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HOTLINE

The Use of Anti-cyclic Citrullinated Peptide (anti-CCP) Antibodies in RA

Bottom line:

Anti-CCP antibodies are potentially important surrogate markers for diagnosis and prognosis in rheumatoid arthritis (RA), because they:

- are as sensitive as, and more specific than, IgM rheumatoid factors (RF) in early and fully established disease
- may predict the eventual development into RA when found in undifferentiated arthritis
- are a marker of erosive disease in RA
- may be detected in healthy individuals years before onset of clinical RA

Introduction and background

First described as a marker for RA in 1964, anti-perinuclear factor (APF) was directed to constituents of the keratohyaline granules near senescent buccal mucosal cell nuclei, later found to contain the "filament aggregating protein" filaggrin. Despite its specificity for RA, because of exacting technical requirements, APF never became widely used. Anti-keratin antibodies (AKA), first described in 1979, bound filaggrin tightly bound to keratin in senescent esophageal cells. As was APF, AKA had greater specificity for RA than RF. Antibodies to the so-called Sa antigen, described first in 1994, bound post-translationally modified vimentin, a cytoskeletal intermediate filament protein found in mesenchymal cells. Since 1998 it has become increasingly evident that all of the above antibodies likely target citrullinated proteins.

Citrulline is a non-standard amino acid, created by de-imination of arginine residues in several proteins by the action of peptidylarginine deiminase (PAD). There are several isotypes of this enzyme; in the inflammatory RA synovium, PAD 2 and PAD 4 are abundant. These enzymes cause the local citrullination of synovial proteins, such as fibrin. Interestingly, citrullinated peptides fit better in the HLA DR4 (DRB1*0401 or *0404) antigen binding grooves than the corresponding arginine containing peptides, findings that link this immune response to the shared epitope hypothesis of RA pathophysiology. Citrullinated extracellular fibrin in the RA synovium may be one of the major autoantigens driving the local immune response, suggested by the discovery of local production of anti-CCP and anti-citrullinated filaggrin antibodies in the joint. Also, functional haplotypes of PADI4 may be associated with RA.

The citrulline moiety is the true determinant on proteins recognized by APF, AKA, and possibly anti-Sa. Detailed studies of citrullinated filaggrin peptides showed that different patients with RA recognized different linear citrullinated peptides, indicating a polyclonal response. Flanking regions around the citrulline residue are important for the reactivity, so not all sera are reactive with every peptide. The first generation of ELISa for anti-CCP (CCP1), using several filaggrin epitopes, had high specificity for RA and a sensitivity of 65-70% **(1)**. Various cyclic epitopes that mimic true conformational epitopes were selected from libraries of citrullinated peptides for the widely available 2nd generation anti-CCP assay (CCP2).

Diagnostic use of autoimmune serology in RA

RF has been used as a marker of RA for more than half a century. IgM RF, the isotype most typically detected, is seen not only in RA but also in various other conditions. IgA RF, more easily detected than IgG RF, may be a better indicator of T-cell dependent affinity matured antibodies directed to particular Fc-gamma epitopes relevant to RA than IgM RF, but it has never gained wide interest. The combined detection of IgM and IgA RFs in a serum is a strong indicator of RA.

Most studies published to date comparing the sensitivity and specificity of RFs and anti-CCP antibodies for the diagnosis of RA have used the CCP1 assay. In general, the sensitivity of anti-CCP has been comparable to RF (50-75%) with a higher specificity (90-95%). More recent studies using the CCP2 assay show higher sensitivity for RA than CCP1, with equally high specificity. Of note, three companies (Euro-Diagnostica, Axis-Shield and Inova) have agreed to use the same coated plates for their CCP2 assays, allowing more direct comparison of results worldwide.

Clinical use of anti-CCP

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 could be of great diagnostic and therapeutic importance. Anti-CCP antibodies may be detected in roughly 50-60% of patients with early RA at 'baseline' (e.g., at their initial encounter with a specialist, 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 are often found in the same patients, but with much lower specificity for RA. One study using a CCP1 assay showed a sensitivity of 55% and a specificity of 97% specificity for RA, when both anti-CCP and IgM RF were positive in the early stage of arthritis **(2)**. More recent studies using the CCP2 assay have shown even higher prevalence at the first visit to clinics; in one study anti-CCP antibodies were found in 70% of such patients. Interestingly, using stored samples, anti-CCP could be detected 1.5 to 9 years before the onset of arthritis **(3)**. 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 **(4)**. 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 **(5)**.

Several observations have indicated that anti-CCP positive early RA patients may develop a more erosive disease than those without anti-CCP **(6)**. Other investigators have confirmed this, and suggested the superiority of anti-CCP over IgM RF in predicting an erosive disease course. The use of anti-CCP results in the decision whether a patient should be treated aggressively at an early stage or not is an important area for research. In addition, the relationship of levels of anti-CCP antibodies and various therapeutic interventions is under investigation.

Conclusions

The use of anti-CCP antibodies may allow the clinical rheumatologist to better predict the diagnosis and prognosis of individual patients with RA. Whether this or other serologic tests will allow more rational therapeutic decision-making and hence influence the long-term outcome of the disease will be determined by further study.

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