Successful treatment with humanised anti-interleukin 6 receptor antibody for multidrug-refractory and anti-tumour necrosis factor-resistant systemic rheumatoid vasculitis

Sirs,

Rheumatoid vasculitis is an inflammatory condition of the small and medium-sized blood vessels that can affect extra-articular tissues and organs. Various clinical manifestations, such as scleritis, cutaneous ulcerations, pericarditis, pleuritis, and peripheral neuropathy, are seen in systemic rheumatoid vasculitis (SRV) (1).

In March 2009, a 69-year-old Japanese woman was admitted to our hospital with severe arthritis and signs of rheumatoid vasculitis such as scleritis with marginal corneal ulcer and interstitial pneumonia. She had been diagnosed with rheumatoid arthritis (RA) 3 months before and was initially treated with disease modifying antirheumatic drugs (DMARDs), including bucillamine and sulfasalazine together with methotrexate, and topical fluorometholone 0.1% without any effect. On admission, laboratory examination revealed C-reactive protein (CRP) of 12.8mg/dl, erythrocyte sedimentation rate (ESR) 110mm/h, rheumatoid factor (RF) 285IU/ml, and anti-cyclic citrullinated peptide (anti-CCP) antibody 528.2U/ml. Three days after admission, treatment with anti-tumour necrosis factor (TNF) agents in combination with methotrexate was started. Intravenous injection of 3mg/kg infliximab at 0, 2 and 4 weeks, and, subsequently, subcutaneous injection of 40mg of adalimumab every other week for two months failed to suppress her disease activity, except for the improvement of interstitial pneumonia in the left lower lobe that was observed on chest computed tomography. The level of CRP was 4.0mg/dl; ESR, 83mm/h; RF, 95IU/ml; and anti-CCP antibody, 341.6U/ml. In June 2009, intravenous administration of tocilizumab, a humanised anti-interleukin (IL) 6 receptor antibody, was started at 8mg/kg/month. After 3 weeks, her disease activity as indicated by symptoms with arthritis, signs of scleritis with corneal ulcer improved dramatically with further improvement of interstitial pneumonia, and the level of RF and anti-CCP antibody decreased to 40IU/ml and 189.0U/ml, respectively (Fig. 1). CRP and ESR fell to normal. At present, after 1 year, the SRV remains in remission with the follow-up including ophthalmoscopies, and the patient is still being treated with tocilizumab at 8mg/kg/month without any adverse effects.

TNF-α has been suggested to play a central role in the pathophysiology of SRV. Recently, an encouraging result with anti-TNF-α treatment has been reported in six out of nine patients with active refractory SRV (2). On the other hand, the use of anti-TNF-α agents has been found to improve clinical manifestations to a certain extent but not in all patients with SRV. Indeed, our present case illustrated that treatment with infliximab and adalimumab at standard dosages each was effective in improving interstitial pneumonia, but did not ameliorate the scleritis with corneal ulcer and arthritis in SRV.

In scleritis, both TNF-α and IL-1 released by the local inflammatory cell infiltrate have been associated with sclera destruction (3, 4). As for the corneal ulcerations, recent analysis has revealed that both TNF-α and IL-6 were widely expressed in the keratocytes of patients with corneal ulcerations and/or perforations associated with RA, and that IL-6 was more frequently detected (100%) than TNF-α (70%) in these patients (5). Anakinra, a human IL-1 receptor antagonist, has been reported to be effective for the treatment of diffuse anterior scleritis in RA refractory to anti-TNF-α treatment with infliximab and etanercept (6). Recently, the effectiveness of rituximab in cases of vasculitis-associated cutaneous ulcers in RA patients has been demonstrated (7). However, treatment with tocilizumab for SRV complicated with ocular manifestation has not been reported before. In our patient, there was a remarkable reduction of signs and symptoms of both ocular and articular inflammations following the administration of tocilizumab.

Our observations demonstrate that tocilizumab is a safe and effective treatment in SRV complicated with ocular manifestation and may become therapeutic option for active refractory SRV.

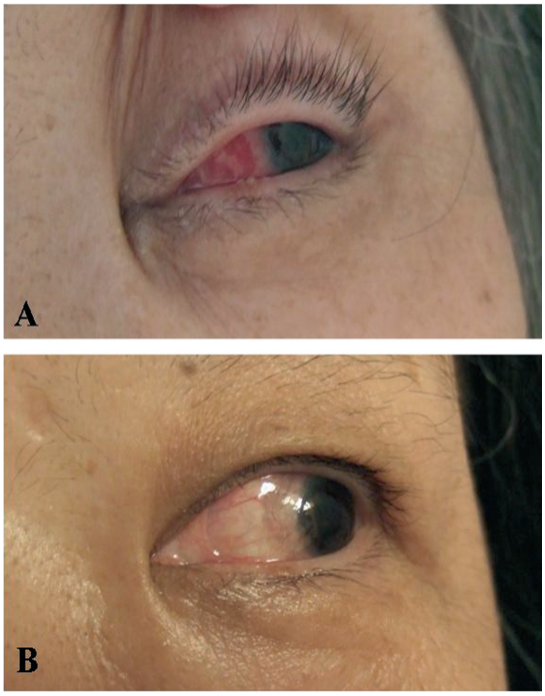

Fig. 1. Scleritis with marginal corneal ulcer of the left eye (**A**) before tocilizumab treatment and (**B**) the same eye 1 month after tocilizumab treatment.

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