Classification criteria for rheumatoid arthritis and ankylosing spondylitis

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ABSTRACT

The history of classification and diagnostic criteria for rheumatoid arthritis (RA) and ankylosing spondylitis (AS) is similar and different. Important criteria sets have been published for both disease in the mid eighties, for AS in 1984 and for RA in 1987. The leading clinical symptoms, inflammatory back pain (IBP) in AS and the predominant polyarticular symmetric involvement of the hands in RA were, of course, central, and so was morning stiffness as a major clinical sign of an inflammatory disease state. In RA, there was more focus on laboratory parameters (rheumatoid factor), while this could have been the case also in AS (HLA B27) but this was not recognized at this point in time. In contrast, imaging has played a more important role in AS - especially because the sacroiliac joints are involved in the vast majority of AS patients, while in RA radiographic changes of the joints of hands and feet may contribute to the diagnosis. However, in both diseases, early structural changes visualized by conventionnal radiography rather have prognostic impact since these patients are much more likely to progress in comparison to others who do not have cartilage and joint damage early in the course of the disease. Further developments of criteria for AS have broadened the spectrum of AS to spondyloarthritis (SpA) and axial SpA which covers most early forms. The leading clinical symptom is chronic back pain in young adults and IBP. New criteria for RA which include more patients with early disease and anti-CCP antibodies as new markers are being developed. This is important since early treatment strategies are increasingly and successfully used to treat inflammatory diseases more efficiently.

Introduction

This essay is not intended to be a historical review, and will summarize recent developments. Nonetheless, it must be noted that it was recognized as early as the 1960s that only 25–50% of people who met 1957 classification criteria for RA were likely to have evidence of disease 3–5 years later (1, 2). This phenomenon has been apparent in subsequent studies over many years.

Rheumatoid arthritis

The best known criteria set for rheumatoid arthritis (RA) is of course the well established ACR 1987 criteria set (3, Table I), while for AS it is the 1984 modified New York criteria (4, Table II). The important issue of criteria for early and very early disease stages differs in RA and AS. While the inclusion of early stages of axial and peripheral spondyloarthritis (SpA) has recently been recognized in AS and related SpA (5-7), this effort has remained ongoing for RA. However, many groups have intensively studied this issue in recent years.

The capacity of ACR criteria to diagnose RA has recently been compared with expert opinion according to disease duration by performing a systematic literature review (8). All articles reporting the prevalence of RA according to ACR criteria and expert opinion in cohorts of early (<1 year duration) or established (>1 year) arthritis were analysed to calculate the sensitivity and specificity of ACR 1987 criteria against the "gold standard" (expert opinion). Of 138 publications initially identified, 19 were analysable (total 7438 patients, 3883 RA). In early arthritis, pooled sensitivity and specificity of the ACR set of criteria were 77% (68% to 84%) and 77% (68% to 84%) in the list format versus 80% (72% to 88%) and 33% (24% to 43%) in the tree format. In established arthritis, sensitivity and specificity were respectively 79% (71% to 85%) and 90% (84% to 94%) versus 80% (71% to 85%) and 93% (86% to 97%). Taken together, the specificity of

Table I. ACR criteria for rheumatoid arthritis 1987 (3).

1) Morning stiffness in and around joints lasting at least 1 hour before maximal improvement
2) Soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician
3) Swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints
4) Symmetric swelling (arthritis)
5) Rheumatoid nodules
6) The presence of rheumatoid factor
7) Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints

Criteria 1 through 4 must have been present for at least 6 weeks. RA is defined by the presence of 4 or more criteria, and no further qualifications (classic, definite, or
probable) or list of exclusions are required. The new criteria demonstrated 91-94% sensitivity and 89% specificity for RA when compared with non-RA rheumatic disease control subjects.
The revised criteria for the classification of RA were formulated from a computerized analysis of 262 contemporary, consecutively studied patients with RA and 262 control subjects with rheumatic diseases other than RA (non-RA).

Table II. Modified New York criteria for ankylosing spondylitis (4).

Clinical criteria
Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest

Reduced spinal mobility in 2 planes (<3 cm)

Reduced thoracic excursion (<3cm)

Radiological criterion
sacroiliitis of ≥grade II bilat, >grade II unilat

For definite AS the radiological plus one clinical criterion need to be fulfilled.

ACR 1987 criteria in early RA is low, and these criteria should not be used as diagnostic tools. Sensitivity and specificity in established RA are higher; this may reflect their use as classification criteria gold standard.

