Exploring the landscape of rheumatoid arthritis: piecing together risk factors and autoantibodies

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Clinical outcomes in relation to autoantibodies

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Correspondence

Anti-citrullinated protein antibodies dominate the association of long-term outcomes and anti-modified protein antibodies in rheumatoid arthritis

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With interest we read the article by Nijjar et al[1] who measured three anti-modified protein antibodies (AMPA): anti-citrullinated protein antibodies (ACPA), anti-carbamylated protein antibodies (anti-CarP) and anti-acetylated protein antibodies (AAPA) in rheumatoid arthritis (RA) patients. They observed more bone erosions in patients positive for three versus one AMPA and conclude that testing for three AMPA would optimally predict future radiographic progression.

We explored whether this could also be found in other cohorts and for additional important outcomes, such as sustained drugfree remission (SDFR).

In 612 RA patients from the Leiden Early Arthritis Clinic, ACPA IgG with anti-CCP2-assays, anti-CarP IgG using homocitrullinated and native (as a control) fetal calf serum, and AAPA IgG by means of novel assays consisting of cyclic peptides with either acetylated or norleucine residues (as a control) were measured. Sharp-van der Heijde scores (SHS) were determined in 2685 sets of radiographs with yearly intervals for 7 years until 2006. A multivariate normal regression model was used as described before.[2] SDFR was defined as the absence of clinical synovitis after discontinuation of DMARD treatment and its association with autoantibody-status was assessed with Kaplan-Meier curves. The very small number of patients single-positive for AAPA (n=4, 1%) precluded analyses in this subgroup.

The baseline characteristics and frequency of autoantibodies are shown in supplementary table 1. Although ordinal regression analyses revealed several associations between baseline characteristics and number of autoantibodies as described before,[3] there was no difference in clinical phenotype between patients positive for one versus three autoantibodies (supplementary table 2).

Regarding radiographic progression, a higher SHS was found in triple-positive versus single-positive patients (figure 1A, p=0·04) as found by Nijjar et al. To investigate if the higher SHS was due to the number of autoantibodies or a specific autoantibody, analyses were stratified for all three AMPAs. Interestingly, no difference was found in SHS between all ACPA-positive strata (figure 1B). In the ACPA-negative stratum, a significant difference was found between patients with zero antibodies and solely anti-CarP (p=0·02).

Concerning SDFR, this was achieved by less triple-antibody-positive patients than single-antibody-positive patients (P<0·001), figure 1C. After stratification, no difference was found in the percentage of SDFR in all ACPA-positive strata (figure 1D), or in the ACPA-negative stratum, figure 1D.

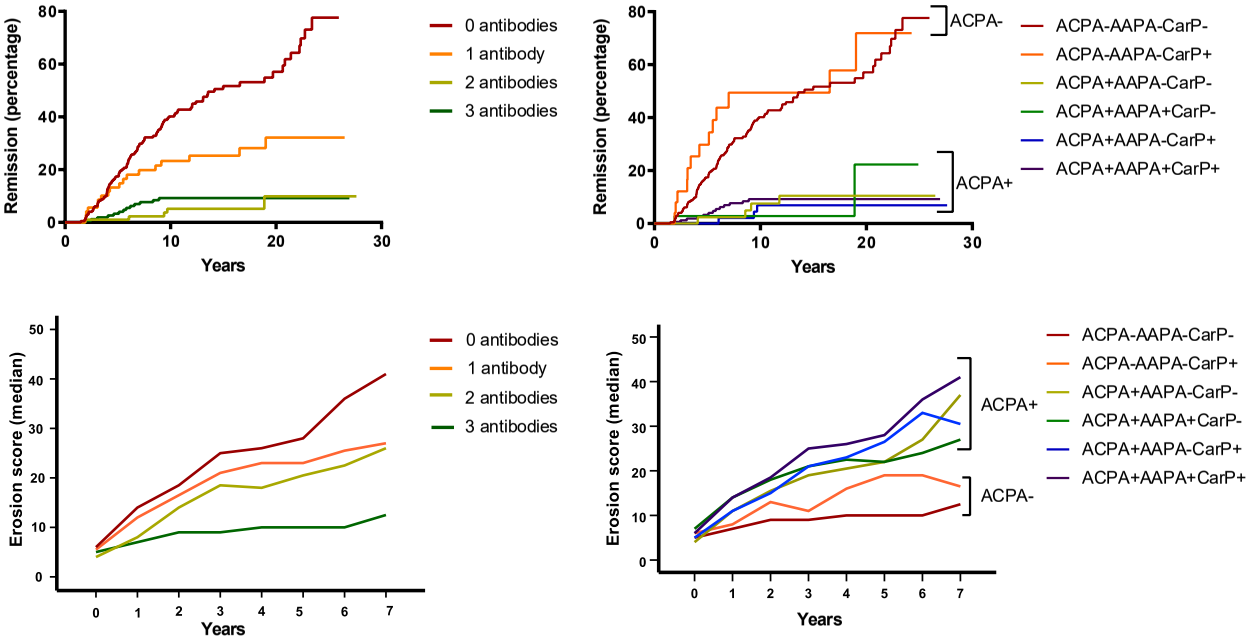

Figure 1. Sustained drug free remission (SDFR) and erosion scores according to the presence of autoantibodies. Figure 1A: Median erosion scores assessed by the Sharp-van der Heijde method (SHS) during the disease course stratified for number of autoantibodies (n=503). All comparisons between groups were statistically significant except between 1 versus 2 and 2 versus 3 antibodies. Figure 1B: Median erosion scores assessed by the SHS during the disease course stratified for anti-acetylated protein antibodies (ACPA), anti-acetylated protein antibodies (AAPA) and anti-carbamylated protein antibodies (anti-CarP) (n=499). SHS did not differ significantly between all ACPA-positive strata. In the ACPA-negative stratum a significant difference was found between 0 antibodies and anti-CarP single-positive patients, (p=0.02). Figure 1C: Kaplan-Meijer curve of the percentage of patients that achieved SDFR stratified for the number of autoantibodies (n=565). All comparisons between groups were statistically significant except between 1 versus 2 antibodies. Figure 1D: Kaplan-Meijer curve of the percentage of patients that achieves SDFR stratified for ACPA, AAPA and anti-CarP (n=561). The percentage of SDFR did not differ between all ACPA-positive strata and did also not differ between the ACPA-negative strata.

Our stratified analyses indicate that in ACPA-positive patients, the presence of other AMPA influences neither radiographic progression, nor the chance of SDFR. Thus, long-term clinical phenotype in RA is particularly dependent on the presence of ACPA, and less on the presence of other AMPA. Therefore, there appears to be no added value of testing the other AMPA for predicting clinical outcome in ACPA-positive patients.

Supplementary material
Supplementary material available at: https://www.sciencedirect.com/science/article/pii/S2665991322000959?via%3Dihub

Declaration of interests
We declare no competing interests.

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