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This study was approved by the Mayo Clinic Institutional Review Board.

Competing interests: None declared.

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Accepted 10 March 2006

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Tumour necrosis factor α blockade and the risk of vasculitis

M De Bandt, B Saint-Marcoux, on behalf of the CRI (Club Rhumatismes et Inflammation)

Ann Rheum Dis 2006;**65**:1534–1535. doi: 10.1136/ard.2006.051888

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, vasculitis 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 rheumatoid arthritis; 3 spondylitis; 1 JCA). Multiple biopsies (skin, nerve, muscle, kidney and bronchus) showed 13 leukocytoclastic vasculitis of the skin, 7 necrotising 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 rheumatoid arthritis (2 with anti-Sjögren's syndrome 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 leukocytoclastic 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

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.

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.

ACKNOWLEDGEMENTS

We thank all the CRI members who gave access to their patients' files: S Steinfeld, JM Berthelot, Ch Roux, P Richette, D Mulleman, D Wendling, B Moura, C Gabay, O Meyer, L Euler-Ziegler, Ch Marcelli, C Job Deslandres, C Richez, X Puechal, J Sibilia, M Dougados, J Morel and S Guignard.

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Competing interests: None declared.

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Accepted 22 January 2006

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Agreement of Mexican rheumatologists with the ASsessment in Ankylosing Spondylitis International Working Group and the EUROpean League Against Rheumatism recommendations for the management of ankylosing spondylitis

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Ann Rheum Dis 2006;**65**:1535–1536. doi: 10.1136/ard.2006.053397

By combining a systematic review of the literature and expert consensus,^{1,2} the ASsessment in Ankylosing Spondylitis (ASAS) International Working Group and the EUROpean League Against Rheumatism (EULAR) produced 10 recommendations for the management of ankylosing spondylitis (ASAS and EULAR-REMAS), including a general statement about patient and disease characteristics, evaluation of efficacy, non-pharmacological and pharmacological treatment, and invasive and surgical treatment. Following ASAS advice, we investigated the level of agreement with the ASAS and EULAR-REMAS among Mexican rheumatologists.

A total of 350 board-certified rheumatologists were sent the ASAS and EULAR-REMAS and a questionnaire in two sections: (1) general data and (2) the 10 ASAS and EULAR-REMAS, each presented as a heading in Spanish followed by a 10-box scale ranging from 0 (no agreement at all) to 10 (complete agreement), where participants marked their level of agreement. Answers, including some written comments and face-to-face observations, were received by e-mail or fax within 4 weeks. We carried out a descriptive analysis, and determined the association between demographic variables and the level of agreement with the ASAS and EULAR-REMAS recommendations. We arbitrarily set the level of agreement for each specific recommendation at ≥ 8 (strong) and < 8 (moderate).

In all, 117 responses were analysed (response rate 43.8%; 150 rheumatologists did not respond and 103 were not contacted). Two thirds were men, their mean (SD) age and years in clinical practice as rheumatologists were 45.3 (9.4) and 14 (8.9) years, respectively, and they consulted a mean (SD) 15.25 (15.3) patients with ankylosing spondylitis a month. Pharmacological treatment included non-steroidal anti-inflammatory drugs (95.6%), sulfasalazine (66.3%), methotrexate (50.9%), anti-tumour necrosis factor blockers (29.2%), local glucocorticoids (25.5%) and systemic glucocorticoids (12.6%).

Overall, $\geq 75\%$ of the Mexican rheumatologists strongly agreed with all 10 ASAS and EULAR-REMAS, except recommendations 6 (73.9%) and 7 (69.0%) (fig 1, upper panel). The overall agreement for the 10 recommendations was 78.3%. The mean agreement for each recommendation was > 8 (8.1–9.8; fig 1, lower panel). The mean (SD) overall agreement for the 10 recommendations was 8.85 (0.98).

Most comments referred to the inadequacy of including more than one statement in the same recommendation and the pertinence of some therapeutic recommendations. Rheumatologists who strongly agreed with recommendation

Abbreviations: ASAS, ASsessment in Ankylosing Spondylitis; EULAR, EUROpean League Against Rheumatism; REMAS, recommendations for the management of ankylosing spondylitis