Tumor necrosis factor-alpha blockade and the risk of vasculitis.

Loïc Guillevin and Luc Mouthon

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The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Tumor necrosis factor-α (TNF-α) blockade is the reference treatment for patients with moderate to severe rheumatoid arthritis (RA) who respond poorly to conventional disease modifying antirheumatic drugs. The impressive antiinflammatory effects of TNF blockers — etanercept, infliximab, and adalimumab — have led to their use in numerous other inflammatory diseases. Notably, some TNF-α antagonists have been approved to treat Crohn’s disease, ankylosing spondylitis, juvenile chronic arthritis, adult Still’s disease, and psoriasis.

In recent years, infliximab has also been used to treat systemic vasculitides, particularly Wegener’s granulomatosis (WG) refractory to corticosteroids and immunosuppressants. Complete or partial remission was obtained in all 13 patients with WG included in the 2 published series, while the corticosteroid dose was maintained or lowered. The infliximab dose infused to induce remission was not standardized, and 3 mg/kg to 5 mg/kg were administered per session. We empirically recommended the latter, but remission may be obtained with lower doses. In our experience, the daily steroid dose could be dramatically lowered, from 20 to 8 mg, at 6 months. Every patient treated obtained a partial or complete remission, and infliximab discontinuation was sometimes possible.

Arbach, et al. also obtained partial to complete remissions in 3 patients with Churg–Strauss syndrome who had severe relapses refractory to cyclophosphamide and corticosteroids. Anti-TNF-α agents were also prescribed to patients with giant cell arteritis, including patients with Takayasu’s arteritis whose disease could not be controlled with corticosteroids or other immunosuppressants. Granulomatous inflammation is a typical feature of Takayasu’s arteritis, and TNF-α contributes to the formation of granulomas. Among 15 patients with active, relapsing Takayasu’s arteritis who received anti-TNF-α agents, 10 achieved complete remission that was sustained for 1–3.3 years without corticosteroids, 4 achieved partial remission with > 50% reduction in their corticosteroid requirement, and one failed therapy. For 9 of the 14 responders, the anti-TNF-α dose had to be increased to sustain remission; 2 of them relapsed during periods when therapy (etanercept) was interrupted, but remissions were again obtained upon its reinsti-

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Although anti-TNF-α agents are usually well tolerated, it is now well documented that they can induce side effects. Infectious complications have been noted, mainly Mycobacterium tuberculosis and other granulomatous infections, and thorough medical history-taking in terms of tuberculosis, including tuberculin testing and radiographic examination, is an essential component of anti-TNF-α therapy.

The development of autoantibodies under anti-TNF-α agents has been well described, with 5%–8% IgM anti-dsDNA in patients receiving infliximab in combination with methotrexate, and 5% anti-dsDNA in patients treated with etanercept. New autoantibody synthesis was associated with both a higher number of infusions and a higher total dose of infliximab infused. More recently, new antinuclear, anti-DNA, anti-Sm, and anti-RNP antibodies were detected in the absence of signs of connective tissue diseases in about 25%–50% of patients with RA treated with infliximab, depending on the antibody specificity. Rare patients with RA developing etanercept- or infliximab-induced systemic lupus erythematosus (SLE) have been described. Lastly, demyelination has also been reported as an adverse effect of TNF-α antagonism.

In this issue of The Journal, Mohan and colleagues describe 35 patients who developed leukocytoclastic vasculitis associated with tumor necrosis factor-alpha blocking agents, page 1955

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tis [biopsy-proven in 17 (48.5%)] during treatment with TNF-α-blocking agents. In the first such case reported, a patient with RA treated with etanercept, drug discontinuation led to complete resolution of the vasculitis. Recently, Jarrett, et al described the same reversal of vasculitis and/or vasculitic rash that had developed in 8 additional RA patients taking anti-TNF-α blockers; 7 of them received infliximab and one etanercept.

Before discussing the potential mechanisms underlying the role of TNF-α blockade in inducing leukocytoclastic vasculitis, it must be emphasized that, in the absence of any relationship with a therapeutic agent, it has long been accepted that RA is associated with or may evolve into vasculitis. Notably, in their earlier study, Mohan, et al reported the occurrence of leukocytoclastic vasculitis in patients, the majority with RA, who had been treated with TNF-α blockers, and observed that 22/35 of them experienced total or marked regression of skin lesions upon treatment withdrawal. Indeed, the number of patients with RA purported to have developed leukocytoclastic vasculitis while taking anti-TNF-α agents is small compared to the large number of patients treated with them. It is, nonetheless, possible that TNF-α blockers induce leukocytoclastic vasculitis. Pertinently, in the current study, 9 patients were rechallenged, 6 of them experiencing leukocytoclastic vasculitis recurrences, while the remaining 3 fared well.

It is worth mentioning that infliximab was well tolerated in our 10 patients with systemic vasculitis during short term follow-up; the only adverse effect observed was a cutaneous eruption that developed in 2 patients: one corresponded to an erythematous macular rash (no skin biopsy was obtained), and the other was considered an allergic reaction to the partially recovered infliximab.

The mechanisms that might participate in the induction of leukocytoclastic vasculitis in patients receiving TNF-α blockers are not completely understood. Humoral mechanisms involving autoantibodies and/or immune complexes deposited in vessel walls might play a role or cause a shift in T cell responses. It has been suggested that anti-TNF-α-TNF-α immune complexes could be deposited in small capillaries, where they activate complement, and thereby trigger a type III hypersensitivity reaction. A further analysis of the infliximab effect on B cell activation in patients with RA demonstrated that this anti-TNF-α agent downregulates CD23 expression on T cell-activated B cells. This downregulation is associated with the presence of circulating immune complexes containing TNF-α. It has been hypothesized that FcγRIIB1 endows IgG-containing immune complexes, e.g., TNF-α-anti-TNF-α, with the capacity to regulate B cells and inflammatory mechanisms.

Since etanercept- or infliximab-induced SLE has been reported, albeit rarely, and because leukocytoclastic vasculitis is encountered relatively frequently in SLE, possible SLE induction by these drugs should be kept in mind. Another possible mechanism is a switch from the predominant T helper type 1 (Th1) cytokine response to a Th2 response. TNF-α blockers are prescribed for diseases characterized as Th1-lymphocyte-driven, with the major T cell cytokines involved being TNF-α, interleukin 2 (IL-2), IL-12, and interferon-γ. Th2 responses are associated with enhanced activities of IL-4, IL-5, IL-6, IL-10, and IL-13, responsible for upregulation of antibody production. Thus, TNF-α antagonists, by inhibiting Th1 lymphocyte functions, might break their control of Th2 clones, thereby favoring the activation of antibody-mediated immune mechanisms.

The prescription of anti-TNF-α antibodies, as for any drug, should take into account the risk of side effects. Vasculitis is one of them. But these drugs are so beneficial that the risk of developing easily reversible vasculitis should not prevent the physician, and in turn deprive the patient, from using them. However, for special indications, like vasculitis, anti-TNF-α antibody use should be restricted to those patients with vasculitis refractory to steroids and immunosuppressants who have relapsed.

LOÏC GUILLEVIN, MD
LUC MOUTHON, MD
Department of Internal Medicine, Hôpital Cochin, AP–HP and Université Paris 5, Paris, France.

Address reprint requests to Dr. L. Guillevin, Department of Internal Medicine, Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75679 Paris Cedex 14, France. E-mail: loic.guillevin@ccb.ap-hop-paris.fr

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