Dr. Perl replies

To the Editor:

In a followup of our report on induction of systemic lupus erythematosus (SLE) by tumor necrosis factor-α (TNF-α) inhibitors[1] and the accompanying editorial[2], Ye, *et al* describe 2 cases of anti-TNF antibody-induced lupus-like disease with anti-DNA antibody production[3]. Both these patients showed remission of anti-DNA but flaring of rheumatoid arthritis (RA) after discontinuation of adalimumab or infliximab. However, treatment with etanercept effectively suppressed synovitis without retriggering lupus or anti-DNA. These 2 cases of successful switching of TNF inhibitors complement 8 similar cases reported earlier. Although the effectiveness of switching from one to another TNF inhibitor may not restart SLE, we had no such success[1], similar to a large number of other cases[4].

As we proposed earlier, the development of lupus in these patients may have resulted from TNF blockade due to a protective effect of this cytokine in SLE[5]. The mechanism of TNF blocker-induced lupus may be explained by a shift from death by apoptosis to necrosis, the latter resulting in the release of nuclear debris, a trigger of antinuclear antibody (ANA) production and lupus[6,7]. It would be important to document whether the 2 cases of TNF inhibitor-induced lupus-like condition was accompanied only by the production of anti-dsDNA or if production of ANA was also detected by immunofluorescence[8]. We continue to advocate that patients treated with TNF blockers, especially those with positive ANA, should be closely monitored for development of SLE. Treatment of such cases with rituximab, recently shown to have clinical benefit not only in RA but also in SLE[9], may be a safer alternative.

In a second followup of our report on the induction of SLE by TNF-α inhibitors[1] and the accompanying editorial[2], Chogle, *et al*[10] describe a case of "rhupus," i.e., an overlap syndrome between RA and lupus that developed in a patient treated with the TNF inhibitor etanercept. Their case closely resembles the second patient of our series, who was diagnosed with anti-cyclic citrullinated peptide-positive RA and developed lupus with photosensitive rash following exposure to etanercept. We agree with Chogle, *et al* that their case also represents TNF inhibitor-induced lupus, since the patient had no evidence of photosensitivity and rash prior to exposure to etanercept. However, we strongly disagree with the authors that their case highlights the efficacy of anti-TNF treatment in rhupus. Our 6 cases clearly illustrate that, despite temporary relief of arthritis, across the board treatment of patients with lupus or rhupus with TNF inhibitors could have life-threatening consequences, such as pericardial effusion and cardiac tamponade[1,4]. Therefore, TNF blockade cannot be recommended in SLE. Moreover, careful monitoring of ANA production and clinical manifestations of lupus is advocated in patients with RA failing to respond or to clinically deteriorate upon treatment with TNF inhibitors. This recommendation is consistent with several mechanistic studies indicating that TNF blockade is detrimental to autoimmunity and nephritis in humans and in animal models of lupus, as reviewed by Soforo, *et al*[1] and Jacob and Jacob[2].

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REFERENCES

1. Soforo E, Baumgartner M, Francis L, Allam F, Phillips PE, Perl A. Induction of systemic lupus erythematosus with tumor necrosis factor blockers [letter]. J Rheumatol 2010;37:204-5.
2. Jacob N, Jacob CO. On anti-tumor necrosis factor-induced systemic lupus erythematosus [editorial]. J Rheumatol 2010;37:3-5.
3. Ye C, Sholter D, Martin L, Keeling S. Successful switch of patients with rheumatoid arthritis developing anti-tumor necrosis factor (anti-TNF)-induced lupus to another anti-TNF agent [letter]. J Rheumatol 2011;38:1216-7.
4. Ramos-Casals M, Brito-Zeron P, Munoz S, Soria N, Galiana D, Bertolaccini L, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. Medicine 2007;86:242-51.
5. Jacob CO, McDevitt HO. Tumour necrosis factor-α in murine autoimmune 'lupus' nephritis. Nature 1988;331:356-8.
6. Ma L, Chan KW, Trendell-Smith NJ, Wu A, Tian L, Lam AC, 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.
7. 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.
8. Bonilla E, Francis L, Allam F, Ogrinc M, Neupane H, Phillips PE, et al. Immunofluorescence microscopy is superior to fluorescent beads for detection of antinuclear antibody reactivity in systemic lupus erythematosus patients. Clin Immunol 2007;124:18-21.
9. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, et al. Efficacy and safety of rituximab in moderately to severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III Systemic Lupus Erythematosus Evaluation of Rituximab Trial. Arthritis Rheum 2010;62:222-33.
10. Chogle AR, Shah CN, Murthy A. Role of anti-tumor necrosis factor-α blockers in inducing lupus erythematosus tumidus in "rhupus" syndrome." J Rheumatol 2011;37:xxxxx

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