Treating leukocytoclastic vasculitis associated with etanercept therapy. Is it necessary to stop etanercept?

Antonio Juan, Bartolome Ribas, Cristina Nadal and Imnaculada Ros

J Rheumatol 2005;32;2061
http://www.jrheum.org/content/32/10/2061.citation

1. Sign up for TOCs and other alerts
   http://www.jrheum.org/alerts

2. Information on Subscriptions
   http://jrheum.com/faq

3. Information on permissions/orders of reprints
   http://jrheum.com/reprints_permissions

*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Our patient was a 60-year-old man with a 10-year history of seropositive and erosive rheumatoid arthritis (RA), who had been treated with gold salts and chloroquine, which were withdrawn because of inefficiency, and methotrexate, which was also withdrawn because the patient developed pulmonary fibrosis. In November 2002, because of the bad clinical evolution, etanercept 25 mg twice a week was added to his regular treatment of deflazacort 7.5 mg, calcium 500 mg, vitamin D 400 IU, and indomethacin 50–100 mg daily. At that time, laboratory examination showed antinuclear antibody (ANA) titer of 1/40; rheumatoid factor (RF) 315 IU/ml; negative dsDNA, anti-Sm, anti-SSA, anti-SSB, and ribonucleoprotein RNP antibodies; and complement levels within normal limits. He improved markedly and synergistic effects in vasculitis. Further, leflunomide has also been associated with vasculitis as a side effect. Indeed, LV has been described in association with etanercept in patients who received leflunomide at the same time. So leflunomide cannot be used preventively as a TNF-α blocking agent. The positive clinical response in our patient suggests leflunomide as a possible therapeutic resource against vasculitis for this kind of patient. It also seems reasonable that the TNF-α blocking agent need not always be withdrawn when this kind of side effect occurs. We have not found previous reports of improved vasculitis associated with treatment with TNF-α blocking agent except when treatment is stopped. In our patient, we ascribe improvement to leflunomide.

ANTONIO JUAN, MD, Department of Rheumatology, Hospital Son Llatzer; BARTOLOMÉ RIBAS, MD, Department of Rheumatology, Hospital San Juan de Dios; CRISTINA NADAL, MD, Department of Dermatology, Hospital Son Llatzer; IMNACULADA ROS, MD, Department of Rheumatology, Hospital Son Llatzer, Palma de Mallorca, Spain.

REFERENCES


Dr. Mohan replies

To the Editor:

In response to Juan, et al, review of available US Food and Drug Administration Adverse Events Reporting System data revealed there were 4 patients in the series that were reportedly continued on etanercept.
Outcomes regarding 2 of them are unknown. One patient improved on lowering the dosing to once a week and worsened again on increasing the dosage to twice a week. The other patient improved partially on discontinuation, but rechallenge one month later did not cause any worsening. Infliximab was continued in one patient with premedication with antihistamines and steroids, who was reported to be slowly improving. This suggests there may be more than one mechanism responsible for development of leukocytoclastic vasculitis (LV).

Three patients (2 on etanercept and one on infliximab) were taking concomitant leflunomide when they developed LV. One patient taking etanercept was not rechallenged, while the other had a positive rechallenge despite being on leflunomide. The patient on infliximab developed LV 4 days after the first infusion. The second infusion, which was due in 2 weeks, was held while awaiting resolution of the skin lesions. The next infusion was given 6 weeks after the first, and no recurrence of skin lesions was noted, indicating a negative rechallenge. This suggests that in these patients, leflunomide was not consistently effective against the development of drug-associated LV.

The response of Juan’s patient to leflunomide, however, adds to the possible list of interventions that one can attempt with a patient who has had a good therapeutic response to tumor necrosis factor (TNF) blockade but has unfortunately developed drug-associated LV. Other interventions include cautious rechallenge after resolution of skin lesions, premedication with antihistamines and corticosteroids, switching to another TNF-blocking agent, and reducing the dosage.

NIVEDITHA MOHAN, MBBS, Avera Research Institute, 2020 S. Norton Avenue, Sioux Falls, South Dakota 57108, USA.

Letters


To the Editor:

Genetic predisposition has been implicated in the pathogenesis of systemic lupus erythematosus (SLE) by various studies, although the etiology of SLE remains unclear. Associations with the complement C4AQ, HLA-DR, HLA-DQ, tumor necrosis factor, interleukin 10 (IL-10), bcl-2, and Fas-L have been reported, but genetic susceptibility has not yet been confirmed.

Cytotoxic T lymphocyte associated-4 (CTLA-4) and CD28 on T cells bind to CD80 and CD86, with CTLA-4 being a negative regulator of T cell activation. The ligation of CTLA-4 blocks CD28-dependent T cell activation and IL-2 accumulation. The CTLA-4 molecule is thought to terminate the immune response by CD28 and to keep the homeostatic balance of the immune system, so CTLA-4 would therefore be an important negative regulator of autoimmune diseases. Moreover, an increased level of soluble CTLA-4 in sera has been reported in SLE.