An earlier approach tried to determine how well the ACR 1987 classification criteria for RA, when used at study inclusion in a cohort of 270 patients with early (<1 year) arthritis, predicted a diagnosis of RA 2 years later, and how well they classified these patients at the end of the 2 years (9). At the last visit, the expert panel diagnosed RA in 98 patients. The classification by the ACR criteria was satisfactory, and the combination of an expert diagnosis of RA and fulfillment of the ACR criteria was sensitive (87%; 85 of 98 RA patients had both) and highly specific (99%; 170 of 172 non-RA patients did not have both). However, application of the criteria at the first visit was of limited value for predicting a diagnosis of RA 2 years later. In addition, some patients who met the criteria at baseline and after 2 years did not have RA, according to the experts, suggesting that incorporating exclusion criteria may improve the performance of the ACR criteria when used without taking into account the diagnosis by a rheumatologist, particularly in early arthritis.

Clinicians already know that not all patients who are diagnosed with rheumatic diseases really have them. Moreover, determining which patients have improved and by how much is also difficult. Classification criteria allow clinical researchers to recruit patients with similar diseases (*e.g.* RA or AS) into studies. Response criteria help to determine whether treatments really work, *i.e.* whether they actually produce clinically important improvement. As the science of clinical research advances, standards for considering classification and response criteria need regular updates. This article does not cover a comparative analyses of response criteria in RA and AS.

The 1987 ACR criteria for RA were developed to identify relatively homogeneous criteria for patients in clinical trials or long-term clinical series. Their capacity to determine which patients presenting with early synovitis have "true" RA (progressive sustained inflammation, *vs.* self-limited polyarthritis) not known. In the U.K., over 3500 patients with recent onset inflammatory polyarthritis (IP) have been recruited by the Norfolk Arthritis Register (NOAR) since 1990 (10). Rheumatoid factor titre, high baseline C-reactive protein and high baseline HAQ score were all predictors of a poor outcome. A strong association between the shared epitope and the development of erosions was found. Patients who satisfy the 1987 ACR criteria for RA had a poorer prognosis than those who did not. However, these patients were considered a poorly defined subset of all those with IP rather than an entirely separate disease entity.

After application of the 1987 ACR criteria at baseline, 486 patients with early IP patients referred to NOAR were followed up (11). The ACR criteria were assessed for their capacity to identify (i) patients referred to hospital for whom the diagnosis of RA was recorded by the hospital physician; (ii) patients at 3 years with (a) persistent synovitis; (b) moderate or greater disability; and (c) erosions. At baseline, 323 (67%) patients satisfied the ACR criteria in the classification tree format. Exactly 50% of those referred to hospital were given a diagnosis of RA. By 3 years, 76% of the 486 patients had persistent disease, 36% had a Health Assessment Questionnaire (HAQ) score >or=1, and 40% had erosions. The sensitivity of the criteria was good, ranging from 77 to 87% depending on the outcome. The specificities were poor, and thus the overall discriminatory ability showed little improvement over random probability.

In conclusion, among patients newly presenting with IP, the 1987 ACR criteria for RA had a low ability to discriminate between patients who developed persistent, disabling, or erosive disease and those who did not. Alternative criteria are required for studies investigating early RA, as already indicated earlier (1, 2).

Another study from the same group (12) studied whether the ACR 1987 criteria for RA when applied in two formats, a standard "x/y" list and a decision tree, perform differently in the ascertainment of RA in 848 patients with IP over the first 5 years of observation. Moreover, the use of clinical surrogates to substitute for missing rheumatoid factor (RF) and radiologic

erosion data was assessed for validity and for its influence on the resulting RA prevalence estimates. At baseline, RA prevalence was higher using a decision tree compared with the list approach (63% *vs*. 47%), although at 5 years of followup, RA estimates were approximately equal (69% *vs*. 72%) and agreement between the approaches was good (kappa=0.67). Substitution of metacarpophalangeal joint swelling for erosion produced a higher RA prevalence estimate (78% *vs*. 70%). Overall, over 5 years, the two formats of the ACR criteria for RA performed similarly, with no important differences between them. The use of surrogates for missing radiologic and serologic data did not have any major influence on disease classification.

