Genetic studies in rheumatoid arthritis

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Chapter 10

Association of tumor necrosis factorα polymorphism and radiographic progression in rheumatoid arthritis: comment on the article by Khanna *et al*.

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To the Editor:

We read with interest the article by Khanna et al regarding the association between the tumor necrosis factor (*TNFA*) -308 polymorphism as well as the HLA–DRB1 shared epitope (SE) alleles and the level of radiographic damage in rheumatoid arthritis (RA) (1). The authors concluded that there is an association between the *TNFA* -308 A allele and the rate of radiographic joint destruction, but that the SE alleles are not associated with the level of joint damage in seropositive RA. In our opinion, both conclusions are questionable. First, Khanna et al investigated the Sharp scores of 189 rheumatoid factor (RF)–positive patients with early RA during 5 years of followup (completed by 45 patients) and compared the scores between patients with and those without SE alleles. The results depended on the method of analysis and on the subgroup of patients. In an analysis unweighted for the number of observations per patient, the presence of SE alleles was not associated with RA severity; in a weighted analysis assessing the total group of patients, the presence of SE alleles was associated with less severe disease; and in an analysis assessing the subgroup of white patients, the presence of SE alleles was associated with more severe joint destruction.

The authors provided no explanation for these discordant findings. The most likely clarification is the fact that the authors selected a group of RF-positive patients. In RA, the presence of RF is highly correlated with the presence of anti–cyclic citrullinated peptide (anti-CCP) antibodies: only 13–18% of RF-positive RA patients are anti-CCP negative (2,3). Furthermore, we recently demonstrated that the SE alleles are primarily a risk factor for the presence of anti-CCP antibodies, and that the presence of SE alleles in RA patients with anti-CCP antibodies is not associated with the development of RA (4). In addition, our analysis on the association between the SE alleles in the presence of anti-CCP antibodies and the Sharp/van der Heijde scores during 4 years of followup was inconclusive; although a trend for more severe joint destruction among SE-positive, anti-CCP–positive patients compared with SE-negative, anti-CCP–positive patients was observed, the number of patients was too low to reach a definite conclusion (5).

The anti-CCP antibody status of patients in the study by Khanna et al is not known, but considering the fact that all patients were RF positive, it is likely that the majority of the patients were anti-CCP positive. The fluctuating results on the absence or presence of an association between SE alleles and the rate of joint destruction in the study by Khanna and colleagues indicates that the sample size of that study was too small to conclude definitely on the association between the SE alleles and the severity of autoantibody-positive RA.

Second, Khanna et al examined whether the *TNFA*-308 G-to-A polymorphism was associated with radiographic joint damage in RF-positive RA. The total Sharp score and the frequency of ≥2 erosions at baseline and during followup were not differently distributed between *TNFA* A and non-A carriers (1). However, when the rate of radiographic progression was derived from the slope of the regression line and weighted for the number of radiographic observations per patient, patients with genotype AA+AG had significantly higher Sharp scores than did patients with genotype GG (1).

The authors also reported that the *TNFA*-308 A alleles are in strong linkage disequilibrium with HLA–DRB1*0301. Because it was recently reported in North American and Dutch patients that the HLA–DRB1*0301 allele (and the A1;B8;DR3 haplotype)is associated with anti-CCP–negative RA (2,3), and, because anti-CCP–negative RA is associated with less severe joint damage, the observation that the *TNFA* -308 A allele is associated with a higher rate of joint destruction seems contrasting. Considering the linkage disequilibrium between the *TNFA* -308 A allele and HLA–DRB1*0301, the analysis on the association between this polymorphism and the rate of joint destruction should be corrected for the presence or absence of anti-CCP antibodies.

Therefore, we determined the *TNFA* -308 polymorphism in 327 white patients who presented to the Leiden Early Arthritis Clinic between 1993 and 2000 and in whom RA was diagnosed during the first year after inclusion. Eight patients (2%) had genotype AA, 94 patients (29%) had genotype AG, and 225 patients (69%) had genotype GG. Anti-CCP antibodies were present in 182 patients (56%). Radiographs were available for 267 patients after 1 year of followup, for 205 patients after 2 years, and for 154 patients after 4 years of followup. The Sharp/van der Heijde scores were not significantly different between the RA patients who carried a *TNFA* -308 A allele and the patients who did not carry an A allele (Figure 1). Subsequently, this analysis was performed in subgroups of patients with and those without anti-CCP antibodies; the results revealed no significant differences. A linear regression analysis with the radiographic progression score as dependent variable and age, sex, *TNFA* _308 A/non-A carriership, and anti-CCP antibody status as possible explanatory variables revealed that only the presence of anti-CCP antibodies (regression coefficient 9.0, standard error 2.3, P <0.001) and age (regression coefficient 0.2, standard error 0.07, P < 0.003) were significantly associated with radiographic joint destruction.

In our opinion, because the *TNFA* -308 A allele is in linkage disequilibrium with HLA–DR3, which is reported to be associated with only anti-CCP–negative RA, and RA patients without anti-CCP antibodies generally experience a less severe disease course compared with RA patients who have anti-CCP antibodies, the analysis of the association between the *TNFA* -308 A allele and the rate of joint destruction should be corrected for the presence or absence of anti-CCP antibodies. Therefore, we analyzed white RA patients who were included in the Leiden Early Arthritis Clinic, and we did not observe an association between the *TNFA* -308 A allele and radiographic joint destruction in RA patients, neither in the presence nor in the absence of anti-CCP antibodies.

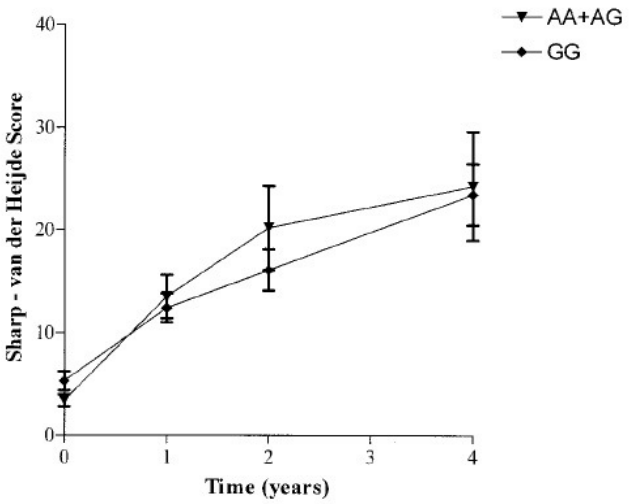

Figure 1. Sharp/van der Heijde scores (mean ± SEM) in rheumatoid arthritis patients with *TNFA* −308 genotype AA + AG and those with genotype GG, during 4 years of followup. P = 0.8, 0.7, 0.8, and 0.7, respectively, at baseline and at 1 year, 2 years, and 4 years of followup, by Mann-Whitney test.