Review

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

HENNING ZEIDLER

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)

Key Indexing Terms:
EARLY RHEUMATOID ARTHRITIS VERY EARLY RHEUMATOID ARTHRITIS
UNDIFFERENTIATED ARTHRITIS MISCLASSIFICATION
2010 ACR/EULAR RHEUMATOID ARTHRITIS CLASSIFICATION CRITERIA

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 disease[1]. 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 activity[2]. 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 symptoms[4]. At that time, RA was considered a nonspecific syndrome that could be triggered by many diverse etiological factors such as psoriasis, urethritis, and ulcerative colitis[5]. 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 1963[6]. In that classification, RA, juvenile Still's disease, ankylosing spondylitis, psoriatic arthritis (PsA), and Reiter's syndrome

From Hannover Medical School, Hannover, Germany.
H. Zeidler, MD, Hannover Medical School.
Address correspondence to Prof. H. Zeidler, Wolfsburger Damm 26c, 30625 Hannover, Germany. E-mail: henningzeidler@aol.com
Accepted for publication September 24, 2011.

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 disease[10]. 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 RA[1]. 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 RA[12].

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 onset[14]. 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 criteria[17]. 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 studies[19]. 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 specificity[19]. 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 validity[20]. 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	Liklihood 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*[1]	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, *et al*[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 visit[23]. 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 years[24]. 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 later[25]. 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 followup[22]. 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 future[26]. 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 years[27]. 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 Japan[28]. 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 erosions[31].

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 cohorts[32]. 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 ERA[33]. A population-based study in southern Sweden using such a comprehensive program diagnosed ReA and UA more frequently than RA[34]. 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 settings[35]. 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 disease[36]. 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 misclassifications[36]. 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 opinion[37]. 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 individuals[38]. 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 EA[3], the multinational evidence-based recommendations on how to investigate and followup undifferentiated peripheral inflammatory arthritis[33], and the algorithm for identification of undifferentiated peripheral inflammatory arthritis[39] 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 elucidation[40]. Such activities should lead to more reliable diagnostic and classification criteria for new-onset RA.

REFERENCES

1. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-8.
2. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
3. Combe B, Landewé R, Lukas C, Bolosiu HD, Breedveld FC, Dougados M, et al. EULAR recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34-45.
4. Egelius N, Havermark NG, Jonsson E. Early symptoms of rheumatoid arthritis. Ann Rheum Dis 1949;8:217-9.
5. Moll JM, Haslock I, Macrae IF, Wright V. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies and Behcet's syndrome. Medicine 1974;53:343-64.
6. Blumberg B, Bunim JJ, Calkins E, Pirani CL, Zvaifler NJ. ARA nomenclature and classification of arthritis and rheumatism (tentative). Arthritis Rheum 1964;7:93-7.
7. Quinn MA, Emery P. Are early arthritis clinics necessary? Best Pract Res Clin Rheumatol 2005;19:1-17.
8. Aletaha D, Huizinga TW. The use of data from early arthritis clinics for clinical research. Best Pract Res Clin Rheumatol 2009;23:117-23.
9. Sokolove J, Strand V. Rheumatoid arthritis classification criteria — It's finally time to move on! Bull NYU Hosp Joint Dis 2010;68:232-38.
10. Mitchella KL, Pisetsky DS. Early rheumatoid arthritis. Curr Opin Rheumatol 2007;19:278-83.
11. van der Linden MP, Batstra MR, Bakker-Jonges LE; Foundation for Quality Medical Laboratory Diagnostics, Detert J, Bastian H, et al. Toward a data-driven evaluation of the 2010 American College of Rheumatology/European League Against Rheumatism criteria for rheumatoid arthritis: Is it sensible to look at levels of rheumatoid factor? Arthritis Rheum 2011;63:1190-9.
12. Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: A systematic literature review. Ann Rheum Dis 2006;65:845-51.
13. van der Linden MP, Knevel R, Huizinga TW, van der Helm-van Mil AH. Classification of rheumatoid arthritis: Comparison of the 1987 American College of Rheumatology criteria and the 2010 American College of Rheumatology/European League Against Rheumatism criteria. Arthritis Rheum 2011;63:37-42.
14. Cader MZ, Filer A, Hazlehurst J, de Pablo P, Buckley CD, Raza K. Performance of the 2010 ACR/EULAR criteria for rheumatoid arthritis: Comparison with 1987 ACR criteria in a very early synovitis cohort. Ann Rheum Dis 2011;70:949-55.
15. Kaneko Y, Kuwana M, Kameda H, Takeuchi T. Sensitivity and specificity of 2010 rheumatoid arthritis classification criteria.

