Lupus erythematosus manifestations exacerbated by etanercept therapy in a patient with mixed connective tissue disease

Sirs,

Several authors have discussed the potential benefit of TNF-α blockers in systemic lupus erythematosus (SLE), a condition in which new therapeutic agents are needed (1-3). Nevertheless, the induction of anti-DNA antibodies in patients with rheumatoid arthritis (RA) treated with TNF-α blockers has been noted since the earliest clinical trials with etanercept and infliximab, a phenomenon emphasized in two recent papers (4, 5). However, although these biological abnormalities frequently occur in 20 to 60% of patients, a few lupus-like syndromes or exacerbations have been reported in patients treated with TNF-α antagonists (3, 7-11). Thus, it remains unclear whether the appearance of antinuclear antibodies (ANA) in RA patients treated with TNF-α blockers could compromise the use of such agents in SLE patients. We report the case of a patient presenting with a mixed connective tissue disease (MCTD) according to the criteria of Amigues et al. (12) who was treated by TNF-α antagonists which precipitated manifestations of SLE.

A 27-year-old woman was admitted because of symmetrical destructive polyarthritis, Raynaud’s phenomenon, sclerodactyly and pericarditis. Immunological investigations revealed positive ANAs (titer 1:8000), anti-double-stranded DNA antibodies (anti-dsDNA; 21.5 Units/ml; negative < 7 U/ml), anti-RNP antibodies and anti-RO antibodies, but no rheumatoid factor. There were no antineutrophil cytoplasmic antibodies (ANCA) or cryoglobulinemia. She was unsuccessfully given hydroxychloroquine, then leflunomide (20 mg/day) and finally methotrexate (up to 20 mg/week) (I). Considering the severity of the polyarthritis and the lack of efficacy of the corticosteroids (up to 20 mg/day) and finally methotrexate, she was given etanercept 25 mg twice a week. One month later, she presented with polyarthritis and a generalized urticarial skin eruption suggesting a lupus-like syndrome. Laboratory results disclosed the following results: erythrocyte sedimentation rate 46 mm/hour, elevated C-reactive protein (45 mg/l), normal C3 (105 mg/ml) and anti-dsDNA antibodies (41 U/ml; IgG isotype). CH50 was low (59 U/ml; normal 63-119 U/ml) and the C4 level was below 10 mg/dl (normal 15-35 mg/dl). There was no proteinuria.

Histological skin analysis showed a perivascular lymphocytic infiltrate in the dermal portion compatible with the diagnosis of lupus. Etanercept was withdrawn and mycophenolate mofetil 2000 mg/day was started. One month later, she was symptom-free. No relapse of clinical SLE symptoms had occurred after one year of follow-up and immunological parameters including ANAs and anti-DNA antibodies had improved.

MCTD may overlap rheumatoid arthritis and SLE and could be an interesting model for studying the impact of TNF-antagonists in the treatment of such diseases, because it can naturally evolve into SLE as well as RA. Interestingly, under etanercept therapy, which was justified considering the severity of the rheumatologic manifestations, our patient added clinical symptoms strongly suggestive of SLE (13) and worsened biological abnormalities. In this cases, anti-TNF treatment have not induced lupus but have exacerbated the SLE symptoms of the MCTD. Because TNF blockers have been proposed for treating lupus patients (1-3), the present case highlights the need to establish the subgroup of SLE patients in whom it could represent a valuable tool. Moreover, MCTD with features of SLE at disease onset may not represent a suitable indication for TNF antagonists.

C. Richez, MD
B. Blanco, MD
C. Dumoulin, MD
T. Schaeffer, BSc, MD, PhD
Service de Rhumatologie and Service d’Immunologie, Groupe Hospitalier Pellegrin, CHU de Bordeaux, and University Victor Segalen Bordeaux, France.

References
MEFV-related mutations may explain why amyloidosis due to BD is more common in Middle East and Mediterranean countries than in Japan.

