Induction of Systemic Lupus Erythematosus with Tumor Necrosis Factor Blockers

To the Editor:

Tumor necrosis factor-α (TNF-α) inhibitors are considered safe and effective for treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA)[1]. Although induction of antinuclear antibodies (ANA) and lupus-like syndromes have been described in patients treated with TNF blockers[1], their use was recently advocated in treatment of systemic lupus erythematosus (SLE)[2]. Most reported lupus-like cases were characterized by malaise, fatigue, and increased arthritis, without major organ system involvement[3]. We describe 6 women who developed active SLE satisfying American College of Rheumatology diagnostic criteria (Table 1) with life-threatening manifestations after receiving TNF blockade for treatment of RA or PsA (Table 2).

The first patient was admitted for dyspnea and chest pain after 3-month treatment of RA with etanercept. She had decreased breath sounds, arthritis, malar and papular rash, leukocytosis, elevated erythrocyte sedimentation rate (ESR), and positive ANA and anticardiolipin antibodies. Chest radiograph and echocardiogram showed pleural and pericardial effusion with right ventricular compression. Two liters of fluid were drained through a pericardial window. Etanercept was discontinued and she was discharged on prednisone and mycophenolate mofetil. Within 3 months, she went into remission. She also had erosive hand arthritis and this may represent an overlap of RA and lupus, termed rhupus[4].

The second patient was treated with sulfasalazine and etanercept when she was admitted with headache, blurry vision, dizziness and leg numbness, unsteady gait, arthritis, and discoid and malar rash. She had elevated ESR, positive ANA and anti-DNA antibodies, and low complement concentrations. Brain imaging showed demyelinating lesions. After discontin-

Table 1. ACR criteria for SLE in 6 patients exposed to TNF inhibitors.

	Patients					
SLE Criterion	1	2	3	4	5	6
Malar rash	+	–	+	+	+	–
Discoid rash	–	–	+	–	–	–
Photosensitivity	+	+	+	+	+	+
Oral ulcer	–	–	–	–	–	–
Arthritis	+	+	+	+	–	+
Serositis	Pericarditis	–	–	–	+	–
Renal disorder	–	–	–	–	–	+
Neurologic disorder	–	Optic neuritis	Headaches, major depression	–	Major depression	–
Immunologic disorders*	Anticardiolipin antibodies	Anti-ds DNA antibodies	–	Anti-ds DNA antibodies	–	Anti-ds DNA, SSA/SSB antibodies
Hematologic disorders	–	–	–	–	–	–
Positive ANA**	Speckled 1:6250	Homogenous 1:6250	Homogenous 1:6250	Nucleolar 1:6250	Homogeneous 1:320	Homogeneous 1:1250

* Anti-double-stranded-DNA antibody, SSA-Ro antibody, SSB-La antibody. ** Positive < 1:50 dilution.

Table 2. Time course of onset of clinical symptoms, serological markers, and ACR diagnostic criteria in 6 patients, all Caucasian women, with TNF inhibitor-induced SLE.

	Patients					
Feature	1	2	3	4	5	6
Diagnostic indication	RA	RA	RA	PsA	RA	RA
Age at onset, yrs	39	49	54	50	33	34
RF	–	+	+	–	–	+
Anti-CCP	–	+	–	–	–	–
Bony erosions	+	+	–	+	–	–
TNF blockers						
Infliximab			2002*			
Etanercept	2001*	1998*	2003*	2002*	2008*	2001*
Adalimumab			2005*			
ANA before treatment	Speckled 1:1250	Unknown	Homogenous 1:1250	Unknown	Negative	Homogenous 1:1250
ANA after treatment	Speckled 1:6250	Homogenous 1:6250	Homogenous 1:6250	Nucleolar and homogenous 1:6250	Homogenous 1:1250	Homogenous 1:1250
Onset of SLE after initiation of TNF blocker	6 mo	6 yrs	2–4 mo	3 yrs	1 mo	7 yrs

* Year TNF inhibitor was started. Anti-CCP: citric citrullinated peptide antibodies.

uation of etanercept and addition of steroids, she improved over 3 months. She had erosive disease and elevated rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP) titers. The latter has been associated with erosive arthritis in SLE[5].

After 2-month infliximab treatment for RA, the third patient developed generalized weakness, malar rash, major depression, and high-titer ANA. Infliximab was discontinued and her symptoms and ANA normalized within 6 months. In 2004, treatment with etanercept for recurrent synovitis caused severe depression, rash, headaches, and ANA positivity. When etanercept was discontinued, her symptoms and ANA disappeared. After receiving adalimumab for recurrent arthritis in 2005, she again developed headaches, mental status changes, and new rash, which resolved with discontinuation of TNF blockade. She is now managed with prednisone and methotrexate and her ANA is negative.

