that 51% of ACR/EULAR “non-RA” patients compared to 86% of patients with RA were treated with MTX in the first year, suggesting that the rheumatologists in their clinic had a more aggressive approach to EA during the same period than the rheumatologists treating the cohorts that were used to derive the criteria¹⁷. Obviously, MTX is neither a “gold standard” for RA nor a static feature, as rheumatologists have a tendency to treat earlier and more aggressively.

In addition to misclassification and unjustified treatment, there are other potential problems with the new criteria. For example, how does defined erosiveness typical for RA according to the 2010 criteria lead to the diagnosis of RA? How reliable is it to compare RF tests done using different methods or different isotypes? Is it reliable to use tender joints equal to swollen joints? What tests have to be done before applying these criteria to patients with arthritis not otherwise explained?

Future directions. Classification criteria serve to define disease groups for clinical and epidemiologic research, facilitate selection of similar patients for clinical trials, and allow for comparison of results across studies¹⁹. If the criteria are not valid, participants without disease may be included in disease groups in studies, and participants with clear-cut disease may be excluded. Thus, the validity of classification criteria is critical to the ability to understand and treat rheumatic diseases. Validation of criteria sets for diagnostic purposes usually requires very high specificity with good sensitivity. By comparison, validation of criteria sets for use in clinical trials and epidemiologic studies requires a balance of sensitivity and specificity¹⁹. It has been argued that disease and classification criteria represent a continuum because every set of disease criteria is created as a classification and has the potential of becoming diagnostic if it has sufficient internal and especially external validity²⁰. Accordingly, a diagnosis is, in fact, making a classification in an individual patient. Different possibilities may exist to address some of the problems and overcome the limitations of the new RA classification criteria to classify and diagnose ERA and VERA in clinical practice and research by using expert opinion and generating future evidence (Table 2)^{21,22}.

In clinical practice, the rheumatologist as the expert can balance between possible or probable RA, depending on the level of confidence. Recently, when using a diagnostic certainty scale at baseline (0 to 100 visual analog scale), all the patients with a score > 75 at their inclusion in an EA cohort subsequently received a diagnosis of RA with, as a gold stan-

Table 1. Studies evaluating the performance of the 2010 ACR/EULAR rheumatoid arthritis classification criteria^{13,14,15,16,17,18}.

Study Characteristics	Patients, n	Symptom Duration	Followup	Remarks
van der Linden ¹³	2258	< 2 years	1 yr for initiation of MTX or any DMARD therapy, 5 yrs for persistent arthritis	Population-based prospective cohort
Kaneko ¹⁵	313	Median 18 wks (range 1-1040)	Interval between first visit and the time of diagnosis, median 2 wks (range 1-40)	Retrospective single-center observational study
Varache ¹⁶	270	< 1 yr	2 yrs	Prospective observational cohort of patients with early arthritis from 1995 to 1997 in 7 hospitals in Brittany, France
Britsemmer ¹⁷	455	< 2 yrs	At least 12 mo	Ongoing prospective cohort of early arthritis at the Jan van Breemen Institute, Amsterdam, Netherlands
Alves ¹⁸	231	≤ 12 mo	12 mo	Ongoing, prospective, inception cohort study in the greater Rotterdam area (set up July 2004), patients who were included from 2000 onwards
Cader ¹⁴	265	< 3 mo	18 mo	Rapid access early inflammatory arthritis clinic at Sandwell and West Birmingham Hospitals NHS Trust, UK
Evaluation Parameters	Sensitivity and Specificity	Predictive Values	Likelihood Ratio (LR)	Area Under the Curve
van der Linden ¹³	+			+
Kaneko ¹⁵	+	+	+ (only positive LR)	
Varache ¹⁶	+	+		+
Britsemmer ¹⁷	+	+	+	+
Alves ¹⁸	+	+		+
Cader ¹⁴	+	+	+	
Results		Sensitivity, %	Specificity, %	
2010 ACR/EULAR RA classification criteria*		87-97	Not Tested	
Early arthritis				
van der Linden ¹³		71-84	60-74	
MTX initiation		84	60	
DMARD initiation		74	74	
Persistent disease		71	65	
Kaneko ¹⁵				
DMARD initiation		73.5	47.1	
Varache ¹⁶		58	86	
Britsemmer ¹⁷		85-91	21-50	
MTX within 1 yr		85	50	
Expert opinion		90	48	
Erosive disease at 3 yrs		91	21	
Alves ¹⁸		69-74	66-72	
MTX use		74	66	
Persistent disease		69	72	
Very early arthritis				
Cader ¹⁴		62-74	66-78	
At baseline				
MTX initiation		68	72	
DMARD initiation		62	78	
During followup				
MTX initiation		74	66	
DMARD initiation		68	73	

* Validation of the final criteria set with 3 independent cohorts that were not used in the identification of factors from phase 1. MTX: methotrexate; DMARD: disease-modifying antirheumatic drug; NHS: British National Health Service; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; RA: rheumatoid arthritis.