Although they are not part of 1987 ACR criteria, antibodies to cyclic citrullinated peptides (anti-CCP) have recently gained strong influence on the diagnosis of RA. The performance of new criteria for RA classification, incorporating anti-CCP antibodies was recently studied in an arthritis centre when 292 consecutive patients were tested for RF and anti-CCP (13). The 1987 ACR criteria were revised in two ways: (a) adding anti-CCP, and (b) replacing rheumatoid nodules and erosions with anti-CCP (CCP 6 criteria). The mean age of the patients was 54 years, 82% were women, the mean symptom duration was 4.1 years, 17% were RF positive and 14% were anti-CCP positive. A definite diagnosis of RA was made in 78 (27%) patients. The CCP 6 criteria increased sensitivity for RA classification for all subjects regardless of symptom duration: 74% *vs*. 51% for ACR criteria with a loss in specificity (81% *vs*. 91%). Sensitivity was greatly improved in subjects with symptoms ≤6 months: 25% *vs*. 63% for ACR criteria with a decrease in specificity. The substitution of RF and erosions by anti-CCP antibodies improved the sensitivity of the ACR criteria, most remarkably when symptoms were ≤6 months. Such criteria could be readily used for the classification of subjects for RA in clinical studies. Nonetheless, it must be recognized that the above is only one study. In a meta-analysis (14), anti-CCP was described in 67% of patients, which unfortunately means that one-third of patients regarded by expert opinion as having RA, did not have anti-CCP antibodies.

Early diagnosis of RA is an important challenge for clinical rheumatologists. This is because there is substantial evidence that early treatment with disease-modifying antirheumatic drugs (DMARDs) leads to a better disease outcome. The 1987 ACR classification criteria for RA do not perform well as a diagnostic tool in early arthritis. Therefore, studies are needed to develop diagnostic criteria or prediction models that enable clinicians to distinguish RA from other arthritides in an early phase of the disease. Diagnostic studies are hampered by the lack of an independent gold standard for RA, or by the fact that the gold standard is a clinical decision. Since the most important clinical features of RA are the persistence of the arthritis and the development of erosions, arthritis outcome is a clinically relevant gold standard.

Therefore, besides univariate studies, multivariable studies are needed to evaluate current diagnostic practice and the added value of new diagnostic procedures (15).

In an important Dutch study, a clinical model was developed to predict, at the first visit, of three forms of arthritis outcome: self-limiting, persistent nonerosive, and persistent erosive arthritis. A standardized evaluation was performed on 524 consecutive, newly referred patients with early arthritis who were followed up for 2 years (16).

The developed prediction model consisted of 7 variables:

1. symptom duration at first visit
2. morning stiffness for ≥1 hour
3. arthritis in ≥3 joints
4. bilateral compression pain in the metatarsophalangeal joints
5. rheumatoid factor positivity
6. anti-cyclic citrullinated peptide antibody positivity, and
7. the presence of erosions (hands/feet).

Application of the model to an individual patient resulted in three clinically relevant predictive values for self-limiting, for persistent nonerosive, and one for persistent erosive arthritis. The ROC AUC of the model was 0.84 (SE 0.02) for discrimination between self-limiting and persistent arthritis, and 0.91 (SE 0.02) for discrimination between persistent nonerosive and persistent erosive arthritis, whereas the discriminative ability of the ACR 1987 RA criteria was significantly lower, with ROC AUC values of 0.78 (SE 0.02) and 0.79 (SE 0.03), respectively.

Very recently, one step earlier was taken to draw consequences of the PROMPT study (17) in which patients with undifferentiated arthritis (UA) had been treated with methotrexate which was shown to be effective for inhibiting symptoms, structural damage, and progression to RA. However, on the other hand, 40–50% of patients with UA experienced spontaneous remission, as in earlier studies (1, 2). Thus, adequate decision-making regarding treatment of patients with early UA requires identification of those patients in whom RA will develop. Therefore, a prediction rule was developed (18) using data of an inception cohort of patients with recent-onset arthritis (n=1700). The patients who presented with UA were selected (n=570), and progression to RA or other diagnoses in this group was monitored for 1 year of follow up.

The prediction rule consisted of 9 clinical variables:

1. sex
2. age
3. localization of symptoms
4. morning stiffness
5. the tender joint count
6. the swollen joint count
7. the C-reactive protein level
8. rheumatoid factor positivity, and
9. the presence of anti-cyclic citrullinated peptide antibodies.

