prednisolone was temporarily increased to 20 mg/day and the symptoms resolved. As treatment for RA, abatacept 500 mg/month was started. Although prednisolone was rapidly tapered, relapse of vasculitis has not been observed so far and she has maintained low DAS28 scores.

The mechanisms that may contribute to the development of leucocytoclastic vasculitis in patients receiving biologics are not completely understood. The proposed mechanism by which anti-TNF agents induce vasculitis is a type III hypersensitivity caused by vascular deposition of an anti-TNF-α–TNF-α immunocomplex [4]. Tocilizumab is an antibody against the IL-6 receptor (IL-6R) and it binds to cell-surface IL-6R and the soluble form of IL-6R. It has been reported that the soluble form of IL-6R is saturated with tocilizumab as long as free tocilizumab is detectable, and this immunocomplex may be related to the development of tocilizumab-induced leucocytoclastic vasculitis [5]. However, it has not been elucidated whether this immunocomplex has a lower potential to induce vasculitis than the anti-TNF-α–TNF-α immunocomplex.

Recently two cases of tocilizumab-induced autoimmune disease have been reported [6, 7]. Interestingly, one case took 18 months to develop glomerulonephritis from the administration of tocilizumab [6] and the other took 28 months to develop sarcoidosis [7]. Our case took 30 months to develop leucocytoclastic vasculitis, and these periods of latency are obviously longer than vasculitis induced by anti-TNF agents. According to BIOGEAS Study Group, vasculitis induced by anti-TNF agents took 32.95 weeks (±0.95) on average [2]. A longer period of latency may indicate lower immunogenicity of the tocilizumab–IL-6R immunocomplex than the anti-TNF-α–TNF-α immunocomplex, although further investigation is necessary.

Compared with anti-TNF agents, the risk of autoimmune events induced by biologics other than anti-TNF agents is underestimated. Rather, tocilizumab was recommended as an alternative when Henoch–Schönlein purpura occurred with the use of etanercept for RA [8]. However, we should be aware of the potential side effects of paradoxical vasculitis in association with tocilizumab.

Rheumatology key message

- Tocilizumab, a biologic agent different from anti-TNF agents, can induce leucocytoclastic vasculitis.

Disclosure statement: K.F. has received research support and honoraria from Chugai Pharmaceutical. K.Y. has provided consultancy services for Chugai Pharmaceutical and has received research support and honoraria from Chugai Pharmaceutical. All other authors have declared no conflicts of interest.

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Accepted 13 January 2014
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Rheumatology 2014;53:1530–1532
doi:10.1093/rheumatology/keu028
Advance Access publication 7 March 2014

Successful multiget therapy using mizoribine and tacrolimus for refractory Takayasu arteritis

Sir, Takayasu arteritis (TA) is a chronic, relapsing vasculitis affecting the aorta and/or its main branches. The presenting manifestations include fever, fatigue, weight loss, hypertension, headaches, strokes and elevated levels of acute-phase reactants, such as CRP, which correlate with disease activity. High-dose corticosteroid therapy is effective in TA, but such therapy alone cannot sustain long-term remission.

Immunosuppressants such as MTX and CYC are used in corticosteroid-resistant patients [1]. Recently anti-TNF [1] and anti-IL-6 receptor [2] antibodies have been used for refractory TA. However, novel therapies for corticosteroid-resistant TA have not yet been standardized.
We present the case of a TA patient who underwent multitarget therapy with the calcineurin inhibitor tacrolimus and the purine anti-metabolic immunosuppressant mizoribine (MZR) after a failed trial of a conventional combination therapy with corticosteroid, MTX and infliximab (IFX). MZR is thought to have a mechanism of action identical to that of MMF, with fewer myelosuppressive and hepatotoxic effects.

A 9-year-old female was admitted to our hospital because of persistent fever. Physical examination showed different blood pressure in the left and right lower extremities (right, 106/58 mmHg; left, 90/36 mmHg) and a weak left dorsalis pedis pulse. Blood examination showed elevated CRP levels (5.5 mg/dl) and ESR (120 mm/1 h). Chest contrast-enhanced CT showed thickening of the walls of the aorta, coeliac artery, superior mesenteric artery, bilateral pulmonary arteries and left femoral artery (Fig. 1A–C).

