Publication of the Month

Excellence in Autoimmunity

March 03/10: Citrullinated peptides and proteins for the diagnosis of RA

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The use of citrullinated peptides and proteins for the diagnosis of rheumatoid arthritis
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Introduction:

The presence or absence of antibodies to citrullinated peptides/proteins (ACPA), such as CCP, vimentin, filaggrin etc., is an important parameter that helps a clinician set a diagnosis of early rheumatoid arthritis (RA) and, hence, initiate treatment. There are several commercial tests available to measure ACPA levels, although it can be difficult to decide what the best test for a given clinical question is. In this review the authors analyzed literature data in which the diagnostic and other properties of various ACPA tests are compared.

Content:

Using the CCP2 test, about 75% of RA patients with a long-term established diagnosis and 61% of patients with established early RA were anti-CCP positive. The number of anti-CCP negative sera that show reactivity with citrullinated antigens other than CCP is very small. Taken together, this data indicates that the vast majority of ACPA can be detected by the CCP2 test.
There are at least six tests available using the CCP2 peptides as antigen (supplied by Axis-Shield, Euro-Diagnostica, Euroimmun, Inova, Phadia, and Abbott). Despite using the same set of CCP2 peptides, these assays tend to show small differences in their dignostic profiles due to differences of solid support materials and reagents.
Besides the CCP2 test, several other ACPA tests using different substrates have been made commercially available, for example a test for antibodies against citrullinated mutated human vimentin (MCV from Orgentec), Inova's CCP3 test and its variant Inova CCP3.1, the Genesis citrullinated recombinant rat filaggrin, the Aesku citrullinated IgG peptide and the Astra citrullinated Epstein-Barr virus nuclear antigen-derived peptide.

A comparison of the sensitivity of various ACPA and RF tests at a stratified specificity of 97.3% looking at 10 different comparative studies showed the following results:

Number of references	Stratified specificity (%)	Sensitivity at stratified specificity (%)			
		CCP2	CCP3	MCV	RF
10	97.3	69.2	66.1	57.4	29.9

In these 10 studies, also positive and negative predictive values (PPV, NPV) of the tests were compared:

Number of references	CCP2		CCP3		MCV		RF	
	PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)
10	91.2	78.4	84.9	79.8	80.4	81.5	75.9	75.3

Conclusion:

The authors summarize, that for diagnostic purposes the CCP2 test has the highest specificity, the highest sensitivity in stratified studies and the highest positive predictive value. For the prediction of future joint destruction the CCP2, MCV, and CCP3 test may be used. The ability to predict the likelihood of not achieving sustained disease-modifying antirheumatic drug-free remission was highest for the CCP2 test.

Comment:

The results of this review show clearly that anti-CCP2 tests are the most useful assays for the diagnosis of rheumatoid arthritis. All other serological assays may possibly give additional information but cannot substitute anti-CCP2 tests.