Each prediction score varied from 0 to 14 and corresponded to the percent chance of RA developing. The positive and negative predictive values were determined for several cut-off values. The AUC values for the prediction rule, the prediction model after cross-validation, and the external validation cohort were 0.89, 0.87, and 0.97, respectively.

Thus, in patients who present with UA, the risk of developing RA could be predicted, thereby allowing individualized decisions regarding the initiation of treatment with DMARDs in such patients.
In the recent EULAR recommendations for the management of early arthritis (19) designed in accordance with EULAR's "standardised operating procedures", 15 research questions, covering the entire spectrum of management of early arthritis, were formulated for further research; and 284 studies were identified and evaluated. Twelve recommendations for the management of early arthritis were selected and presented with short sentences. The selected statements included recognition of arthritis, referral, diagnosis, prognosis, classification, and treatment of early arthritis.

Ankylosing spondylitis and spondyloarthritis

As in all aspects of the two diseases, the situation for AS in comparison to RA is partly overlapping but also different. In the widely used modified New York classification criteria for AS (Table II, 2) the presence of radiographic sacroiliitis is mandatory to fulfill these criteria. However, the chronic structural changes seen by x-rays are the consequence of inflammation and do not directly indicate inflammation itself (20). Indeed, it may take several years of ongoing or relapsing inflammation before chronic changes in the sacroiliac (SI) are visible on radiographs (21). However, on the other hand, 20% of the patients in an early cohort with inflammatory back pain (Table III, 22) lasting <2 years already had structural changes in the SI joints (23). Since investigation of the the SI joints and the spine by MRI has become available, it is now clear that these patients have ongoing inflammation sometimes for years with potentially severe symptoms before any radiological changes can be detected. The degree of sacroiliitis at baseline may predict a future development to AS (24).
These findings have led to efforts in recent years to develop new and/or modified approaches for earlier diagnosis and classification for patients with AS. The new term 'axial SpA' covers both the group of patients with (early) SpA detected by MRI but not radiographs, as well as patients with established AS according to the modified New York criteria (4,5). The latter should probably be further divided in patients with chronic changes confined to the SI-joints and those in whom syndesmophytes of the spine are also present.
In the early phase of AS, several clinical, laboratory and imaging parameters characteristic for SpA may be combined to get a reliable diagnosis (21) - a situation which is not so different from other chronic inflammatory rheumatic diseases. Based on an analysis of the available literature, sensitivity and specificity and the resulting likelyhood ratio for these parameters were calculated and developed into a diagnostic recent algorithm for early axial SpA. Using such an approach, a diagnosis of axial SpA can be reached with a probability of 90% or more, if a sufficient number of parameters are present (21). Subsequently, the "Assessment in Spondylo-Arthritis international Society" (ASAS) initiated a prospective international two-stage project, ultimately analysing 649 patients from 25 centers worldwide which resulted in new classification criteria for axial SpA (4, 5). The presence of sacroiliitis is – similar to the modified New York criteria – still an important part of these criteria. But now sacroiliitis cannot only be detected by x-rays but also active inflammation MRI as subchondral bone marrow oedema. In addition to this modified imaging criterion, at least one further SpA-typical feature must be present (Fig. 1). Alternatively, if patients are HLA-B27 positive and fulfil two further SpA-typical feature, they can also be classified as axial SpA, always on the background of chronic back pain starting at an age younger than 45 years. In a rheumatological setting with a relatively high pretest probability for the presence of axial SpA in patients referred because of unclear back pain these criteria perform also well as diagnostic criteria (5). This situation most probably differs in

