Anti-CCP abs in the management and pathogenesis of RA

by Prof. Dr. Walther J. van Venrooij and Dr. Erik Vossenaar

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease affecting about 1% of the population. Diagnosing RA as early in the disease process as possible is important, since a significant proportion of patients develop irreversible joint damage shortly after disease onset. A new test measuring anti-CCP antibodies shows remarkable specificity for RA (97-98%) with a sensitivity of 75-80%. Recently, three independent studies have shown that these specific antibodies can be detected years before the first clinical signs of RA, and thus accurately predict disease development. It is also becoming increasingly clear that the presence of anti-CCP antibodies indicates that erosive RA is developing.

Attention has recently been drawn [1] to a novel serological test for the diagnosis of rheumatoid arthritis (RA). This test, marketed by Axis-Shield Diagnostics (Scotland) and Euro-Diagnostica (The Netherlands), measures antibodies directed to cyclic citrullinated peptides (CCP), and is generally referred to in the scientific literature as the anti-CCP test.

Specificity and sensitivity of anti-CCP for RA
From a clinical point of view, the ideal serological marker for RA should not only be highly specific for the disease but also be able to distinguish RA from other arthritides that mimic RA. The marker should also be present in the majority of patients (good sensitivity). Furthermore, the marker should be present very early in the disease and have the ability to predict disease outcome. From the viewpoint of laboratory management, the serological marker should be detectable with a reproducible and easily performed test. Recent data from several laboratories indicate that the CCP2 system meets all these requirements.

The first version of the CCP test (CCP1), although very specific for RA, was not very sensitive (40-60%; reviewed in [2]). Following further development a second generation test (CCP2) was introduced in 2002. This newer test was not only very specific for RA (97-98%), but also demonstrated good sensitivity (75-80%). As detailed in several recent reviews e.g. [3, 4] and publications [1, 5], there is general agreement about the excellent diagnostic properties of the CCP2 test. Universally the performance of the CCP2 test has been reported to be superior to that of rheumatoid factor (RF), the antibody system that has been used for more than 50 years, and is currently the only serological parameter in the ACR criteria for the classification of RA.

The high specificity of the CCP2 test enables it to distinguish RA from other rheumatic diseases such as systemic lupus erythematosus (SLE) or Sjögren’s syndrome or other forms of joint disease. For example, patients with chronic hepatitis C virus (HCV) infection often display extra-hepatic manifestations among which arthropathy is common, affecting up to 20% of HCV-infected individuals. Since many HCV infected patients are RF positive, this test has limitations in discriminating HCV-related arthritis from RA. In two very recent studies, reviewed in [3], it was shown that in a group of randomly selected HCV patients none were positive for anti-CCP2, while more than 31% were positive for RF. These results further support the utility of the CCP2 test as a specific and reliable diagnostic tool for RA.

The sensitivity of the CCP2 test for RA is comparable to the sensitivity of the IgM-RF test, generally around 75-80% [3, 5]. It is however important to appreciate that the apparent sensitivity is dependent upon the composition of the patient population. Typically, the sensitivity is high when the cohort is comprised of established RA patients, and lower when more early RA patients are included (by definition these cohorts will contain a relatively high proportion of patients with other forms of arthritis).

Anti-CCP is present early in disease
In healthy individuals the occurrence of anti-CCP antibodies is less than 1%. When a random population attending a rheumatology clinic were tested for anti-CCP, about 2-5% of the patients tested positive, but did not appear to have RA (our unpublished observations). A similar phenomenon was observed when the population of an early arthritis clinic was tested. Two recent studies [6, 7] have provided clear evidence that such supposedly "false positive" individuals might actually be in the process of developing RA.

Rantapää-Dahlqvist and collaborators [6] analysed blood samples from 83 blood donors who subsequently developed RA [Figure 1]. These investigators reported that anti-CCP2 antibody could be detected in some patients 10 years before appearance of the first clinical symptoms. The percentage of anti-CCP2 positive individuals (25% were positive more than 1.3 years before onset of the first symptoms) increased sharply to 52% in the last 1.5 years before manifestation of the first symptoms of the disease. RFs were also detectable in the pre-disease serum samples, although at lower frequencies than anti-CCP antibodies (IgM-RF: 15% >1.5 yr, 30% ≥1.5 yr; IgG-RF: 12% and 27%; IgA-RF: 29% and 39%). More than 70% of the patients were anti-CCP2 positive at their first visit to the rheumatology clinic [6].