Table 2. Proposals to advance the classification and diagnosis of early and very early rheumatoid arthritis in clinical practice and to overcome the problems and limitations of the 2010 ACR/EULAR RA classification criteria.

Setting	Proposals
Clinical practice	The rheumatologist as the expert strikes a balance between possible or probable RA, depending on the level of confidence Replacement of rheumatoid nodules with ACPA as a criterion in the 1987 ACR classification criteria The rheumatologist uses a diagnostic certainty scale at baseline (0 to 100 visual analog scale) Instead of RA, use of “undifferentiated arthritis” (UA) as the diagnostic term until the accurate diagnosis after followup Use of the prediction rule developed by van der Helm-van Mil, <i>et al</i> ²⁷ to estimate the chance of progression to RA in individual patients presenting with UA Use of imaging techniques (sonography, MRI) to identify erosions earlier
Future research	Discriminative value of HLA-B27 and diagnostic programs for reactive arthritis Definition of exclusion criteria, e.g., not fulfilling classification criteria for PsA and for peripheral SpA Testing with the “classification tree” method Testing likelihood ratios for diagnostic decision-making based on the Bayesian approach Automated, multiplex biomarker assay testing for autoantibodies, cytokines, and bone-turnover products

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; RA: rheumatoid arthritis; ACPA: anticitrullinated protein antibodies; MRI: magnetic resonance imaging; PsA: psoriatic arthritis; SpA: spondyloarthritis.

dard, satisfaction of the 1987 ACR criteria at the 2-year visit²³. In another study, the replacement of rheumatoid nodules with ACPA as a criterion in the 1987 ACR classification criteria increased the sensitivity (87% vs 82%) without losing specificity (95.6% vs 95.6%) in ERA patients who had a disease duration ≤ 2 years²⁴. An outcome study of EA reflecting the patient population seen by rheumatologists in everyday practice (symptom duration < 1 year) assessed levels of agreement between a diagnosis of RA recorded by an office-based rheumatologist at inclusion, then 2 and 10 years later²⁵. Agreement between the baseline diagnosis and the final diagnosis was low. Therefore, Fautrel, in an editorial, favored other diagnostic terms such as “persistent arthritis” and “erosive arthritis” until the accurate diagnosis after followup²². The problem with the term “persistent arthritis” is that it can only be used in retrospect after 1–2 years have passed. Also, “erosive arthritis” is not a term to be used before RA can be diagnosed, since erosive arthritis leads to the diagnosis of RA directly, according to the 2010 criteria. Therefore, the term “UA” should be favored to stress the preliminary diagnosis and various possible outcomes: early stage of a defined arthritis that will meet criteria in time, a *forme fruste* or partial form of a classifiable disease, an overlap of more than 1 disease entity, or an arthritis of unknown origin that may (or may not) become differentiated in the future²⁶. The term “UA” also encourages the physician to recognize the potential dynamic nature of inflammatory arthritis, which over time can persist as UA, progress to a specific diagnosis, or enter into remission, which implies the need for ongoing reevaluation.

The accuracy of a prediction rule developed to estimate the chance of progression to RA in individual patients presenting with UA was investigated in 3 cohorts of patients with disease duration between 4 weeks and 2 years²⁷. The prediction rule has an excellent discriminative ability for assessing the likelihood of progression to RA (classified according to the 1987 criteria) after ≥ 1 year of followup with positive predictive

values between 93% and 100% and negative predictive values between 83% and 86%. Moreover, the prediction rule is validated using data from early arthritis clinics in Germany, the United Kingdom, Canada, Russia, and Japan²⁸. The application of this rule will allow individualized treatment decision-making for patients with UA as long as the 2010 criteria are not improved to classify ERA and VERA.

