

Etanercept Treatment in Sweet's Syndrome with Inflammatory Arthritis

To the Editor:

A 55-year-old Caucasian man initially presented 6 years earlier to an outside facility with a photosensitive rash, arthritis, fatigue, and mild neutrophilia. He had a history of liver cirrhosis, felt to be secondary to previous alcohol consumption. He had several inflammatory papules and plaques on his trunk and forearms that clinically were suggestive of Sweet's syndrome. A skin biopsy showed a dense, perivascular, neutrophilic infiltrate, which confirmed the diagnosis¹. He was prescribed prednisolone and a calcium-vitamin D3 preparation. Standard investigations for an underlying malignancy were undertaken², with results that were normal. Both his arthritis and his skin disease improved dramatically under steroid treatment, but both flared again once the steroid dose was tapered below 20 mg per day. Over the next 5 years he was followed up by a dermatology service and was maintained on 20–40 mg prednisolone. Concomitant treatment with colchicine, hydroxychloroquine, and chloroquine was ineffective, nonsteroidal antiinflammatory drugs were not tolerated because of gastrointestinal side effects, and liver function tests became abnormal with mycophenolate therapy.

One year before presenting to our service, he developed a pancytopenia, with hemoglobin 8.4 g/dl, elevated mean cell volume of 110 fl, a white cell count of $5.1 \times 10^9/l$ (lymphocytes $1.4 \times 10^9/l$), and a platelet count of $87 \times 10^9/l$. His only treatment at this time was prednisolone 20 mg. Erythrocyte sedimentation rate was elevated at 120 mm/h and ferritin was 477 $\mu g/l$. Reticulocytes were normal. JAK-2 mutation was negative. Computed tomography scans of thorax, abdomen, and pelvis were normal, as were esophagogastroduodenoscopy and colonoscopy. Bone marrow examination revealed a hypercellular marrow with dysplastic features; fat:cell ratio was 10:90. The myeloid series was prominent and matured with mild left shift. The erythroid series showed multiple maturing clusters with mild dyserythropoiesis. There was no stainable iron. Chromosomal analysis was normal.

A rheumatology review at this stage confirmed a severe nonerosive seronegative inflammatory arthritis involving metacarpophalangeal, wrist, elbow, knee, and ankle joints. Given previous treatment failures he was given etanercept 50 mg/week subcutaneously and was maintained on prednisolone 20 mg.

There was a dramatic improvement in his synovitis within 2 weeks. By 6 months he reported a gradual but marked improvement in his cutaneous disease with no new lesions. This allowed steroids to be tapered for the first time in 6 years. To date his joint and skin disease remains well controlled with etanercept and prednisolone 7.5 mg. He continues to have a moderate pancytopenia that is being followed closely by the hematology service.

Tumor necrosis factor- α (TNF- α) is a proinflammatory cytokine that is released by activated monocytes, macrophages, and T lymphocytes; it promotes inflammatory responses including stimulation of synovial fibroblasts, osteoclasts, and chondrocytes that in turn release tissue-destroying matrix metalloproteinases. TNF- α can be detected in high concentrations in synovial fluid from patients with active rheumatoid arthritis (RA)^{3,4}, and its inhibition leads to amelioration in joint disease⁵. TNF receptors are expressed on a wide variety of cell types^{6,7}.

The pathogenesis of Sweet's syndrome remains to be definitively determined. Cytokines may have an etiologic role. Granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, interferon- γ , interleukin 1 (IL-1), IL-3, IL-6, and IL-8 are potential cytokine candidates in the pathogenesis of Sweet's syndrome. Therefore there does appear to be a rationale for treating Sweet's syndrome with anti-TNF- α therapies^{8,9}. In our patient, the therapy was highly effective at treating the arthritis and skin disease, although, surprisingly, it took 6 months for the skin disease to respond.

There is concern regarding the safety of anti-TNF agents in this population. TNF plays an important role in host defence and tumor growth control; therefore, anti-TNF antibody therapies may increase the risk of seri-

ous infections and malignancies. A metaanalysis to assess the extent to which anti-TNF antibody therapies may increase the risk of malignancies in patients with RA found that the pooled odds ratio for malignancy was 3.3 (95% confidence interval 1.2–9.1)¹⁰. Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses of anti-TNF antibodies. For patients treated with anti-TNF antibodies in the included trials, the number needed to harm was 154 (95% CI 91–500) for 1 additional malignancy within a treatment period of 6 to 12 months¹⁰. A recent trial in patients with Wegener's granulomatosis revealed a statistically significant increase in the incidence of solid malignancies in patients treated with etanercept, with 6 solid cancers in 89 patients treated with etanercept plus cyclophosphamide versus no malignancy in 91 control patients treated with cyclophosphamide alone¹¹.

As an estimated 25% of patients with Sweet's syndrome may eventually be found to have an underlying malignancy^{12,13}, with some of these patients having a lag time up to 11 years between presentation with cutaneous symptoms and the diagnosis of the underlying malignancy¹⁴, we feel that anti-TNF- α therapies should be used with caution in this high-risk group.

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