During the past few years, much enthusiasm has greeted a new laboratory test that measures autoantibodies reactive with synthetic peptides containing the unusual amino acid citrulline, a posttranslationally modified arginine residue (1). Data from several investigators indicated that anti-citrullinated peptide autoantibodies (ACPAs), including anti-cyclic citrullinated peptide (anti-CCP) antibodies, were specifically present in the sera of patients with rheumatoid arthritis (RA); increased specificity is the major advantage of this test (1, 2). Now, in this issue of the Journal, Hoffman et al. (3) prospectively evaluated, in a setting reflecting everyday rheumatologic practice for prevalence of RA, the diagnostic performance of two classic assays for rheumatoid factor (RF) and methods for ACPA detection. Using ROC curve analysis, their study showed that RF has a better overall diagnostic performance than ACPAs. However, when high-specificity cutoffs were selected, one of the ACPA assays (anti-pepA) performed better than RF assays. Importantly, combining one RF assay with one of the ACPA assays increased positive predictive value. Combining one serologic marker with the finding of swollen joints also reveals high positive predictive value.

Two of the strengths of their study were that its design reflected everyday rheumatologic practice and that the composition of the control group reflected the natural prevalence of diseases in cases for which serologic markers for RA are requested. Their data for specificity, sensitivity, and predictive values are thus easier to interpret. The study included 1003 consecutive patients in situations where the rheumatologist would typically request RF determination. Importantly, diagnoses were established after a 1-year follow-up, and the clinicians were unaware of the test results obtained through the study. In addition, ACPA results were not available to the clinicians during the follow-up period.

One caution is warranted with respect to the study design; patients were entered in the study when they were seen with a new diagnostic problem for which RA was included in the differential diagnosis. Thus, these patients were not necessarily early arthritis patients. Moreover, because RF was part of the criteria used for diagnosis, the diagnostic value of RF could be overestimated, as pointed out by the authors.

Another particular feature of the study by Hoffman et al. (3) is that the test values used are scan values so that continuous data can be obtained. Moreover, the authors have focused on the data obtained with a cutoff corresponding to a specificity of 98%. Because of these features, the diagnostic performance characteristics of their assay may differ from those obtained by laboratories that use commercial assays in which the test results are reported as positive or negative based on predetermined cutoff values. A cautionary note is also warranted with respect to the potential differences among ACPA assay reagent sets used in clinical laboratories, as was clearly shown in this study in which the sensitivity of anti-pepA antibodies was significantly better than that of anti-pepB antibodies.

From the clinician’s point of view, it is beneficial to outline briefly the current clinical practice to better understand the diagnostic performance and predictive value of RF, ACPAs, and HLA class II shared epitope for the diagnosis of RA, as discussed by Hoffman et al. (3). Clinicians are using more aggressive forms of therapy fairly early in the course of disease in the hope of diminishing the long-term morbidity associated with RA. Because such treatments can have major side effects, it is important to diagnose RA accurately before initiating early aggressive therapy. To determine a strong likelihood of RA, one needs a laboratory test that is more specific than RF; ACPA may meet that requirement.

What lessons can we learn from the study by Hoffman et al. (3)? The main implication from these data is that use of ACPAs in addition to RF has a better predictive value than the use of RF alone in the detection of RA in high-risk populations. The second lesson is that, as with all tests, the sensitivity and specificity of the ACPA assay vary with the cutoff values used. Nonetheless, although false-positive results with this test are possible, one would anticipate a much lower false-positive rate than with RF at reasonable cutoff points for the two tests. A cautionary note is warranted with respect to the use of this assay for routine use as a screening test. Even a highly specific test will generate many false-positive results if used in a population that does not have a reasonably high prior probability of having RA. This is in agreement with the authors’ own opinion, as outlined in their discussion of the results. In addition, the sensitivity of these assays is likely to depend on the population examined. Hospital-based patients tend to have more advanced disease; those patients are more likely to be ACPA-positive.

Hoffman et al. (3) found in their study that combining HLA class II shared epitopes with RF or ACPAs did not increase the diagnostic performance of serologic markers alone. This is in contrast to findings by other investigators who have recently reported that the presence of anti-CCP antibodies together with shared epitope (SE) gene carriage is associated with a very high relative risk for future development of RA (4). Interestingly, HLA class II RA susceptibility alleles were found to be associated with production of anti-CCP antibodies, and more severe disease progression was found in RA patients who had both anti-CCP antibodies and SE alleles (5). Despite these interesting observations, the usefulness of testing for HLA class II RA susceptibility alleles in clinical settings is likely...
to be complicated by the racial and ethnic variation of these HLA class II susceptibility alleles.

What is the role of ACPA assays in clinical practice? Experts will likely disagree about how ACPA assays should be used. Nevertheless, recent studies allow us to speculate. On the basis of such studies, testing for anti-CCP antibodies in undifferentiated arthritis allows accurate prediction of a substantial number of patients who will fulfill the American College of Rheumatology criteria for RA. In some patients, the latency between detection of anti-CCP antibodies and appearance of disease was several years (7, 8).

Anti-CCP antibodies may also help in differentiating other arthritides from RA, such as in patients who have a positive RF test and equivocal findings for RA. Examples include hepatitis C infection, sarcoidosis, and occasionally, spondyloarthropathy and pseudogout. The finding that anti-CCP antibodies were not observed in patients with hepatitis C viral infections with or without RF and/or cryoglobulinemia (9, 10) is indicative of the specificity of the anti-CCP test. Moreover, anti-CCP antibodies were also found in patients with juvenile idiopathic arthritis (11).

Other investigators have recently reported that anti-CCP antibodies are an independent predictor of radiologic damage and progression and that the combined analysis of anti-CCP antibodies and IgM RF provides the most accurate prediction of erosive and progressive disease (12, 13). Although prediction in early RA is still far from perfect, the use of anti-CCP tests in clinical practice could help rheumatologists to reach judicious treatment decisions. However, we still need to know whether high anti-CCP concentrations correlate with more disabling disease and where the “high-titer” cutoff should be.

Taken together, if the early promise of ACPA testing holds true, this test could become the test of choice in patients with undiagnosed polyarthritis and may even influence the diagnostic practices in rheumatology. At the present time, it is likely that clinicians will use a combination of RF and ACPA tests routinely. Additional prospective studies are necessary to further evaluate the clinical utility of ACPA assays in RA.

References


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DOI: 10.1373/clinchem.2004.043018