Leflunomide induced vasculitis—a dose–response relationship

SIR, Following the correspondence by McCain et al. [1] about cutaneous vasculitis associated with etanercept and infliximab, we describe a patient who developed cutaneous vasculitis with leflunomide. In addition to a temporal relationship between the onset of vasculitis and drug therapy, there was also a dose–response relationship between leflunomide and development of cutaneous vasculitis in our patient.

A 50-yr-old man with a 10-yr history of seropositive rheumatoid arthritis (RA) was commenced on leflunomide at 100 mg for 3 days followed by 20 mg daily. He had severe erosive RA which had only partially responded to six previous disease-modifying anti-rheumatic drugs (DMARDs). Three months after commencing leflunomide, he developed vasculitic lesions in the tips of his third and fourth fingers on his right hand (Fig. 1). There was also patchy discoloration in the digits of his left finger.

Investigations at this time were as follows. The haemoglobin level was 13.4 g/dl, white blood count $6.11 \times 10^9/l$ (normal differential count) and platelets $293 \times 10^9/l$. Serum electrolytes and liver function tests were normal. Erythrocyte sedimentation rate was 68 mm/h and C-reactive protein 42.5 mg/l. Antinuclear antibody, anticytoplasmic antibody, extractable nuclear antigens and double-stranded DNA were all negative. Complements C3 and C4 were normal. Blood cultures were negative. Chest radiography was normal. Transthoracic echocardiography did not reveal any valvular vegetations.

Leflunomide was stopped at this stage and the

Fig. 1. Vasculitic lesions on distal end of fourth finger of right hand.
vasculitis resolved. However, there was a worsening of his RA with the withdrawal of leflunomide. He was then commenced on infliximab at a dose of 3 mg/kg and this induced remission of his RA. Due to intolerance of methotrexate previously, leflunomide at 10 mg on alternate days was given concurrently with infliximab. He did not develop any vasculitic lesions with this dose and the leflunomide was increased to 10 mg/day after 3 months. Within 1 week of starting 10 mg/day he developed vasculitic lesions on the right ring and left middle fingers. The dose of leflunomide was reduced back to 10 mg on alternate days. At his subsequent follow-up 2 weeks later, his vasculitic lesions had disappeared. There was no change in his other medications during this period and no change in his RA disease activity. He continues on leflunomide at 10 mg on alternate days and infliximab.

In this case of cutaneous vasculitis there was a strong temporal relationship between the onset of vasculitis and its resolution and leflunomide introduction and withdrawal, respectively. The dose–response relationship between leflunomide and vasculitis also supports a causal relationship. Bruyn et al. [2] reported two cases of cutaneous leucocytoclastic vasculitis with leflunomide therapy in a phase III randomized controlled trial. Smolen et al. [3] noted eight (0.6%) of 1339 patients on leflunomide developed vasculitis during treatment. However, none of these reports clarified whether the vasculitis was due to leflunomide or to rheumatoid arthritis itself. Immunomodulation by leflunomide may result in hypersensitivity (leucocytoclastic) vasculitis by the alteration of inflammatory mediators and formation of immune complexes. This may be dose responsive as shown in our case report. The mechanism of vasculitis induction requires further investigation.

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