The frequency of MEFV mutations among patients with BD-related amyloidosis has not been investigated previously and our study showed a frequency of 32%. Although the patient with homozygous M680I did not have sufficient clinical findings for FMF, it was not possible to exclude type 2 MEFV (4, 5). The main shortage of this study is the absence of a control group (BD patients without amyloidosis), but we can compare our findings with previous studies evaluating MEFV mutations in BD. The frequency of MEFV mutations may vary between regions, countries and ethnic groups and as far as we know, there are three studies evaluating MEFV mutations in BD (one from Turkey (6), one from Israel and one an international study) (6-8). In an international collaborative study in which we have also participated, the M694V, V726A and E148Q mutations were found to be 2.6%, 2.6% and 5.2%, respectively (7). The other two studies, one from Turkey (6) and one from Israel (8), reported MEFV frequencies of 26% and 38%, respectively. Atagunduz et al. have concluded that MEFV mutations are increased in BD and are associated with vascular involvement (6).

A significant difference regarding the frequency of MEFV mutations among patients with BD-related amyloidosis was not found in our study and the absence of a control group does not affect our interpretation. In addition, it should be kept in mind that different ethnic groups, unmentioned patient characteristics (presence or absence of amyloidosis) and differences in the number and type of mutations screened in these studies may influence the integrity of the comparison.

The relationship between rheumatological diseases and MEFV mutations has been reported previously (9, 10). The presented data does not offer conclusive data on MEFV mutations being one of the risk factors for the development of amyloidosis in another inflammatory disease, BD. However, larger studies are needed to clarify whether the altered inflammatory response introduced by the pyrin mutations are one of the predisposing modifying genetic factors for the development of amyloidosis in a patient who already has an inflammatory disease.

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T. AKPOLAT, Professor
E. YILMAZ, Associate Professor
H. ÖZDOGAN, Professor
M. MELIKOGLU, Assistant Prof.

E. ALTOK, Associate Professor
S. OZEN, Professor

Dumlupınar University School of Medicine, Sivas; Hacettepe University School of Medicine, Ankara; Istanbul University, Cerrahpasa Medical School, Istanbul; Ataköyadan Hospital, Istanbul, Turkey.

Address correspondence to: Tekin Akpolat, MD, Dumlupınar University, Bebek Kampusu, Nefroloji Birlik Kliniği, Sivas, Turkey 55139. E-mail: tekinakpolat@yahoo.com

Letters to the Editor

New-onset acute heart failure and ventricular tachycardia after therapy with a tumor necrosis factor antagonist

Sir,

Numerous adverse effects have been reported with TNF antagonists, mainly infections and lymphomas (1). Other potential adverse effects, cardiac in particular, must be kept in mind (2). We report one case of new-onset acute heart failure and one case of ventricular tachycardia during treatment with infliximab.

A woman aged 52 was followed for Behçet’s disease. She had no history of cardiovascular disorder. Because of severe joint involvement in spite of treatment with methotrexate, intravenous infliximab 3 mg/kg was prescribed. Initial electrocardiogram and echocardiography were normal. Fifteen minutes after the start of the fourth infusion, she presented an acute heart failure with dyspnea and crepant rales of both lungs, bilateral alveolar opacity on chest radiography and sinus tachycardia on electrocardiogram. After immediate discontinuation of infusion, treatment with intravenous furosemide and nasal oxygen, the episode resolved in a few hours.

Search for the cause of this episode revealed signs of lower supra-epicardial ischemia on the electrocardiogram, a coronary artery spasm reproducing the ventricular tachycardia on cardiac angiography and minimal sequelae of lower necrosis on myocardial scintigraphy.

Behçet’s disease may be complicated by pericarditis, myocarditis, endocarditis or coronary aneurysms. Our patient had no such cardiac involvement and no cardiovascular history. Search for the cause of the episode of new-onset acute heart failure was negative. This finding and the chronology suggest a serious adverse event which can be attributed to infliximab. TNF antagonists are contra-indicated in patients with NYHA class III and IV heart failure. This contraindication results from the premature discontinuation of the ATTACH study which evaluated infliximab in the treatment of heart failure, because of increased mortality and hospital admissions for cardiac decompensation in patients treated with infliximab (3), and from the premature halting of the RECOVER and RENAISSANCE studies which evaluated etanercept in the treatment of heart failure, because of inefficacy of etanercept (4). TNF antagonists may also induce heart failure even in the absence of any cardiovascular history. A recent study revealed in 38 cases of new-onset heart failure in patients treated with TNF antagonists, which partially or totally resolved when this treatment was stopped (2).

Spondyloarthropathies may be complicated by aortic insufficiency and aortic dilatation. These conditions may influence the integrity of the comparison.

References