

# CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS – TIME TO ABANDON RHEUMATOID FACTOR?

D.P.M. Symmons

ARC Epidemiology Unit, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

## Abstract

Criteria for rheumatoid polyarthritis diagnosis (PR) have been proposed and used for more than 10 years, and have been elaborated based on a large group of patients in which the illness evolved on average in 7 years. Therefore, these criteria do not satisfy the present requests of the early PR. At least two individual criteria are in debate under this particular aspect: the presence of erosions and of rheumatoid factor (FR). Articular erosions can be nowadays discovered in the pre-radiographic phase, through methods such as sonography and magnetic resonance, and our recommendation is to introduce the remissive therapy before their appearance. On the other hand, though FR is a marker for the persistence of the disease, it isn't present in all cases, and its specificity is low. Since the year 2000 there have been introduced in practice the methods for discovering the anti-cyclic citrullinated peptide antibodies (PCC), which have the advantage of precocity, specificity, and predictability of the evolution of the disease under the aspect of the appearance of articular erosions. The right attitude should be the concomitant determination of FR and anti-PCC antibodies, for an early recognition of PR, and the evaluation of its evolutionary potential.

## Rezumat

### Criteriaile de diagnostic pentru poliartrita reumatoidă. Este momentul să abandonăm factorul reumatoid?

Criteriaile pentru diagnosticul poliartritei reumatoidă (PR) au fost propuse și sunt utilizate de mai bine de 10 ani și au fost elaborate pe un grup larg de pacienți la care boala evolua în medie de 7 ani. Ca atare, acestea nu mai satisfac exigențele actuale ale diagnosticului PR precoce. Cel puțin două criterii individuale sunt în discuție sub acest aspect: prezența eroziunilor și factorul reumatoid (FR). Eroziunile articulare pot fi astăzi depistate în etapa pre-radiografică, prin metode cum ar fi ultrasunetele și rezonanța magnetică, iar recomandarea este de a introduce terapia remisivă înainte de apariția acestora. Pe de altă parte, cu toate că FR este un indicator de persistență a bolii, acesta nu apare în toate cazurile, iar specificitatea sa este scăzută. Din anul 2000 au fost introduse în practică metodele pentru depistarea anticorpilor anti-peptid ciclic citrulinat (PCC), care se bucură de avantajul precocității, specificității și predictibilității evoluției bolii sub aspectul apariției eroziunilor articulare. Atitudinea potrivită ar fi determinarea concomitentă a FR și anticorpilor anti-PCC pentru recunoașterea PR precoce și evaluarea potențialului evolutiv al acesteia.

The 1987 classification criteria for rheumatoid arthritis (RA) (1) are nearly 20 years old. Ever since they were introduced, there have been rumblings of discontent. Predominantly there has been a concern that they do not perform well in the context of early inflammatory arthritis (2, 3). This lack of sensitivity in early disease was acknowledged in the original paper. The criteria were developed by an analytical approach using data from patients attending specialist clinics for RA who had an average disease duration of over 7 years. The comparison group of patients had other established diagnoses such as osteoarthritis, fibromyalgia and lupus. They did not have early undifferentiated arthritis. As with almost all criteria sets in rheumatology, the 1987 ACR criteria use the “physician’s opinion” as the gold standard. The problem with early RA is that the physician cannot recognize it on clinical grounds alone. In fact, we have

argued that early RA does not exist and that patients either have established RA or an undifferentiated inflammatory arthritis (4).

Unfortunately there has been a tendency to use the ACR criteria to tell the physician which patients with early arthritis have RA and which do not-i.e., for diagnosis, which was clearly never intended. This has introduced special problems in the field of therapeutics. The great majority of clinical trials in early arthritis has used the ACR criteria as part of the inclusion criteria for the trial. Since trial results can only be generalized to patients who would have satisfied the entry criteria for the trial, this means that we have a very limited evidence base for treating patients with early arthritis who do not satisfy a set of criteria (the 1987 ACR criteria), which were never developed to be used in this setting!