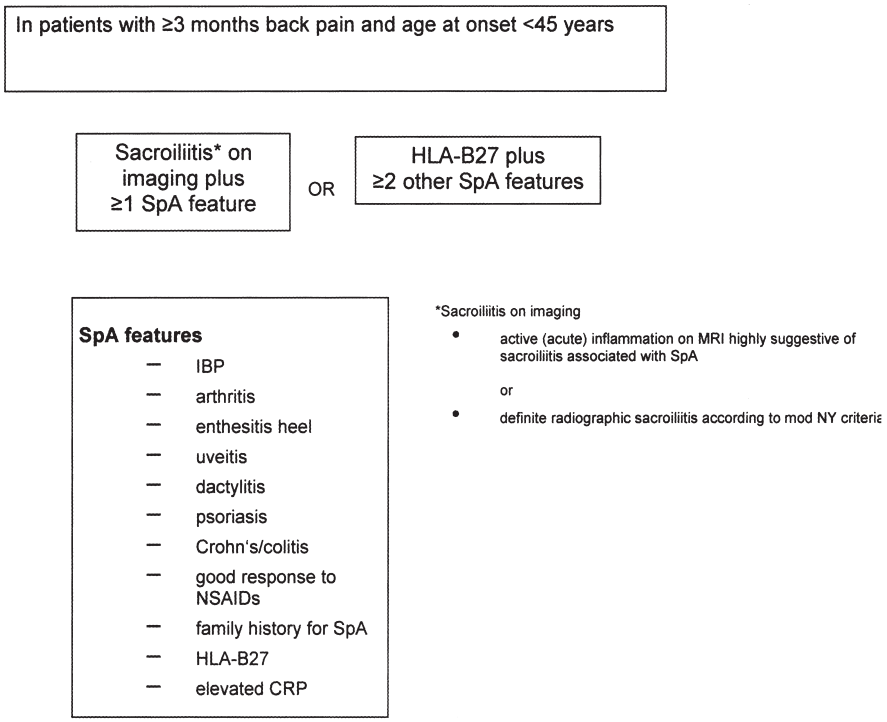

Fig. 1. ASAS Classification Criteria for Axial Spondyloarthritis (5).

Table III. Criteria for inflammatory back pain (22).

Morning stiffness >30 min
Improvement with exercise, not with rest
Awakening at 2am. Awake half of the night because of pain
Alternating buttock pain
2/4 of these criteria must be positive

primary care settings with a much lower pretest probability for a diagnosis of axial SpA. These new criteria were also clearly superior to older criteria which have been used pre-viously in patients with earlier forms of SpA, such as the ESSG (European Spondyloarthropathy Study Group) criteria or the Amor criteria (25, 26).

In view of active inflammation of the SI-joints as seen by MRI as an important part of the new criteria, ASAS has also recently published a manuscript on how to define active sacroiliitis by MRI (27). Subchondral bone marrow oedema is essential for the definition of a positive MRI (27). However, it must be borne in mind that such a criterion never reaches a hundred percent specificity and that other causes of bone marrow oedema exist, such as bacterial infection or tumour of the SI-joint, bone fracture or other severe mechanical stress. Nonetheless, a specificity and sensitivity of at least 90% each appears likely with the new criteria, although further formal studies are needed.

There had been an unmet need to diagnose and classify these patients earlier because the level of symptoms is very similar, independently from whether patients have already (chronic) radiographic changes or not, as shown recently (28). Furthermore, two studies in patients with early axial SpA treated with TNF-blockers have demonstrated very good response rates (29, 30).

In contrast to RA, it is as yet unclear whether early treatment of patients with axial SpA can prevent longterm structural damage. The situation is in general rather complex and complicated (as discussed in more detail elsewhere in this issue), since in AS both erosive structural damage and structural damage by new bone formation are present (31). Furthermore, it is not completely clear how inflammation and new bone formation are related in AS (32). Future research is needed to clarify these important questions.

Nevertheless, the development of new classification criteria is a major step forward to identify patients early and to perform trials in order to study the likely benefits of early intensive anti-inflammatory therapies.

