J R Coll Physicians Edinb 2006; **36:**220–221
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Anti-CCP2 may replace rheumatoid factor test in rheumatoid arthritis

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TITLE Use and significance of anti-CCP autoantibodies in rheumatoid arthritis

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JOURNAL *Rheumatology (Oxford)* 2006;**45:**20–25

KEYWORDS Anti-CCP, rheumatoid arthritis, rheumatoid factor

LIST OF ABBREVIATIONS Anti-CCP auto-antibodies (anti-CCP), anti-CCP2 auto-antibodies (anti-CCP2), cyclic citrullinated peptides (CCP), disease modifying anti-rheumatic drug (DMARD), enzyme-linked immunosorbent assay (ELISA), extra-articular rheumatoid disease (EARD), immunoglobulin (Ig), peptidylarginine deiminase (PAD), rheumatoid arthritis (RA), rheumatoid factor (RF), tumour necrosis factor (TNF)

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***September 2006***

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SUMMARY

This paper reviews the current state of knowledge on CCP and anti-CCP. It has been known for decades that RA patients generate auto-antibodies to citrullinated peptide antigens. Citrullination occurs by the action of the PAD enzymes upon the amino acid arginine. Auto-antibody reactivity to native epidermal filaggrin was originally identified in RA serum (anti-perinuclear factor and anti-keratin antibodies). Filaggrin is a naturally occurring source of CCP and formed the basis of the first generation of anti-CCP ELISA (anti-CCP1). Subsequent synthesis of a panel of CCP gave rise to more superior epitopes and thus to a second generation ELISA (anti-CCP2) with improved sensitivity and specificity for RA in comparison with RF.

Anti-CCP2 fulfil the three criteria required for a good diagnostic marker: high sensitivity – detects a high percentage of patients with RA (80% vs 70% for RF); high specificity – low false positive rate (98% vs 62% for RF); early detection – allowing early diagnosis (present more than 10 years before, and in more patients with rising titres in the years before development of symptoms compared with RF). Furthermore, as many as 60% of RA patients negative for RF are anti-CCP2 positive.[1]

Anti-CCP2 is also a prognostic marker with positivity at baseline, predicting early progression to radiological damage, manifest by erosions and a more aggressive clinical course at two/three years of follow-up.

There is no correlation between anti-CCP2 and EARD, in contrast to RF. Nor does there appear to be a correlation with clinical response to anti-TNFα (biologic) therapy unlike RF. Both anti-CCP2 and RF titres fall in patients who respond clinically to conventional disease-modifying therapy. These findings might suggest contrasting pathogenic roles for anti-CCP autoantibodies and RF, with the synovium as the greater focus for anti-CCP.

COMMENT

Rheumatoid arthritis is associated with significant morbidity and mortality. There is likely to be a 'window of opportunity' early in the disease when disease-modifying treatment can significantly alter the disease course and prevent or modify the development of erosions which can eventually lead to joint failure, and even alter mortality. Best practice is to identify and treat the disease early.[2] Rheumatoid arthritis remains a clinical diagnosis, especially very early in the course of the disease when radiological change specific to RA or erosions may not yet be evident.

Rheumatoid factor is IgM auto-antibody against the Fc portion of IgG. Despite its relatively low specificity with respect to other diseases (especially connective tissue diseases) and presence in the healthy population (especially the elderly), RF has been retained largely because of it prognostic utility (correlating with radiological and functional outcomes), and the lack of a better test. It is a relatively poor diagnostic test defined by the criteria described above, yet continues to be used

widely as a screening test for patients who present with joint pain.

We now see the advent of an era when our ideal of early identification and treatment might be more accurately realised. This is particularly exciting at a time when our approach to treatment has been revolutionised by the advent of the concept of tight RA disease control and with both combination of conventional DMARDs and with biologic therapies.

Important insights into the pathogenesis of RA may be the result of discovery of anti-CCP: CCP are present primarily in dying cells, but anti-CCP only develop in patients with susceptibility genes governing antigen presentation and T cell activation in RA. It is possible that a number of these cells release PAD enzymes which in turn citrullinate synovial proteins, for example vimentin (citrullinated proteins do not normally occur in synovium). In patients with the susceptibility genes, an inflammatory response may be generated with up-regulation of the inflammatory milieu. Scientific endeavour in this area is ongoing and may yet see the development of therapies specifically targeted to breaking the cycle of RA chronicity.

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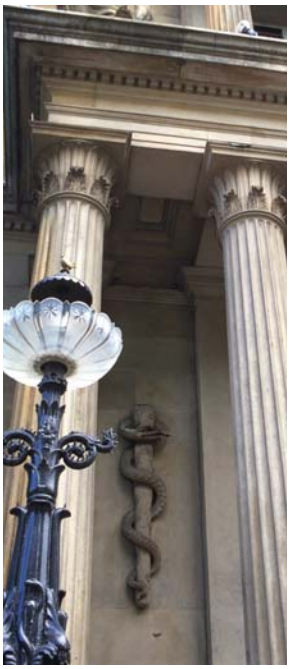

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