Rheumatology 2011;50:1268-74.
16. Varache S, Cornec D, Morvan J, Devauchelle-Pensec V, Berthelot JM, Le Henaff-Bourhis C, et al. Diagnostic accuracy of ACR/EULAR 2010 criteria for rheumatoid arthritis in a 2-year cohort. J Rheumatol 2011;38:1250-7.
17. Britsemmer K, Ursum J, Gerritsen M, van Tuyl L, van Schaardenburg D. Validation of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: Slight improvement over the 1987 ACR criteria. Ann Rheum Dis 2011;70:1468-70.
18. Alves C, Luime JJ, van Zeben D, Huisman AM, Weel AE, Barendregt PJ, et al. Diagnostic performance of the ACR/EULAR 2010 criteria for rheumatoid arthritis and two diagnostic algorithms in an early arthritis clinic (REACH). Ann Rheum Dis 2011;70:1645-7.
19. Johnson SR, Goek ON, Singh-Grewal D, Vlad SC, Feldman BM, Felson DT, et al. Classification criteria in rheumatic diseases: A review of methodologic properties. Arthritis Rheum 2007;57:1119-33.
20. Yazici H. Diagnostic versus classification criteria — A continuum. Bull NYU Hosp Joint Dis 2009;67:206-8.
21. Zeidler H. How can misclassification be prevented when using the 2010 American College of Rheumatology/European League Against Rheumatism rheumatoid arthritis classification criteria? Comment on the article by van der Linden et al [letter]. Arthritis Rheum 2011;63:2544-6.
22. Fautrel B. Diagnosing early or rheumatoid arthritis. Which is better: expert opinion or evidence? J Rheumatol 2009;36:2375-7.
23. Benhamou M, Rincheval N, Roy C, Foltz V, Rozenberg S, Sibilia J, et al. The gap between practice and guidelines in the choice of first-line disease modifying antirheumatic drug in early rheumatoid arthritis: Results from the ESPOIR cohort. J Rheumatol 2009;36:934-42.
24. Zhao J, Liu X, Wang Z, Li Z. Significance of anti-CCP antibodies in modification of 1987 ACR classification criteria in diagnosis of rheumatoid arthritis. Clin Rheumatol 2010;29:33-8.
25. Morvan J, Berthelot JM, Devauchelle-Pensec V, Jousse-Joulin S, Le Henaff-Bourhis C, Hoang S, et al. Changes over time in the diagnosis of rheumatoid arthritis in a 10-year cohort. J Rheumatol 2009;36:2428-34.
26. Zeidler H, Merkesdal S, Hülsemann JL. Early arthritis and rheumatoid arthritis in Germany. Clin Exp Rheumatol 2003;21:S106-12.
27. van der Helm-van Mil AH, Detert J, le Cessie S, Filer A, Bastian H, Burmester GR, et al. Validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: Moving toward individualized treatment decision-making. Arthritis Rheum 2008;58:2241-7.
28. Huizinga TW, van der Helm-van Mil A. Quantitative approach to early rheumatoid arthritis. Bull NYU Hosp Joint Dis 2011;69:116-21.
29. Freeston JE, Wakefield RJ, Conaghan PG, Hensor EM, Stewart SP, Emery P. A diagnostic algorithm for persistence of very early inflammatory arthritis: The utility of power Doppler ultrasound when added to conventional assessment tools. Ann Rheum Dis 2010;69:417-9.
30. Boutry N, do Carmo CC, Flipo RM, Cotten A. Early rheumatoid arthritis and its differentiation from other joint abnormalities. Eur J Radiol 2009;71:217-24.
31. Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. Ann Rheum Dis 2011;70:500-7.
32. Funovits J, Aletaha D, Bykerk V, Combe B, Dougados M, Emery P, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Methodological report phase 1. Ann Rheum Dis 2010;69:1589-95.
33. Hülsemann JL, Zeidler H. Diagnostic evaluation of classification criteria for rheumatoid arthritis and reactive arthritis in an early synovitis outpatient clinic. Ann Rheum Dis 1999;58:278-80.
34. Söderlin MK, Börjesson O, Kautiainen H, Skogh T, Leirisalo-Repo M. Annual incidence of inflammatory joint diseases in a population based study in southern Sweden. Ann Rheum Dis 2002;61:911-5.
35. Machado P, Castrejon I, Katchamart W, Koevoets R, Kuriya B, Schoels M, et al. Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: Integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2011;70:15-24.
36. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
37. Corrao S, Calvo L, Licata G. The new criteria for classification of rheumatoid arthritis: What we need to know for clinical practice. Eur J Intern Med 2011;22:217-9.
38. Chandra PE, Sokolove J, Hipp BG, Lindstrom TM, Elder JT, Reveille JD. Novel multiplex technology for diagnostic characterization of rheumatoid arthritis. Arthritis Res Ther 2011;13:R102.
39. Hazlewood G, Aletaha D, Carmona L, Landewé RB, van der Heijde DM, Bijlsma JW, et al. Algorithm for identification of undifferentiated peripheral inflammatory arthritis: A multinational collaboration through the 3e initiative. J Rheumatol Suppl 2011 Mar;87:54-8.
40. Cush JJ. Early rheumatoid arthritis — Is there a window of opportunity? J Rheumatol Suppl 2007 Nov;80:1-7.