References

1. MIKKELSEN WM, DODGE H: A four year follow-up of suspected rheumatoid arthritis: the Tecumseh, Michigan, community health study. *Arthritis Rheum* 1969; 12: 87-91.
2. O'SULLIVAN JB, CATHCART ES: The prevalence of rheumatoid arthritis: follow-up evaluation of the effect of criteria on rates in Sudbury, Massachusetts. *Ann Intern Med* 1972; 76: 573-7.
3. ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
4. VAN DER LINDEN S, VALKENBURG HA, CATS A:Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.
5. RUDWALEIT M, METTER A, LISTING J, SIEPER J, BRAUN J: Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006; 54: 569-78.
6. RUDWALEIT M, LANDEWÉ R, VAN DER HEIJDE D *et al.*: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009; 68: 770-6.
7. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al.*: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
8. BANAL F, DOUGADOS M, COMBESCURE C, GOSSEC L: Sensitivity and specificity of the American College of Rheumatology 1987 criteria for the diagnosis of rheumatoid arthritis according to disease duration: a systematic literature review and meta-analysis. *Ann Rheum Dis* 2009; 68: 1184-91.
9. SARAUX A, BERTHELOT JM, CHALÈS G *et al.*: Ability of the American College of Rheumatology 1987 criteria to predict rheumatoid arthritis in patients with early arthritis and classification of these patients two years later. *Arthritis Rheum* 2001; 44: 2485-91.
10. SYMMONS DP, SILMAN AJ: Aspects of early arthritis. What determines the evolution of early undifferentiated arthritis and rheumatoid arthritis? An update from the Norfolk Arthritis Register. *Arthritis Res Ther* 2006; 8: 214.
11. HARRISON BJ, SYMMONS DP, BARRETT EM, SILMAN AJ: The performance of the 1987 ARA classification criteria for rheumatoid arthritis in a population based cohort of patients with early inflammatory polyarthritis. American Rheumatism Association. *J Rheumatol* 1998; 25: 2324-30.
12. LUNT M, SYMMONS DP, SILMAN AJ: An evaluation of the decision tree format of the American College of Rheumatology 1987 classification criteria for rheumatoid arthritis: performance over five years in a primary care-based prospective study. *Arthritis Rheum* 2005; 52: 2277-83.
13. LIAO KP, BATRA KL, CHIBNIK L, SCHUR PH, COSTENBADER KH: Anti-cyclic citrullinated peptide revised criteria for the classification of rheumatoid arthritis. *Ann Rheum Dis* 2008; 67: 1557-61.
14. VISSER H: *Best Pract Res Clin Rheumatol* 2005; 19: 55-72
15. VISSER H, LE CESSIE S, VOS K, BREEDVELD FC, HAZES JM: How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. *Arthritis Rheum* 2002; 46: 357-65.
16. VAN DONGEN H, VAN AKEN J, LARD LR *et al.*: Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2007; 56: 1424-32.
17. VAN DER HELM-VAN MIL AH, LE CESSIE S, VAN DONGEN H, BREEDVELD FC, TOES RE, HUIZINGA TW: A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis Rheum* 2007; 56: 433-40.
18. NISHIMURA K, SUGIYAMA D, KOGATA Y *et al.*: Meta-analysis: Diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med* 2007; 146: 797-808.
19. COMBE B, LANDEWÉ R, LUKAS C *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.
20. BRAUN J, SIEPER J: Early diagnosis of spondyloarthritis. *Nat Clin Pract Rheumatol* 2006; 2: 536-45.
21. RUDWALEIT M, KHAN MA, SIEPER J: The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum* 2005; 52: 1000-8. Review.
22. RUDWALEIT M, METTER A, LISTING J, SIEPER J, BRAUN J: Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis Rheum* 2006; 54: 569-78.
23. HEUFT-DORENBOSCH L, LANDEWÉ R, WEIJERS R *et al.*: Combining information obtained from magnetic resonance imaging and conventional radiographs to detect sacroiliitis in patients with recent onset inflammatory back pain. *Ann Rheum Dis* 2006; 65: 804-8.
24. BENNETT AN, MCGONAGLE D, O'CONNOR P *et al.*: Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum* 2008; 58: 3413-8.
25. DOUGADOS M, VAN DER LINDEN S, JUHLIN R *et al.*: The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34: 1218-27.
26. AMOR B, DOUGADOS M, MIJIYAWA M: Criteria of the classification of spondylarthropathies. *Rev Rhum Mal Osteoartic* 1990; 57: 85-9.

27. RUDWALEIT M, JURIK AG, HERMANN KG *et al*.: Defining active sacroiliitis on Magnetic Resonance Imaging (MRI) for classification of axial spondyloarthritis - a consensual approach by the ASAS/ OMERACT MRI Group. *Ann Rheum Dis* 2009 May 18. [Epub ahead of print].
28. RUDWALEIT M, HAIBEL H, BARALIAKOS X *et al*.: The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum* 2009; 60: 717-27.
29. HAIBEL H, RUDWALEIT M, LISTING J *et al*.: Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum* 2008; 58: 1981-91.
30. BARKHAM N, KEEN HI, COATES LC *et al*.: Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis Rheum* 2009; 60: 946-54.
31. SIEPER J, APPEL H, BRAUN J, RUDWALEIT M: Critical appraisal of assessment of outcomes. *Arthritis Rheum* 2008; 58: 649-56. Review.
32. BARALIAKOS X, LISTING J, RUDWALEIT M, SIEPER J, BRAUN J: The relationship between inflammation and new bone formation in patients with ankylosing spondylitis. *Arthritis Res Ther* 2008; 10: R104.