Polymorphic alleles in Exon 1 of the CTLA4 gene do not predict the response to Abatacept

Sirs,

Abatacept (CTLA4–Ig) (ABA) is a fusion protein designed to modulate the T cell co-stimulatory signal mediated by the CD28–CD80/86 pathway, approved for the treatment of moderate to severe rheumatoid arthritis (RA) (1). However, in our experience, more than half of the patients failed to achieve a clinical response after six months of treatment. CTLA4, CD80 and CD86 polymorphisms have been widely investigated in relation to susceptibility to autoimmune diseases (2-4), and three single nucleotide polymorphisms (SNPs) (5) of the CTLA4 gene seem to be associated with a lack of peripheral tolerance (6).

The aim of this study was to evaluate the efficacy of six months' treatment with ABA on the basis of the EULAR improvement criteria and analyse polymorphic variants of the CD80, CD86 and CTLA4 genes in a cohort of RA patients. We evaluated 32 consecutive RA patients (29 F, 3 M); mean age 55.9±11.2 years; mean disease duration 16.9±10.2 years; diagnosed using the new ACR/EULAR criteria (7), treated with ABA. Thirty-one of patients had been previously treated with at least one TNF blocker. Table I shows the demographic and clinical characteristics of the patients under the study. All of the patients were clinically and laboratory assessed at baseline and after six months of therapy. Disease activity was assessed at the same times using the disease activity score 28 (DAS28) and response was evaluated according to the EULAR improvement criteria. The study was approved by the hospitals' ethics committees, and the written informed consent of the patients was obtained before they were enrolled.

We analysed the rs3087243 (CT60), rs231775 (+49A>G) and rs5742909 (318 C>T) SNPs of the CTLA4 gene, the rs1129055 (1057 A>G) SNP of the CD86 gene, and the rs 57271503 (1304 A>G) single polymorphism nucleotides (SNP) of the CD80 gene. The genotypes were determined using fluorogenic allele-specific oligonucleotide probes (TaqMan assay C_7514879_10, Applied Biosystems, Foster City, CA) and a 7900HT Fast real-time PCR system (Applied Biosystems).

The patients were divided into responders and non-responders on the basis of their DAS28 scores at baseline and after six months of treatment. The multivariate analyses were performed using logistic regression models.

The mean DAS28 score decreased from 5.06±1.4 at baseline to3.98±1.35 after six months' treatment with ABA. On the basis of the EULAR criteria, 57% of the patients were non-responders, 28% were moderate responders, 15% were good responders.

In relation to the polymorphisms of the CTLA4 gene, the CT60 AA genotype was found in 14 subjects, the GA genotype in eight, and the GG genotype in ten. Eight patients carried the +49AA genotype, 21 the +49GA genotype, three the +49GG genotype. The -318 CC, CT and TT genotypes were respectively found in 21, nine and two subjects.

AA CD86 SNP was found in three patients, the GA variant in 12, and the GG variant in 17, whereas the GG, GA and AA CD80 SNPs were respectively found in three, 27 and two patients. A higher probability of a good EULAR response was associated with higher CRP at baseline (OR 1.16, 95% CI 1.01-1.34; p=0.041), while age at the start of treatment (p=0.9534), the presence of the AA CD80 (p=0.922) or AA CD86 (p=0.999) was not associated.

No significant association was found between clinical response at six months and the each SNPs examined.

A systematic literature review identified the +49A>G, -318 C>T, and CT60 SNPs as candidate polymorphisms involved in the susceptibility to autoimmune diseases (2-4, 8, 9). However, no significant association was found between the +49A>G SNP, -318 C>T SNP, CT60 SNP, 1304 G>A CD80, 1057G>A CD86 SNPs and clinical response after six months of treatment. Data from previous literature mostly agree on the statement that the +49AA genotype is associated with higher production of CTLA4 (10), while the GG genotype is associated with a deficit in the molecule, resulting in a lack of peripheral tolerance (11).

However, our data suggest that the +49 A>G SNP of CTLA4 is independent from clinical outcome, as well as from clinical activity. In conclusion, to the best of our knowledge, this is the first study that has investigated the impact of allelic variants of the CD80/86-CD28/CTLA4 co-stimulatory system on the therapeutic response to ABA in a cohort of RA patients.

Table I. Demographic and clinical characteristics of the 32 patients studied. Mean values ± standard deviation (SD) or absolute numbers.

Variables	Patients
Age, years	55.9 ± 11.2
Females (%)	29 (90.6%)
Disease duration, years	16.9 ± 10.2
DAS28 at baseline	5.06 ± 1.4
Rheumatoid factor positive (number of the patients,%)	22 (68.75%)
Ongoing treatment	Number of patients
Methotrexate	20
Leflunomide	2
Hydroxychloroquine	1
Cyclosporine A	2
Corticosteroids	29

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