She was diagnosed with TA on the basis of these findings. Treatment with 55 mg/day (2 mg/kg/day) prednisolone (PSL) relieved symptoms and CRP levels decreased.

![Fig. 1 Contrast CT findings and clinical course](image-url)

Contrast-enhanced CT of the chest shows thickening of the wall of the (A) aorta, (B) right pulmonary artery and (C) coeliac artery and superior mesenteric artery. (D) Clinical course of this patient.
to within the normal range (<0.05 mg/dl). Subsequently the PSL dose was decreased to 13 mg/day.

However, she developed chest pain, with high CRP (0.8 mg/dl) and ESR (58 mm/1 h) levels, suggesting TA relapse. Accordingly, methylprednisolone pulse therapy (15 mg/kg for 3 days) was started and MTX (12 mg/week) was added to PSL. This treatment induced TA remission. However, disease activity became exacerbated again after PSL dose reduction to 15 mg/day. Thereafter combination treatment with PSL, MTX and tacrolimus (3 mg/day) was started. This treatment induced TA remission. However, disease activity was exacerbated again after PSL dose reduction to 10 mg/day (Fig. 1D). IFX was started (3 mg/kg at weeks 0 and 2) instead of tacrolimus, but disease activity was again exacerbated. Consequently, the PSL dose was increased to 20 mg/day. Also, tacrolimus at 3–4 mg/day (serum trough level 5–10 ng/ml) was restarted and combined with MZR (300 mg/day). Combination treatment again induced remission of TA. Subsequently the PSL dose was tapered to 6.5 mg/day. Two years after combination therapy was started, a renal biopsy was performed to evaluate tacrolimus-induced chronic renal toxicity. We did not observe interstitial fibrosis or significant vascular lesions.

Only limited evidence exists regarding the efficacy of immunosuppressants or biologic agents for treating corticosteroid-resistant TA. Yokoe et al. [3] reported on the effectiveness of tacrolimus in a corticosteroid-resistant patient who was MTX intolerant. Yamazaki et al. [4] also reported on the effectiveness of tacrolimus in a patient refractory to corticosteroid, MTX and IFX.

Multitarget treatment with tacrolimus and MMF has been used for severe LN [5]. The efficacy and safety of this combination therapy is reported to be higher than that of an i.v. CYC-based regimen [5]. Originally MZR, an imidazole nucleoside isolated from *Eupenicillium brefeldianum* culture medium, was isolated as an antibiotic agent, and was subsequently found to have immunosuppressive activity. Although there are some differences in its chemical properties and metabolic profile, its mechanism of action is almost identical to that of MMF. Both agents inhibit guanosine monophosphate synthesis by inhibiting inosine-5'-monophosphate dehydrogenase. Thus MZR is expected to have similar efficacy to that of MMF. One advantage of MZR may be its safety. In a study of maintenance therapy for LN, few adverse events were reported, with a good corticosteroid-sparing effect [6]. The reason we introduced MZR is because MMF is not approved for LN treatment in Japan. Thus MZR is a good candidate for combination therapy with its established efficacy and safety. We adopted a combination treatment regimen of corticosteroid, MZR and tacrolimus for the treatment of refractory TA and achieved good results. Furthermore, MZR has a unique effect in that it suppresses macrophage infiltration to the renal interstitium [7]. Therefore MZR can decrease chronic renal damage by calcineurin inhibition [8]. Our patients did not show findings of interstitial fibrosis or significant vascular lesions in renal biopsy specimens after 2 years of combination therapy.

In conclusion, these findings suggest that multitarget therapy comprising a corticosteroid, tacrolimus and MZR is a potential alternative therapeutic regimen in patients with corticosteroid-resistant or anti-TNF-resistant TA. Further studies with a larger patient cohort are needed to confirm these findings.

**Rheumatology key message**

- Multitarget therapy is a potential alternative therapy in patients with corticosteroid-resistant or anti-TNF-resistant Takayasu arteritis.

**Disclosure statement:** The authors have declared no conflicts of interest.

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Accepted 22 January 2014

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