Rheumatoid Arthritis – Anti CCP Antibodies

Rheumatoid Arthritis (RA) is the commonest inflammatory joint disease, affecting nearly 1% of the adult population worldwide. It is characterized by multiple deformities and is associated with considerable morbidity and mortality. Although the precise etiology of RA remains unknown; there is strong evidence for autoimmunity since several auto-antibodies are associated with the disease. Besides the rheumatoid factor (RF), another group of auto-antibodies has recently been detected in serum of patients with RA patients: the anti-cyclic citrullinated peptide antibodies (anti CCP).

Anti perinuclear factor (APF) and anti keratin antibodies (AKA), two tests known for a long time, have a high specificity of up to 70% for RA. The tests are done by immunofluorescence but did not become popular in clinical practice, despite high specificity, due to various technical difficulties in doing the assays.

Filaggrin was identified as the antigen that was targeted by both these auto-antibodies. Antibodies to Sera antigen have also been detected in sera of patients with RA.

It is now evident that APF, AKA, and anti Sera antibodies target citrullinated proteins. The difficulty of obtaining pure filaggrin antigen has been overcome by development of citrullinated peptides in laboratory. The first generation of ELISA for anti-CCP (CCP1), using several filaggrin epitopes, had high specificity for RA (>85%) and a sensitivity of 65-70%. With 2nd generation anti-CCP assay (CCP2) assays the specificity for RA has increased to 96-98%.

Role in pathogenesis

Citrulline is formed by de-imination of arginine residues in several proteins by the action of enzyme peptidylarginine deiminase (PAD). PAD 2 and PAD 4 isoenzymes are abundant in the inflammatory RA synovium and cause the local citrullination of synovial proteins, such as fibrin. Citrullinated extracellular fibrin in the RA synovium may be one of the major auto-antigens driving the local immune response, suggested by the discovery of local production of anti-CCP and anti-citrullinated filaggrin antibodies in the joint. Also, citrullinated peptides fit better in the HLA

DR4 (DRB1*0401 or *0404) antigen binding grooves than the corresponding arginine containing peptides. HLA class II RA susceptibility alleles have been shown to be associated with production of anti-CCP antibodies. Moreover, more severe disease progression is found in RA patients with both anti-CCP antibodies and shared epitope alleles.

Limitations of Rheumatoid Factor (RF)

RF is antibodies directed to the constant region of immunoglobulins of the IgG class and are found in 70-80 % of patients with RA. IgM RF, the isotype most typically detected, is seen not only in RA but also in various other conditions like other autoimmune diseases, infections and in up to 5-10% of healthy individuals[5]. The combined detection of IgM and IgA RFs in a serum is a strong indicator of RA. However, IgA RFs are not widely available.

Clinical use of anti-CCP antibodies

1. Diagnosis of early RA

The current therapeutic strategy uses increasingly aggressive regimens early in the course of the disease as most of bony damage occurs in first two years in 90% of patients. Thus, early diagnosis is crucial.

The 1987 American College of Rheumatology (ACR) criteria are rarely met during the first few months of the disease. In many early cases of RA, clinical symptoms are milder and nonspecific, and patients will not fulfill ACR classification criteria for RA. Therefore, the detection of a disease specific autoantibody like anti-CCP is important. Anti-CCP antibodies may be detected in roughly 50-60% of patients with early RA usually after 3-6 months of symptoms. The specificity of anti-CCP is around 95-98% as regards undifferentiated forms of arthritis that do not develop into RA.

IgM RF is often found in the same patients, but with much lower specificity for RA. Anti-CCP antibodies may pre-date arthritis by several years. A study using the CCP2 assay found progression from undifferentiated polyarthritis to RA in 93% of anti-CCP positive patients but only in 25% of anti-CCP negative patients after 3 years

of follow-up. Presence of a positive anti-CCP test gave an odds ratio of 37.8 in predicting development of RA at 3 years. In a study of patients with RA or palindromic rheumatism, anti-CCP (CCP1) were found in 55% of both conditions, indicating that palindromic rheumatism is closely related to and often progresses to RA.

2. Prediction of severe disease

Several observations have indicated that anti-CCP positive early RA patients may develop a more erosive disease than those without anti-CCP. Other investigators have confirmed this, and suggested the superiority of anti-CCP over IgM RF in predicting an erosive disease course. The likelihood of a total Sharp score increases after six years was significantly greater among patients with anti-CCP but not rheumatoid factor. Anti-CCP has been shown to be an independent predictor of radiological damage and progression. The combination of anti-CCP and IgM RF increased the ability to predict erosive and progressive disease in another study.

3. Differentiation from other diseases

In significant number of patients the differential diagnosis between elderly onset rheumatoid arthritis (EORA) and polymyalgia rheumatica (PMR) is very difficult because of the lack of specific serum markers. The presence of anti-CCP antibodies in a patient with clinical symptoms of PMR must be interpreted as highly suggestive of EORA. The presence of anti-CCP antibodies may be useful in distinguishing RA from erosive SLE. Anti-RA33 antibodies and RF are unhelpful.

4. Relationship with therapeutic interventions

In a study of 62 patients with refractory RA treated with infliximab, a significant reduction in RF titers was shown during infliximab treatment, whereas anti-CCP antibodies were not modulated ($p=0.240$). This led to the suggestion that that RF and anti CCP antibodies are two different, independent auto-antibody systems in RA.

Recent studies however indicate that anti-TNF alpha treatment in RA results in a decrease in the serum titers of RF and anti-CCP antibod-

ies in patients showing clinical improvement, suggesting that these measurements may be a useful adjunct in assessing treatment efficacy.

Conclusions

Anti CCP-2 antibodies show a great promise as a diagnostic marker of RA as they can be detected very early in RA. They may predict the eventual development into RA when found in undifferentiated arthritis. They have also shown the ability to distinguish between erosive and non erosive disease, making them a good prognostic marker. These antibodies represent an important addition to the diagnostic armamentarium in RA.