The CTLA-4 gene is located on chromosome 2q33, and dimorphisms are reported to be at positions –1661 and –1772 in the promoter region. The former is a substitution of adenine to guanine (–1661A/G), and the latter is a substitution of thymine to cytosine (–1772T/C). Recently, significant associations of the CTLA-4 –1772TT genotype and the –1772T allele with SLE were reported among Koreans. Fernandez-Blanco, et al also showed the involvement of CTLA-4 (–1772T/C) dimorphisms in SLE susceptibility. Controversially, Aguilar, et al observed no association in Spanish patients with SLE. Considering the immune-regulatory function of CTLA-4, the CTLA-4 gene is an interesting candidate as a disease-susceptible gene or genetic marker.

Sixty randomly selected unrelated Japanese patients with SLE (57 women and 3 men; age 38.4 ± 12.5 y) diagnosed according to the criteria of the American Rheumatism Association were examined. The control population consisted of 104 unrelated healthy volunteers.

The dimorphisms at positions –1661 and –1772 were detected by the polymerase chain reaction (PCR)-restriction fragment length polymorphism method of Hudson et al, using the specific oligonucleotide primers 5′-CTA AGA GCA TCC GCT TG ACC T-3′ and 5′-TTG GTG TGA TGC ACA GAA GCC TTT T-3′. PCR was performed under the following conditions: initial denaturation for 4 min at 94°C, annealing for 1 min at 58°C, extension for 1 min at 72°C, denaturation for 1 min at 94°C (30 cycles), and a final extension for 10 min at 72°C. The PCR product was digested using MseI for –1661 or Bbv1 for –1772 at 37°C for 4 h. Fisher’s exact test was used for comparisons.

Genotype frequencies of the –1661A/G and –1772T/C dimorphisms are shown in Table 1. The frequency of the –1772TT genotype was not increased in patients with SLE (31.7%). No CTLA-4 –1661A/G or –1772T/C genotypes were found to be significantly associated with SLE. The frequencies of alleles in patients and controls are also shown in Table 1. In the controls, the –1661A allele (89.9%) and the –1772T allele (57.7%) are predominant among Japanese. The allele frequency of –1772C was slightly increased in patients with SLE compared to the controls (47.5% vs 42.3%), but the difference was not significant. No –1661A/G or –1772T/C alleles were found to be significantly associated with SLE.

Associations between the CTLA-4 (–1772T/C) dimorphism and SLE have been described in several reports; however, these results are controversial. In our experiment, using Japanese SLE patients, no association of the –1772C/T dimorphism was observed. Our results are compatible with the observations by Aguilar, et al, Lee, et al also reported no association of the –1772C/T dimorphism with SLE using a metaanalysis, although they did observe a significant association of the +49A/G dimorphism with SLE. The significant increase in the –1772C allele reported in Spanish patients with SLE was different from the increase in the –1772TT allele observed in Koreans with SLE. Fernandez-Blanco, et al assumed that the different associations observed in Koreans and Spaniards with SLE would most likely be related to genetic differences in the pattern of haplotypes on the CTLA-4 locus between the Korean and Spanish populations. The frequencies of the –1772T/C genotypes and alleles were different between Korean controls and Spanish controls. The different observations between Koreans and Spaniards with SLE could also indicate that CTLA-4 (–1772T/C) itself would not contribute directly to the pathogenesis of SLE. Our results showed no association of the –1772T/C dimorphism in Japanese patients with SLE, although the distributions of the –1772T/C genotypes and alleles in Japanese controls were almost equal to the Korean controls. These data strongly suggest that the –1772T/C is not the susceptibility gene in Japanese with SLE. There also was no association of the –1661A/G dimorphism.

On the other hand, no association had previously been shown between SLE in Japanese and the CTLA-4 dimorphisms at positions –308 and +491. This observation was compatible with reports by Heward, et al, D’Alfonso, et al and Mehrian, et al, although the results are still controversial.

Taking our previous observations into consideration, it is very likely that the CTLA-4 gene is not genetically involved in the pathogenesis of SLE in Japanese.

FUJIO TAKEUCHI, MD, Department of Internal Medicine (Allergy and...
Rheumatology), Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; SHOJI KUWATA, MD, Associate Professor, 3rd Department of Internal Medicine, Faculty of Medicine, Teikyo University School of Medicine, Ichihara; MASAKI MORI, MD, Department of Internal Medicine (Allergy and Rheumatology), Faculty of Medicine, University of Tokyo. Address reprint requests to Dr. Takeuchi; E-mail: fujio-tky@umin.ac.jp

Supported by grants from the Ministry of Education, Culture, Sport, Science and Technology of Japan and The Manabe Foundation.

We thank Dr. Keiichiro Nakano and Dr. Kiyoaki Tanimoto, Tokyo University, for sampling; and Naoko Nakane and Natsuko Kobayashi for technical support.

REFERENCES


Correction