LETTERS

Tumour necrosis factor α blockade and the risk of vasculitis

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We report on a French national retrospective survey, showing 39 cases of biopsy-proved drug-induced vasculitis in patients treated with tumour necrosis factor (TNF) blockers for inflammatory arthritis, conducted among 1200 rheumatology and internal medicine practitioners registered on our website (http://www.CRI-net.com) between December 2004 and March 2005.

As, in France, the prescription for TNF blockers is limited to the hospitals, all the units using biologicals were contacted. The study included all patients ever known to have developed a vasculitic-like illness when under treatment with TNF blockers, and not only those who developed vasculitis during the 3-month study period.

Patients had longstanding destructive rheumatoid arthritis, spondylitis or juvenile chronic arthritis (JCA). Table 1 lists the main characteristics and treatments. Patients developed localised (29 cases) or systemic vasculitis (10 cases). None had a special risk factor for vasculitis (hepatitis C infection, cryoglobulinaemia, etc). All patients received the usual TNF-blocker doses; 10 also had a disease-modifying antirheumatic drug (mostly methotrexate).

Clinical manifestations were skin lesions in 33 patients (purpuric or necrotic rash, papules, nodules, livedo, etc), manifestation in the peripheral nervous system in 11 (1 mononeuritis; 3 mononeuritis multiplex; 7 sensory neuropathy), kidney disease in 7 (3 haematuria; 7 proteinuria; 1 renal insufficiency), abnormalities of the central nervous system in 3 (retinal thrombosis, epilepsy and cognitive defect), serositis in 4 (2 pleurisy; 2 pericarditis), myocarditis, disease of the gallbladder and lung in 1 each.

In all, 29 patients had 1 documented organ disease (mostly skin), 7 patients had 2 (skin and kidney, skin and nerve, nerve and kidney) and 3 patients had 3 or more.

Histological proof was obtained in 27 (23 rheumatiod arthritis; 3 spondylitis; 1 JCA). Multiple biopsies (skin, nerve, muscle, kidney and broncus) showed 13 leukocytoclastic vasculitis of the skin, 7 necrosing vasculitis (medium or small size vessels), 2 extravascular necrotising granuloma, 2 dermal inflammatory infiltrates and 3 extracapillary glomerulonephritis.

Immunological abnormalities before treatment were antinuclear antibody in 11 patients with rheumatiod arthritis (2 with anti-Sjögren's syndrome A) and 1 with spondylitis. After onset of vasculitis, we observed high levels of antinuclear antibody in 23 patients (4 with anti-DNA antibodies); anticardiolipin antibodies in 2; hypocomplementaemia in 7; perinuclear antineutrophil cytoplasmic antibody in 5; and cryoglobulinaemia in 6.

TNF blockers were discontinued in 33 of 39 patients. A remission was observed in 18 without any other treatment. Steroids and immunosuppressors were required in 15 cases. In 6 of 39 patients (with isolated skin manifestations), treatment was resumed but the manifestations slowly abated. One patient died. In 12 patients, TNF blockers were started again, owing to flare of arthritis, either with the same (n = 4) or with another molecule (n = 8); in 6 patients, a flare of vasculitis was observed.

A few cases of vasculitis in patients receiving treatment with TNF blockers have been published in the literature[1–9]—mostly leucocytoblastic vasculitis. Our experience is different, with cases of necrotising vasculitis of medium-sized vessels or extravascular granulomas. We observed multiorgan disease not limited to the skin, with a high frequency of kidney and nerve manifestations occurring in patients with spondylarthritis, JCA or seronegative rheumatoid arthritis—diseases not usually associated with vasculitis. The imputability of TNF blockers is likely, given the temporal relationship between the onset of signs with treatment, resolution after withdrawal of the drug and flare after reintroduction. These results suggest that TNF blockers could trigger systemic necrotising vasculitis.

Table 1 Main characteristics of 39 patients

Women (n)	32
Mean disease duration (years)	14.1 (7.1)
Mean age at onset of vasculitis (years)	51.6 (11.3)
Sero-positive RA (n)	30
Sero-negative RA (n)	4
JCA (seen in adulthood)	2
Spondylitis	2
Psoriatic arthritis (mainly axial)	1
Previous DMARDs	4.4 (2)
Etanercept	21
Infliximab	15
Adalimumab	2
Other TNF inhibitor	1
Mean treatment duration (months)	9.6 (13)

DMARD, disease-modifying antirheumatic drug; JCA, juvenile chronic arthritis; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

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