

## Tumor Necrosis Factor- $\alpha$ Blockade and the Risk of Vasculitis



Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) 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- $\alpha$  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<sup>1,2</sup>. 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<sup>1,2</sup>. The infliximab dose infused to induce remission was not standardized, and 3 mg/kg<sup>2</sup> to 5 mg/kg were administered per session<sup>1</sup>. 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*<sup>3</sup> also obtained partial to complete remissions in 3 patients with Churg–Strauss syndrome who had had severe relapses refractory to cyclophosphamide and corticosteroids. Anti-TNF- $\alpha$  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- $\alpha$  contributes to the formation of granulomas. Among 15 patients with active, relapsing Takayasu's arteritis who received anti-TNF- $\alpha$  agents<sup>4</sup>, 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- $\alpha$  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 reinstatement<sup>4</sup>.

TNF- $\alpha$  blockers have also been used successfully in several patients with RA-associated vasculitis<sup>1</sup>, those with refractory vasculitis secondary to mixed cryoglobulinemia associated or not with hepatitis C virus infection<sup>1,5</sup>, and in a child with refractory Kawasaki disease<sup>6</sup>. Finally, TNF- $\alpha$  blockade has also been described in case reports and in small series of patients with Behçet's disease, particularly in the presence of severe refractory uveitis, central nervous system involvement, gastrointestinal involvement, or severe orogenital ulcers<sup>7</sup>.

Although anti-TNF- $\alpha$  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<sup>8</sup>, and thorough medical history-taking in terms of tuberculosis, including tuberculin testing and radiographic examination, is an essential component of anti-TNF- $\alpha$  therapy.

The development of autoantibodies under anti-TNF- $\alpha$  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<sup>9</sup>. 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<sup>10</sup>. Rare patients with RA developing etanercept- or infliximab-induced systemic lupus erythematosus (SLE) have been described<sup>11,12</sup>. Lastly, demyelination has also been reported as an adverse effect of TNF- $\alpha$  antagonism<sup>13</sup>.

In this issue of *The Journal*, Mohan and colleagues describe 35 patients who developed leukocytoclastic vasculi-

---

See Leukocytoclastic vasculitis associated with tumor necrosis factor-alpha blocking agents, page 1955

tis [biopsy-proven in 17 (48.5%)] during treatment with TNF- $\alpha$ -blocking agents<sup>14</sup>. In the first such case reported, a patient with RA treated with etanercept<sup>15</sup>, drug discontinuation led to complete resolution of the vasculitis. Recently, Jarrett, *et al*<sup>16</sup> described the same reversal of vasculitis and/or vasculitic rash that had developed in 8 additional RA patients taking anti-TNF- $\alpha$  blockers; 7 of them received infliximab and one etanercept.

Before discussing the potential mechanisms underlying the role of TNF- $\alpha$  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<sup>16</sup>. Notably, in their earlier study<sup>17</sup>, Mohan, *et al* reported the occurrence of leukocytoclastic vasculitis in patients, the majority with RA, who had been treated with TNF- $\alpha$  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- $\alpha$  agents is small compared to the large number of patients treated with them. It is, nonetheless, possible that TNF- $\alpha$  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 followup<sup>1</sup>; 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 humanized antibody.

The mechanisms that might participate in the induction of leukocytoclastic vasculitis in patients receiving TNF- $\alpha$  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- $\alpha$ -TNF- $\alpha$  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- $\alpha$  agent downregulates CD23 expression on T cell-activated B cells<sup>18</sup>. This downregulation is associated with the presence of circulating immune complexes containing TNF- $\alpha$ . It has been hypothesized that Fc $\gamma$ -RIIb1 endows IgG-containing immune complexes, e.g., TNF- $\alpha$ -anti-TNF- $\alpha$ , with the capacity to regulate B cells and inflammatory reactions<sup>17</sup>.

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 pos-

sible mechanism is a switch from the predominant T helper type 1 (Th1) cytokine response to a Th2 response. TNF- $\alpha$  blockers are prescribed for diseases characterized as Th1-lymphocyte-driven, with the major T cell cytokines involved being TNF- $\alpha$ , interleukin 2 (IL-2), IL-12, and interferon- $\gamma$ . 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- $\alpha$  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- $\alpha$  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- $\alpha$  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@cch.ap-hop-paris.fr*

## REFERENCES

1. Bartolucci P, Ramanoelina J, Cohen P, *et al*. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. *Rheumatology Oxford* 2002;41:1126-32.
2. Lamprecht P, Voswinkel J, Lilienthal T, *et al*. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology Oxford* 2002;41:1303-7.
3. Arbach O, Gross WL, Gause A. Treatment of refractory Churg-Strauss-syndrome by TNF-alpha blockade. *Immunobiology* 2002;206:496-501.
4. Hoffman G, Merkel P, Brasington R, Lenschow D, Liang P. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum* 2004;50:2296-304.
5. Chandesris M, Gayet S, Schleinitz N, Doudier B, Harle J, Kaplanski G. Infliximab in the treatment of refractory vasculitis secondary to hepatitis C-associated mixed cryoglobulinaemia. *Rheumatology Oxford* 2004;43:532-3.
6. Weiss J, Eberhard B, Chowdhury D, Gottlieb B. Infliximab as a novel therapy for refractory Kawasaki disease. *J Rheumatol* 2004;31:808-10.
7. Ohno S, Nakamura S, Hori S, *et al*. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behcet's disease with refractory uveoretinitis. *J Rheumatol* 2004;31:1362-8.
8. Hamilton CD. Infectious complications of treatment with biologic agents. *Curr Opin Rheumatol* 2004;16:393-8.
9. Weinblatt M, Kremer J, Bankhurst A, *et al*. A trial of etanercept, a

- recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340:253-9.
10. Louis M, Rauch J, Armstrong M, Fitzcharles M. Induction of autoantibodies during prolonged treatment with infliximab. *J Rheumatol* 2003;30:2557-62.
  11. Shakoor N, Michalska M, Harris C, Block J. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002;359:579-80.
  12. Charles P, Smeenk R, De Jong J, Feldmann M, Maini R. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha. Findings in open-label and randomized placebo-controlled trials. *Arthritis Rheum* 2000;43:2383-90.
  13. Robinson W, Genovese M, Moreland L. Demyelinating and neurologic events reported in association with tumor necrosis factor and antagonism. *Arthritis Rheum* 2001;44:1977-83.
  14. Mohan N, Edwards ET, Cupps TR, et al. Leukocytoclastic vasculitis associated with tumor necrosis factor-alpha blocking agents. *J Rheumatol* 2004;31:1955-8.
  15. Galaria N, Werth V, Schumacher H. Leukocytoclastic vasculitis due to etanercept. *J Rheumatol* 2000;27:2041-4.
  16. Jarrett S, Cunnane G, Conaghan P, et al. Anti-tumor necrosis factor-alpha therapy-induced vasculitis: case series. *J Rheumatol* 2003;30:2287-91.
  17. Mohan A, Edwards E, Cote T, Siegel J, Braun M. Drug-induced systemic lupus erythematosus and TNF-alpha blockers [comment]. *Lancet* 2002;360:646.
  18. De Miguel S, Jover J, Vadillo C, Judez E, Loza E, Fernandez-Gutierrez B. B cell activation in rheumatoid arthritis patients under infliximab treatment. *Clin Exp Rheumatol* 2003;21:726-32.