The 1987 criteria exist in two formats. The most widely used format is a list of seven criteria – any four of which must have been present for at least 6 weeks for a patient to be classified as having RA. There is an alternative “decision tree” format that enables substitution for missing items. Even though the decision tree has been shown to be more sensitive in early and evolving disease (5), few studies have used this method.

Some of the individual criteria are also now coming into question. In the last 5-10 years there has been concern about the inclusion of erosions. When the criteria were introduced it was rare to consider using disease-modifying anti-rheumatic drug (DMARD) therapy before the development of erosions. Now the goal is to introduce DMARD therapy early in order to prevent the development of erosions (6, 7). The discovery that bone and cartilage changes can be seen on MRI (8, 9) or ultrasound (10) long before the development of radiologically visible erosions means that new criteria sets should focus on these rather than erosions.

Now rheumatoid factor (RF) falls under the spotlight. RF positivity is a strong predictor of persistence (11, 12). However, the specificity of RF is relatively low – RF is often detected in other conditions associated with chronic inflammation (e.g., lupus, primary Sjögren’s syndrome, chronic osteomyelitis) and (usually in low titres) in up to 10% of the general population. The discovery – or rather rediscovery – of the potential role of auto-antibodies directed against citrullinated peptides in the diagnosis and classification of patients with inflammatory arthritis raises questions as to whether testing for these antibodies should be substituted for, or added to, testing for RF in classifying and diagnosing RA.

In 1964, the Dutch researchers Nienhuis and Mandema detected the auto-antibody anti-perinuclear factor (APF) in the serum of some RA patients using human buccal mucosal cells as substrate. After fifteen years, Young et al (14) detected anti-keratin antibodies (AKA) in the serum of some RA patients using rat oesophagus as the substrate. Assays for APF and AKA were never adopted in routine clinical practice for technical reasons. More recently, Schellekens (15) and the Leiden group reported that APK and APF are both directed against citrulline residues in filaggrin – a protein involved in the aggregation of cytokeratin filaments during cornification of the epidermis. Schellekens facilitated the detection of such auto-antibodies by synthesizing a single cyclic citrullinated peptide with a three-dimensional structure. This first generation

assay for anti-cyclic citrullinated peptide (anti-CCP) auto-antibodies was introduced in 2000. It used a filaggrin-based cyclic peptide. However, filaggrin is not present in synovium. A second generation assay was developed that uses a library of citrullinated peptides. It became commercially available in 2002. A third generation assay is in development.

Citrullination (or deimination) is the post-translational conversion of the amino acid arginine to citrulline. Arginine is positively charged and citrulline is neutral. This change leads to increased hydrophobicity and unfolding of the protein in which the amino acid is found. Proteins that normally include citrulline residues include myelin basic protein, filaggrin and some histones. Other proteins may be citrullinated as a consequence of inflammation, cell-injury and cell-death. These include fibrin and vimentin. Anti-Sa antibodies (another auto-antibody found in patients with RA) are directed against citrullinated vimentin. A family of enzymes called peptidylarginine deiminases (PAD) is responsible for the conversion of arginine to citrulline. The reaction is calcium ion dependent. The normal intracellular  $\text{Ca}^{2+}$  concentration ( $10^{-7}$  mmol/l) is lower than the threshold for PAD activity ( $10^{-5}$  mmol/l). However, during cell death the integrity of the cell membrane is lost, resulting in an influx of calcium, thus enabling citrullination to take place. Citrullinated proteins have been found in the inflamed synovium in humans and animal models of arthritis. However, the presence of citrullinated proteins does not routinely lead to the development of auto-antibodies directed against them.

There is a considerable degree of overlap between the presence of anti-CCP antibodies and RF in patients with arthritis. The overlap is less in early arthritis (80% of patients with RF were also anti-CCP antibody-positive in a Swedish early arthritis study) (16) than in established RA (93% in a study of 784 RA patients with a mean disease duration of 18 years) (17). Anti-CCP antibodies are slightly less sensitive but more specific for established RA than RF. In a recent systematic review, Avouac et al (18) reported that, overall, anti-CCP 2 antibodies have a sensitivity of 70-80% and a specificity of 95-98% in patients with established RA, compared with the sensitivity of 75-85% and a specificity of 80-90% for RF. It is the high specificity of anti-CCP 2 antibodies that gives them their appeal with regards to the diagnosis of RA. The prevalence in other diseases that might be confused with RA is low. The prevalence in the general population is around 0.4%.

