Anti-Citrullinated Peptide/Protein Antibodies and Structural Prognosis of Rheumatoid Arthritis: Quantity Versus Quality

Anti-citrullinated peptide antibodies (ACPA) are the most specific known marker for rheumatoid arthritis (RA) in adults. ACPA develop several years before the first clinical manifestations of arthritis and are highly predictive of progression from undifferentiated arthritis to definite RA¹, as demonstrated in several longitudinal cohort studies of patients with early undifferentiated arthritis. The presence of ACPA is among the 2010 American College of Rheumatology/European League Against Rheumatism criteria for persistent, nonerosive polyarthritis requiring methotrexate therapy. Of the 6 points needed to warrant methotrexate therapy, the presence of ACPA provides 2 points if the titer is low (2–3 times the upper limit of normal) and 3 points if the titer is high (more than 3 times the upper limit of normal). Thus, quantitative considerations are important when using ACPA for diagnostic purposes.

ACPA also help to predict outcomes. In cross-sectional and longitudinal cohort studies of patients with early RA, the presence of ACPA was independent from the disease phenotype (presentation and topographic distribution of the affected joints) but was significantly associated with disease activity², evaluated for instance using the Health Assessment Questionnaire score and, to an even greater extent, with structural disease progression evaluated using the Larsen radiographic score or, preferably, the Sharp score as modified by van der Heide^{2,3}.

An article by Shiozawa, *et al*⁴ in this issue of *The Journal* reports that a positive ELISA-cyclic citrullinated peptide antibody-2 (CCP) test for ACPA was associated with greater radiographic progression in a cohort of 396 patients with early RA (< 2 yrs), compared to patients having negative tests for ACPA. Given that many patients with RA with ACPA also have IgM rheumatoid factors (IgM-RF), the authors considered the subgroup of 41 patients with ACPA but not IgM-RF. When the 2-year followup radiographs in this subgroup were compared to the 86 patients with neither ACPA nor IgM-RF, having ACPA was again associated with greater radiographic progression.

Although ACPA titer seems positively correlated with the modified Sharp score, the cumulative proportion of patients with joint destruction is not significantly different between RA patients with low titers and those with high titers. This result is at variance with findings reported in 2008 by Norwegian investigators who studied 238 patients with fairly recent RA at baseline (mean disease duration 2.3 yrs), including 125 patients for whom hand radiographs were available at baseline and 10 years later⁵. The odds ratio (OR) for radiographic progression increased from 2.5 (95% CI 0.9–7.2) in the subgroup with low to moderate ACPA titers (as assessed using an anti-CCP test) to 9.9 (95% CI 2.7–36.6) in those with high ACPA titers⁵. The available data, therefore, suggest that changes in either direction in the ACPA titer versus baseline have no value for predicting subsequent outcomes⁶.

Thus, the results discussed above are conflicting. No independent studies other than the one described above⁵ are available to date. Therefore, in the current state of knowledge, high ACPA titers cannot be used to predict a greater risk of radiographic progression compared to low titers. In addition, there was no adjustment for a number of confounding factors such as smoking history⁷ or lung disease⁸.

Apart from quantitative considerations, qualitative features of ACPA may help to predict joint damage severity. These features may include the ACPA isotype, the number of isotypes produced, the IgG subclass, the type of citrullinated protein targeted by the antibodies^{9,10}, or even, for a given citrullinated protein, the epitopes present on the surface of the molecule or concealed within the molecule (cryptic epitopes)¹¹. To date, published studies on ACPA isotypes and subclasses have been inconclusive.

Among all these features of ACPA, those investigated in the most advanced studies are the various citrullinated targets such as filaggrin, mutated vimentin^{12,13}, alpha-eno-lase¹⁴, fibrin and its peptides, myelin basic protein, Sa protein¹⁵, Epstein-Barr proteins¹⁶, binding immunoglobulin protein, and citrullinated collagen. Few studies compared

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the predictive value of the various ACPA present in the same serum, and qualitative studies focused on a small number of specificities^{15,17,18,19,20}. Most published studies used non-commercial, inhouse tests, which is an obstacle to replication of the findings.

Lastly, emphasis has recently been placed on antibodies that target homocitrullinated proteins (produced by conversion via carbamylation of lysine residues to homocitrulline residues). The joint prognosis in RA without ACPA but with anti-carbamylated protein antibodies seems similar to that of RA with ACPA/CCP, i.e., more severe than that of RA without either type of antibody²¹. Studies are needed to determine the specificity of anti-carbamylated protein antibodies compared to ACPA for diagnosing RA. However, these newly identified antibodies hold promise for predicting the outcome of early RA.

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