
**INSTRUCTIONS FOR LETTERS TO THE EDITOR**

**Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 4 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.**

***Contact.*** **The Managing Editor, The Journal of Rheumatology, 365 Bloor Street East, Suite 901, Toronto, ON CANADA M4W 3L4. Tel: 416-967-5155; Fax: 416-967-7556; E-mail:jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.**

## Treating Leukocytoclastic Vasculitis Associated with Etanercept Therapy. Is It Necessary to Stop Etanercept?

*To the Editor:*

We read with great interest the article by Mohan, *et al*[1], describing a series of 35 patients with leukocytoclastic vasculitis (LV) possibly related to tumor necrosis factor-α (TNF-α) blocking agents. The information is significant because a great number of patients presented unusual manifestations that were not observed during premarketing studies.

We would also like to describe a patient who presented some special manifestations that might complete the facts of the above series. At the same time, we would like to learn more about Mohan's group of patients.

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of seropositive and erosive rheumatoid arthritis (RA), who had been treated with gold salts and chloroquine, which were withdrawn because of inefficiency, and methotrexate, which was also withdrawn because the patient developed pulmonary fibrosis.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, but in July 2003 he developed a red rash on his legs, diagnosed as LV. ANA titer was over 1/320, other immunological findings were normal, and RF was 320 IU/ml. Etanercept treatment was continued because of the positive evolution of the RA and with the patient's agreement.

His vasculitis was treated by adding leflunomide 20 mg daily, without any other change in medication. The rash clearly improved 4 weeks after leflunomide was begun and remitted after 3 months. His RA continued to improve, with ANA titer 1/160. On followup 9 months after leflunomide was introduced, the patient did not present any skin reaction and continued to receive his usual treatment, with acceptable control of his RA.

LV has been described as a side effect associated with etanercept, related or unrelated to ANA, that does not occur in systemic lupus erythematosus[2-4]. On the other hand, etanercept has been successfully tried in different vasculitic syndromes[5]. Although we consider that our patient's LV etiology may be caused by etanercept, RA and other medicines cannot be ruled out as factors. The increased ANA titers seem to be related to etanercept. His resolved rash and laboratory data seem to be linked to the leflunomide treatment. We decided to continue with etanercept because of the patient's very positive clinical response. Administration of infliximab was not considered because it could not be prescribed at the same time as the methotrexate, due to prior lung fibrosis in this patient. Further, adalimumab was not commercially available in Spain. Leflunomide was administered at the same time because it was thought to have possible therapeutic and synergistic effects in vasculitis[6]. Further, leflunomide has also been associated with vasculitis as a side effect[7]. Indeed, LV has been described in association with etanercept in patients who received leflunomide at the same time[4]. 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.

Mohan, *et al* describe a patient whose skin lesions disappeared when etanercept was decreased to once a week dosing and worsened when the dosing was increased to twice a week.

We believe that the clinical course of our patient adds interesting data to those presented by Mohan, *et al.* We would like to know if the TNF-α blocking agent in any patient in this series was *not* withdrawn. We also wonder which patients were taking leflunomide in combination with TNF-α blocking agent at the time that the LV appeared.

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## 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.

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## CTLA-4 –1661A/G and –1772T/C Dimorphisms in Japanese Patients with Systemic Lupus Erythematosus

*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 C4AQ0, 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[1,2].

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[3]. 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[4]. Moreover, an increased level of soluble CTLA-4 in sera has been reported in SLE[5].

The CTLA-4 gene is located on chromosome 2q33, and dimorphisms are reported to be at positions –1661 and –1772 in the promoter region[6]. 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[6]. Fernandez-Blanco, *et al* also showed the involvement of CTLA-4 (–1772T/C) dimorphisms in SLE susceptibility[7]. Controversially, Aguilar, *et al* observed no association in Spanish patients with SLE[8]. 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 yrs) diagnosed according to the criteria of the American Rheumatism Association[9] 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*[6], using the specific oligonucleotide primers 5'-CTA AGA GCA TCC GCT TGC 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[10].

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[6-8]. 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*[8]. Lee, *et al*[10] 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[7] was different from the increase in the –1772T allele observed in Koreans with SLE[6]. 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[7]. The frequencies of the –1772T/C genotypes and alleles were different between Korean controls and Spanish controls[6-8]. 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[6]. 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 +49[11]. This observation was compatible with reports by Heward, *et al*[12], D'Alfonso, *et al*[1] and Mehrian, *et al*[2], although the results are still controversial.

Taking our previous observations[11] into consideration, it is very likely that the CTLA-4 gene is not genetically involved in the pathogenesis of SLE in Japanese.

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*Table 1.* Association of CTLA-4 dimorphisms (–1661A/G and –1772T/C) with SLE.

| | | CTLA-4 (–1661A/G), % | | | | | CTLA-4 (–1772T/C), % | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Genotype | | | Allele | | Genotype | | | Allele | |
| | N | AA | AG | GG | A | G | TT | TC | CC | T | C |
| SLE | 60 | 78.3 | 21.7 | 0 | 89.2 | 10.8 | 31.7 | 41.7 | 26.7 | 52.5 | 47.5 |
| Controls | 104 | 79.8 | 20.2 | 0 | 89.9 | 10.1 | 32.7 | 50.0 | 17.3 | 57.7 | 42.3 |

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# Correction

Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol 2005;32 Suppl 75:6-21. The legend for Figure 2 should read: Size of effect by type of outcome measure in 9 controlled studies of tricyclic treatment of FM. From Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia: a meta-analysis and review. Psychosomatics 2000;41:104-1396. Reprinted with permission from Psychosomatics, Copyright (2000). American Psychiatric Association. We regret the error.