Anti-CCP antibody positivity is strongly associated with the shared epitope. 74% of the patients with anti-CCP2 antibodies were shared epitope positive in a study from the Netherlands (19) and nearly 90% of RA patients with two copies of the shared epitope were anti-CCP-positive in a study from Sweden (16).

The presence of anti-CCP antibodies strongly predicts the development of erosions. In the Norfolk Arthritis Register, patients with anti-CCP antibodies were 10.2 times more likely to develop erosions than those who were anti-CCP antibody negative. However, anti-CCP and RF do appear to have independent associations with the development of erosions (20) and radiographic severity (17). However, anti-CCP antibodies are less strongly associated with extra-articular disease, in particular nodules, than RF (21).

In a recent randomized controlled trial (RCT) from the Netherlands (the Probable Rheumatoid Arthritis: Methotrexate vs Placebo Treatment (PROMPT) study) which enrolled 110 patients with early undifferentiated arthritis, only the patients with anti-CCP antibodies showed any benefit from treatment with methotrexate (22). This has led the Leiden group to suggest that anti-CCP-positive arthritis is a distinct disease entity. Their hypothesis has been supported by the finding that smoking seems to lead to the development of anti-CCP antibodies only in patients who are shared epitope positive (16, 23). The hypothesis then is that a second trigger is required in these patients which leads to the development of arthritis.

Thus a positive anti-CCP antibody test provides important prognostic information in a patient with early inflammatory arthritis. What, however, happens to those patients with early inflammatory arthritis who are anti-CCP antibody negative? It is important that this group do not get overlooked. Among such patients 25% will satisfy the ACR criteria for RA within 3 years of follow-

up (24). Over half the patients who ultimately evolve into RA are anti-CCP negative at presentation (24). In the Norfolk Arthritis Register, 39% of patients who were anti-CCP antibody negative already had erosions at the time of presentation. It may be that we have no effective treatments for this sub-group of patients (22). These may be the silent minority of patients with mild disease who slowly deteriorate and who gain no benefit from any of our current therapies (25).

So should we stop measuring RF and measure anti-CCP antibodies instead? If cost was not an issue, we should probably measure both. However, the current consensus is that measuring anti-CCP antibodies in patients who are already known to be RF-positive, in particular if the titre is > 50 IU/l, adds little additional information (26). Conversely, the finding of RF in a patient known to be anti-CCP-positive may predict extra-articular disease. The finding of anti-CCP antibodies in patients who are RF-negative is important and predicts those who will develop progressive erosive disease. However, it is important that those patients who have a significant early inflammatory arthritis that is anti-CCP antibody and RF-negative should still be referred for specialist care. Their needs may be even greater than those with the worst prognosis who will respond to early aggressive therapy. The development and introduction of assays for the measurement of anti-CCP antibodies is an important step forward in the study of early arthritis, but it is not a substitute for a more fundamental fresh approach in predicting prognosis and treatment response in patients with early arthritis using a variety of genetic tests and biomarkers.

This will feed into a re-evaluation of the classification criteria for RA. In the short term, RF assays should not be abandoned for but supplemented by anti-CCP antibody testing.

## REFERENCES

1. 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: 315-324.
2. 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: 2324-2330.
3. Saraux A, Berthelot JM, Chales 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: 2485-2491.
4. Dixon WG, Symmons DP – Does early rheumatoid arthritis exist? *Best Pract Res Clin Rheumatol*, 2005, 19: 37-53.
5. 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: 2277-2283.
6. Lard LR, Visser H, Speyer I et al – Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med*, 2001, 111: 446-451.
7. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS – Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology*, 2004, 43: 906-914.
8. McQueen FM, Stewart N, Crabbe J et al – Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals progression of erosions despite clinical improvement. *Ann Rheum Dis*, 1999, 58: 156-163.

