

Successful Switch of Patients with Rheumatoid Arthritis Developing Anti-tumor Necrosis Factor (anti-TNF)-induced Lupus to Another Anti-TNF Agent

To the Editor:

We read with interest the recent letter¹ and editorial² discussing anti-tumor necrosis factor (anti-TNF)-induced lupus requiring cessation of therapy for disease resolution. A lack of published experience of successful TNF inhibitor switching (8 total cases in the literature) causes concern for rheumatologists faced with this clinical scenario. We describe 2 more patients who successfully switched to different TNF inhibitor after developing anti-TNF-induced lupus.

Patient 1. A 43-year-old woman with a 15-year history of seropositive rheumatoid arthritis (RA) achieved remission when treated with adalimumab 50 mg biweekly 8 years ago. Adalimumab was increased to 50 mg weekly when she developed an arthritis flare. Her arthritis worsened and she developed severe pleuritis but no other lupus features. Laboratory investigations revealed anti-dsDNA antibodies that were not present in her pre-adalimumab antibody profile and persistence of anti-SSA antibodies that were present prior to adalimumab. A diagnosis of adalimumab-induced lupus was made and adalimumab was discontinued. Her symptoms resolved while taking prednisone 60 mg daily. One month later, she was asymptomatic on a tapering course of prednisone. Her antibody profile at that time remained positive for anti-SSA antibodies but was negative for anti-dsDNA antibodies. She had a flare of RA off prednisone; therefore, she was treated with etanercept 25 mg twice weekly. The disease went into remission and has remained so for the past 4 years. Her antibody profile remains positive for anti-SSA antibodies and negative for anti-dsDNA antibodies.

Patient 2. A 58-year-old woman with a 20-year history of seropositive RA was treated with infliximab 3 mg/kg in addition to leflunomide 20 mg/day. Ten weeks after starting infliximab she developed oral ulcers and increased joint symptoms with active synovitis on examination. Laboratory investigations revealed anti-dsDNA antibodies that were not present in her pre-infliximab antibody profile. Her extractable nuclear antigen (ENA) profile was negative. She was diagnosed with infliximab-induced lupus and the infliximab was discontinued. She was maintained on leflunomide 20 mg/day. Her joint symptoms improved and oral ulcers resolved 2 months later. A repeat antibody profile showed that her ENA remained negative and her anti-dsDNA antibodies were negative. Her disease remained under control for 3 years taking leflunomide. She subsequently developed a disease flare and etanercept 25 mg twice weekly was added, with resolution of her synovitis. Two and a half years later she remains asymptomatic and her ENA and anti-dsDNA antibody profiles are negative.

Treatment of patients with active RA who have had anti-TNF-induced lupus with a second TNF inhibitor should be monitored closely. Anti-TNF-induced lupus may be a class effect, as it has been reported to occur with all forms of this therapy. It is recognized that antinuclear antibodies occur in association with anti-TNF therapies but anti-TNF-induced lupus is uncommon. In one study of RA patients treated with one of 3 anti-TNF therapies, infliximab, etanercept, and adalimumab were all shown to cause the development of anti-nucleosome antibodies, antibodies that have a role in the diagnosis and followup of patients with systemic lupus erythematosus³. However, the investigators comment that the development of anti-TNF-induced lupus is uncommon with these agents. In another study over 50% of infliximab-treated patients and 10% of etanercept-treated patients developed anti-dsDNA antibodies, suggesting differences in immunogenicity between the drugs⁴. This observation is of interest in view of the data reported in another study of anti-TNF-induced lupus that shows infliximab is associated with anti-TNF-induced lupus more frequently than etanercept or adalimumab⁵.

Anti-TNF-induced lupus differs from the classic drug-induced lupus in that it is characterized by a greater frequency of skin involvement, the presence of anti-dsDNA antibodies, and the lack of anti-histone antibodies.

Affected patients have also been reported to have renal involvement, an uncommon finding in classic drug-induced lupus⁵.

Our experience in successfully switching from an anti-TNF therapy that caused anti-TNF-induced lupus to another anti-TNF provides further data for rheumatologists to manage these challenging patients. Our patients were successfully switched from a monoclonal antibody to etanercept with sustained RA disease control and no recurrence of anti-TNF-induced lupus. Our experience mirrors that of similar successful switches to another anti-TNF therapy^{6,7,8,9}; however, the cases presented by Soforo, *et al*¹ remind us to use caution in performing this switch. Treatment choices will inevitably depend upon how severe the initial features of anti-TNF-induced lupus were.

A recent case report suggests that anti-SSA antibodies in the pretreatment serum of patients may increase the risk of developing anti-TNF-induced lupus¹⁰. Perhaps these cases have a closer immunological relationship to SLE than the ENA-negative patient. Although Patient 1 had anti-SSA antibodies she was able to switch successfully to a second anti-TNF therapy without developing anti-TNF-induced lupus. The decision to switch to another TNF inhibitor in the event of anti-TNF-induced lupus requires close clinical and serological review of the patient.

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