The fourth patient was treated for PsA with etanercept from 2002. Her arthritis went into remission, but she developed a malar rash, increased fatigue, positive ANA, anti-histone (1342 IU/ml; normal ≤ 99) and anti-dsDNA antibodies of 2412 IU/ml in 2005. After etanercept was stopped, her malar rash disappeared, fatigue improved, and ANA, anti-histone (297 IU/ml) and anti-dsDNA titers decreased (945 IU/ml).

The fifth patient presented after one-month etanercept treatment for RA with new-onset chest pain, malar rash, fatigue, photosensitivity, major depression, and positive ANA requiring hospitalization. Pericarditis was diagnosed, with multiple ST-segment elevations on electrocardiogram. Etanercept was discontinued. Symptoms improved and ANA became negative after 3 months.

The sixth patient had a 14-year history of RA, positive RF, ANA, anti-SSA, anti-SSB, anti-DNA, and hypocomplementemia. Her arthritis was treated effectively with etanercept. She had no deformities or anti-CCP suggesting SLE at presentation. However, after 7 years of etanercept therapy, she developed hematuria and proteinuria. Kidney biopsy showed mesangiocapillary proliferative immune-complex glomerulonephritis. Three months after etanercept was discontinued and a tapering regimen of prednisone was given, her hematuria and proteinuria stopped.

The induction of ANA and SLE in anti-TNF-treated patients has been attributed to different mechanisms. Ramos-Casals, *et al* proposed that such patients may have a preexisting overlap between RA and SLE[3]. However, SLE emerged in 5 of our 6 patients with underlying tendencies only after initiation of TNF blockade, and it abated after TNF inhibitors were stopped. Therefore, we propose that the development of lupus in these patients may have resulted from TNF blockade due to a protective effect of this cytokine in SLE. TNF is a mediator of activation-induced cell death; its production is reduced in lupus T cells, which exhibit diminished activation-induced apoptosis[6]. TNF production is also reduced in lupus-prone mice, where exogenous TNF delays the development of nephritis[7]. TNF blockade may further accentuate defective apoptosis, which in turn could enhance survival of autoreactive T cells and promote nephritis. Moreover, the mechanism of TNF blocker-induced lupus may be related to a shift from death by apoptosis to necrosis, the latter resulting in the release of nuclear debris, a trigger of ANA production and lupus[8,9]. Therefore, additional basic research and controlled clinical studies are needed to determine the safety of TNF blockade in patients with SLE. Patients treated with TNF blockers, especially those with positive ANA, should be closely monitored for development of SLE.

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REFERENCES

1. Imperato AK, Smiles S, Abramson SB. Long-term risks associated with biologic response modifiers used in rheumatic diseases. Curr Opin Rheumatol 2004;16:199-205.
2. Aringer M, Graninger WB, Steiner G, Smolen JS. Safety and efficacy of tumor necrosis factor alpha blockade in systemic lupus erythematosus: an open-label study. Arthritis Rheum 2004;50:3161-9.
3. Ramos-Casals M, Brito-Zeron P, Munoz S, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. Medicine 2007;86:242-51.
4. Panush RS, Edwards NL, Longley S, Webster E. 'Rhupus' syndrome. Arch Intern Med 1988;148:1633-6.
5. Hoffman IEA, Peene I, Cebecauer L, et al. Presence of rheumatoid factor and antibodies to citrullinated peptides in systemic lupus erythematosus [letter]. Ann Rheum Dis 2005;64:330-2.
6. Kovacs B, Vassilopoulos D, Vogelgesang SA, Tsokos GC. Defective CD3-mediated cell death in activated T cells from patients with systemic lupus erythematosus: role of decreased intracellular TNF-alpha. Clin Immunol Immunopathol 1996;81:293-302.
7. Jacob CO, McDevitt HO. Tumour necrosis factor-alpha in murine autoimmune 'lupus' nephritis. Nature 1988;331:356-8.
8. Ma L, Chan KW, Trendell-Smith NJ, et al. Systemic autoimmune disease induced by dendritic cells that have captured necrotic but not apoptotic cells in susceptible mouse strains. Eur J Immunol 2005;35:3364-75.
9. Perl A, Gergely P Jr, Nagy G, Koncz A, Banki K. Mitochondrial hyperpolarization: a checkpoint of T cell life, death, and autoimmunity. Trends Immunol 2004;25:360-7.

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