9. McGonagle D, Conaghan PG, O'Connor P et al – The relationship between synovitis and bone changes in early untreated rheumatoid arthritis: a controlled magnetic resonance imaging study. *Arthritis Rheum*, 1999, 42: 1706-1711.
10. Wakefield RJ, Gibbon WW, Conaghan PG et al – The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum*, 2000, 43: 2762-2770.
11. Tunn EJ, Bacon PA – Differentiating persistent from self-limiting symmetrical synovitis in an early arthritis clinic. *Br J Rheumatol*, 1993, 32: 97-103.
12. Wolfe F, Ross K, Hawley DJ, Roberts FK, Cathey MA – The prognosis of rheumatoid arthritis and undifferentiated polyarthritis syndrome in the clinic: a study of 1141 patients. *J Rheumatol*, 1993, 20: 2005-2009.
13. Nienhuis RL, Mandema E – A new serum factor in patients with rheumatoid arthritis, the antiperinuclear factor. *Ann Rheum Dis*, 1964, 23: 302-305.
14. Young BJ, Mallya RK, Leslie RD, Clark CJ, Hamblin TJ – Anti-keratin antibodies in rheumatoid arthritis. *Br Med J*, 1979, 2: 97-99.
15. Schellekens GA, Visser H, de Jong BA et al – The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum*, 2000, 43: 155-163.
16. Klareskog L, Stolt P, Lundberg K et al – A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum*, 2006, 54: 38-46.
17. Mewar D, Coote A, Moore DJ et al – Independent associations of anti-cyclic citrullinated peptide antibodies and rheumatoid factor with radiographic severity of rheumatoid arthritis. *Arthritis Res Ther*, 2006, 8: R128.
18. 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: 845-851.
19. van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Huizinga TW, Toes RE, de Vries RR – The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis. *Arthritis Rheum*, 2006, 54: 1117-1121.
20. Visser H, le CS, Vos K, Breedveld FC, Hazes JM – How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. *Arthritis Rheum*, 2002, 46: 357-365.
21. De Rycke L, Peene I, Hoffman IE et al – Rheumatoid factor and anticitrullinated protein antibodies in rheumatoid arthritis: diagnostic value, associations with radiological progression rate, and extra-articular manifestations. *Ann Rheum Dis*, 2004, 63: 1587-1593.
22. van Dongen H, van Aken J, Lard L et al – Probable rheumatoid arthritis methotrexate versus placebo therapy (prompt)-study: indications for a window of opportunity in the treatment of patients with undifferentiated arthritis. *Ann Rheum Dis*, 2006, 65(Suppl II), 54. 2006. (Abstract).
23. Linn-Rasker SP, van der Helm-van Mil AH, van Gaalen FA et al – Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles. *Ann Rheum Dis*, 2006, 65: 366-371.
24. van Gaalen FA, Linn-Rasker SP, van Venrooij WJ et al – Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum*, 2004, 50: 709-715.
25. Symmons D, Tricker K, Harrison M et al – Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs-results of the British Rheumatoid Outcome Study Group randomized controlled clinical trial. *Rheumatology*, 2006, 45: 558-565.
26. Nell VP, Machold KP, Stamm TA et al – Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis. *Ann Rheum Dis*, 2005, 64: 1731-6.

## În actualitate

### Guta și consumul de cafea

Cafeaua este cea mai răspândită băutură de agrement și poate influența hiperuricemia și guta prin mai multe mecanisme. Autorii au efectuat un studiu prospectiv pe o perioadă de 12 ani asupra unui grup de peste 45.000 de bărbați fără

antecedente gutoase care consumau cafea obișnuită, cafea decafeinizată sau ceai. S-a calculat cantitatea de cafeină cumulativă pe 4 ani și incidența gutei stabilită cu ajutorul unui chestionar validat. Au fost descoperite 757 de cazuri incidente de

gută, care s-au găsit în relație inversă cu consumul de cafea ( $p < 0,009$ ). Cantitatea totală de cafeină consumată din oricare sursă nu s-a asociat cu riscul de gută.

Sursa: Choi HK, Willett W, Carhan G, *Coffee consumption and risk of incident gut in men* *Arthr Rhem* 2007, 56: 2049-2055

Vizitați site-ul

**SOCIETĂȚII ROMÂNE DE REUMATOLOGIE**

**www.srreumatologie.ro**