Interleukin 6 Blockade as Steroid-sparing Treatment for 2 Patients with Giant Cell Arteritis

To the Editor:

Giant cell arteritis (GCA) is the most common idiopathic systemic vasculitis of large vessels. It affects individuals over 50 years of age. The prevalence is approximately 200 per 100,000 persons[1]. Although it may be generalized, vessel inflammation most frequently involves the muscular arteries originating from the aortic arch and their branches and usually presents with new-onset or worsened headache, jaw claudication, scalp or temporal artery tenderness with decreased pulsation, or visual symptoms such as eye pain, amaurosis fugax, diplopia and visual loss. High-dose corticosteroid (CS) therapy, which may last 1 to 5 years, is the basic treatment for GCA. However, in about 60% of patients the long duration of treatment causes serious, dose-related side effects[2]. For patients whose disease is resistant to or dependent on CS therapy, methotrexate (MTX) or azathioprine (AZA) is used as steroid-sparing second-line treatment, with conflicting results[3]. While MTX seems to be effective in controlling GCA[4,5], the data on AZA remain controversial[6]; the tumor necrosis factor-blocking agents infliximab and etanercept were not successful in inducing and maintaining disease remission[7,8].

Interleukin 6 (IL-6) plays an important role in the pathogenesis of GCA. IL-6 levels are elevated in active disease, correlate with the acute-phase response (such as C-reactive protein; CRP), and remain higher in patients who have experienced more relapsing disease[9].

We describe 2 patients with refractory biopsy-proven GCA who were at high risk for longlasting high-dose CS, and who were treated successfully with the humanized anti-IL-6 receptor (IL-6R) antibody tocilizumab (TCZ), given monthly at a dose of 8 mg/kg.

Our 2 female patients (aged 76 and 77 years old) had a clinical history of diabetes mellitus with oral therapy (metformin) and hypertension needing at least 2 antihypertensive drugs. Additionally, they had osteoporosis (T scores –3.1 and –2.8 on dual energy x-ray absorptiometry). Patient 1 was previously treated with high-dose steroids for 14 months (up to 75 mg/day of prednisone) and subsequently with associated MTX (20 mg weekly dose, intramuscularly). MTX failed to allow a steroid-sparing target as signs and symptoms of relapsing GCA presented when prednisone dose was reduced to less than 25 mg/day.

Apart from the noted comorbidities, a reduction of steroid dose was largely desirable in Patient 2 because in 2010 she underwent 2 orthopedic interventions for right hip replacement due to aseptic necrosis attributed to CS treatment, when she was still taking 25 mg/day of oral prednisone and 20 mg/week of intramuscular MTX.

The patients were followed at our center from August 2010 for TCZ treatment for a mean period of 7 months (6 and 8 months, respectively). The acute-phase responses (erythrocyte sedimentation rate and CRP) decreased rapidly after the first TCZ infusion, and were completely normal in both patients after 3 months of treatment (Figure 1).

Circulating levels of IL-6 were measured by immunoassay using Quantikine kits (R&D Systems), according to the manufacturer's instructions. Four patients with recently diagnosed GCA (duration not more than 2 months), treated with CS according to the current guidelines[10], were enrolled as a control group to compare serum levels of IL-6. The serum level of IL-6 decreased more rapidly in the 2 GCA patients treated with TCZ compared to the controls. Mean baseline values were 46 pg/ml and 51 pg/ml, respectively; then 17 pg/ml and 39 pg/ml after 2 months; and 11 pg/ml and 27 pg/ml after 6 months ($p = 0.04$; Figure 1). Of note, after 2 months the starting dose of prednisone was halved, and then reduced to the maintenance dose of 5 mg/day. We based our definition of disease activity on clinical and serologic indicators. At a mean followup of 7 months both the patients were in remission and inflammation markers were within the normal range.

TCZ has been proposed as a safe and effective treatment for cases of large-vessel vasculitis, that is, for Takayasu arteritis[11] and GCA[12]. In our experience the additional clinical benefit of treatment with TCZ was its CS- and immunosuppressant-sparing effect without disease flare. Indeed, the rapid remission with TCZ treatment allowed early reduction of daily CS even in patients who were CS-dependent. Current data derived from randomized controlled clinical trials in rheumatoid arthritis suggest an acceptable tolerability profile for TCZ, and longterm exposure to TCZ during open-label extension studies did not reveal any new safety signals or increased risks of serious adverse events[13].

TCZ may be considered a steroid-sparing agent in patients with GCA, but before results of controlled trials become available, it may be considered as a therapeutic option for patients who do not improve or stabilize with conventional therapy or in subjects in whom a reduction of steroid dose is largely desirable.

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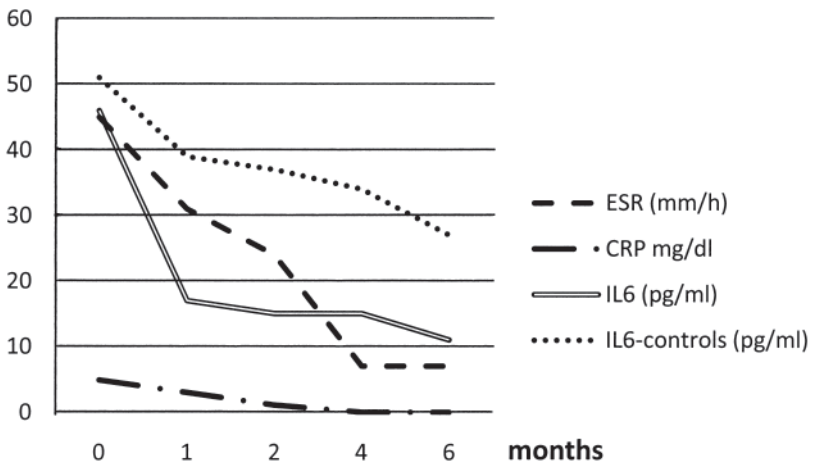

Figure 1. Serologic assessment of the 2 patients treated with TCZ during the followup.

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