In addition, modern imaging techniques (sonography, magnetic resonance imaging) not included in the 2010 criteria are very effective in identifying erosions and are increasingly performed in clinical practice to diagnose ERA and VERA^{29,30}. A study evaluating the use of ultrasound joint counts in the prediction of RA in patients with very early synovitis (duration ≤ 3 months) showed that by adding grey-scale and power Doppler scanning of metacarpophalangeal joints, wrists, and metatarsophalangeal joints to the 2010 criteria, more patients were classified as having RA, including several later classified as RA by the 1987 criteria, one with ultrasound erosions³¹.

There are also worthwhile targets for future research (Table 2). Remarkably, no appropriate clinical and laboratory measurements for spondyloarthritis (SpA) and reactive arthritis (ReA) were systematically recorded in the datasets selected for phase 1 of the 2010 RA criteria despite availability of tests for HLA-B27 and bacterial infections at the initiation of the EA cohorts³². Applying a comprehensive diagnostic program including HLA-B27 typing and microbiological testing for infective agents (*Chlamydia trachomatis*, *Yersinia enterocolitica*, pseudotuberculosis, *Borrelia burgdorferi*, *Campylobacter jejuni*), we have shown in a prospective 2-year survey of patients with EA (< 1 year duration) that the 1987 ACR criteria have a good diagnostic performance (sensitivity 90%, specificity 90%) for ERA³³. A population-based study in southern Sweden using such a comprehensive program diagnosed ReA and UA more frequently than RA³⁴. Therefore, it seems essential to include these diagnostic measurements into

datasets for development of future diagnostic and classification criteria, although the 3E Initiative in Rheumatology recommended not testing for ReA, and deemed that HLA-B27 typing was helpful only in specific settings³⁵. In addition, one may test if the application of evaluated classification criteria, such as not fulfilling classification criteria for PsA and for peripheral SpA, perform as exclusion criteria instead of leaving it to expert opinion whether the synovitis is not better explained by another disease. This may enhance the specificity of the 2010 ACR/EULAR criteria. Further, it would be worthwhile to reinvestigate the 2010 ACR/EULAR criteria with the “classification tree” method used for the 1987 ACR classification criteria, which yields a better accuracy than the traditional format (4 of 7 criteria) of the 1987 ACR classification criteria, especially in early disease³⁶. A tree format is available for the 2010 criteria: presence of synovitis is required (condition 1), followed by absence of a better alternative diagnosis (condition 2), and then by absence of erosions typical for RA (condition 3). Only patients meeting all 3 conditions are eligible for scoring. This tree format is therefore a prerequisite and does not change the results. The situation is different from the tree versus list versions of the 1987 ACR classification criteria, where the tree format is an alternative to the list format giving the lowest number of misclassifications³⁶. Finally, Corrao, *et al* suggested use of a statistically driven process to weight each criterion by likelihood ratios, instead of the formulation process of the 2010 criteria, based on a form of structured consent by expert opinion³⁷. Positive and negative likelihood ratios (and their 95% CI) could be computed for groups with similar criteria to help clinicians manage patients with EA effectively, using Bayesian reasoning. A totally new approach may be a very recently described highly reproducible, automated, multiplex biomarker assay testing for autoantibodies, cytokines, and bone-turnover products that can reliably distinguish between patients with early RA (< 6 months’ duration), those with other inflammatory arthritides (PsA, AS), and healthy individuals³⁸. The exploratory study provided high sensitivity (84.2%) and specificity (93.8%) in the diagnostic discrimination of RA, paving the way for future optimized classification and diagnosis.

Improvement of the accuracy of diagnosis and classification of ERA and VERA is a continuous challenge. The recent EULAR guidelines for the management of EA³, the multinational evidence-based recommendations on how to investigate and followup undifferentiated peripheral inflammatory arthritis³³, and the algorithm for identification of undifferentiated peripheral inflammatory arthritis³⁹ are steps forward to promote awareness among treating physicians of the importance of treating early and to improve patient outcomes. But the overriding risk of misclassification is that of overtreatment with potentially toxic agents (e.g., DMARD), even considering that poor recognition and inadequate intervention in the earliest phases of inflammatory arthritis may occur more

often. Therefore, a consensus is needed to better define the early phase of RA and differentiate it from other EA. A possible effect of misclassification on the “window of opportunity” hypothesis and on spontaneous and drug-free remission of ERA and VERA also awaits further elucidation⁴⁰. Such activities should lead to more reliable diagnostic and classification criteria for new-onset RA.

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