In a similar type of study, Nielen and co-workers [7] measured anti-CCP1 and IgM-RF levels in serial blood samples of 72 blood donors that later developed RA.
Anti-CCP positivity could be observed up to 14 years before the first clinical symptoms and 41% of the patients were CCP1 positive at presentation to the clinician. For IgM-RF the corresponding parameters were 10 years and 28% positivity. Thus, anti-CCP detected more positive subjects and detected them longer before the start of the complaints compared to IgM-RF [7]. The conclusion from these studies was that anti-CCP antibody is superior to RF in its ability to predict the development of RA.

Other recent studies point to the same conclusion. Jansen and co-workers [8] tried to discriminate RA from undifferentiated polyarthritis at presentation. They reported that the combined presence of IgM-RF and anti-CCP1 is able to predict which patients with early arthritis ultimately develop RA with a sensitivity of 55% and a specificity of close to 97%. A similar study using the CCP2 test was performed by van Gaalen and co-workers [9]. In this study 318 patients out of 936 patients attending an early arthritis clinic could not be diagnosed as having RA at first presentation and were thus classified as undifferentiated arthritis (UA). After 3 years of follow-up 40% of the UA patients were clinically classified as RA. Of the UA patients that were negative for anti-CCP at baseline, 25% developed RA in 3 years. By contrast, 93% of the UA patients with a positive anti-CCP2 test at baseline, developed RA within 3 years (79% after 1 year), giving an odds ratio (OR) of 38. A very recent study of Vittecoq and co-workers studying 314 early arthritis patients confirmed these observations. In this study within 12 months of follow-up 90% of the patients that were CCP positive at baseline were classified as established RA patients [10]. The conclusion from these studies is that anti-CCP antibodies are present early in disease, and that their presence is able to accurately predict the development of RA.

**Prognostic ability of anti-CCP**

It has been known for some time that IgM-RF antibodies are able to predict joint erosions in RA patients. Several studies performed with the relatively insensitive first generation CCP1 test also showed that the presence of anti-CCP may predict erosive disease (reviewed in [2]). Similar results have now been obtained using the CCP2 test. Forslind and colleagues [11] assessed anti-CCP2 in 379 early-RA patients and measured radiological joint damage and disease progression after two years follow-up. They found that the presence of anti-CCP2 at baseline was associated with significantly higher Larsen scores both at baseline and at endpoint compared to RF and other disease parameters [11]. In another study, Kastbom and co-workers [12] followed 242 patients with recent-onset RA for three years. Their results showed that anti-CCP2 antibody had similar diagnostic sensitivity to RF in early RA, but was superior as a predictor of the disease course over three years.

All these studies indicate that the presence of anti-CCP antibodies may predict erosive disease. However, the weight of evidence that anti-CCP antibody is present preferentially in patients with erosive disease cannot exclude the fact that this may not be the case in all individual patients. How can we be sure that (erosive) RA is developing in a CCP-positive individual without obvious clinical complaints? The answer to this question is the Holy Grail in RA and certainly needs additional study. Given the fact that RA is likely to be a multi-factorial disease, future investigations will focus on combination models to identify individuals who have the highest probability of developing RA. Arguably such an "RA passport" [Table 1] should contain serological data (IgM-RF, OR of about 2 and anti-CCP2, OR of about 25-39), genetic data (e.g. HLA-DR4, OR of about 2) and some clinical parameters as suggested by Visser and co-workers [13]. At this time it is clear that given its high odds ratio, the measurement of anti-CCP2 antibody adds an important parameter in such an RA passport.

**References**


**Table 1. RA passport: factors predicting the future development of RA**

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<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Genetic factors</strong></td>
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<tr>
<td>HLA-DR4</td>
<td>~2</td>
<td>[14]</td>
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<tr>
<td><strong>Serological factors</strong></td>
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<tr>
<td>Presence of IgM-RF</td>
<td>~2</td>
<td>[6,9,14]</td>
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<tr>
<td>Presence of anti-CCP2</td>
<td>25-39</td>
<td>[6,9,14]</td>
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