Refractory Takayasu arteritis responding to the oral janus kinase inhibitor, tofacitinib

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**Key message:** Tofacitinib in combination with methotrexate is a possible treatment strategy in refractory Takayasu arteritis.

Dear Editor, Takayasu arteritis (TAK) is a rare autoinflammatory disease, characterized by aortitis affecting the aorta and its major branches, coronary arteries, and pulmonary arteries. Long-term inflammation often causes severe vascular injury, including thickening of the aorta and its main branches, fibrosis, stenosis, and thrombus formation, leading to organ failure and subsequent numerous symptoms due to ischemia. The pathogenesis of TAK is yet to be elucidated, leading to limitations in therapeutic strategies and prognosis.

Tofacitinib (TOF) is an oral janus kinase (JAK) inhibitor, which blocks cytokine-mediated inflammatory signaling through the suppression of JAK 1 and 3. TOF is clinically indicated in the treatment of rheumatoid arthritis and ulcerative colitis. However, the efficacy and safety of TOF in patients with refractory TAK remain unclear. Here, we present the first case reporting the successful TOF treatment in TAK refractory to glucocorticoids (GCs), immunosuppressants, TNF-α blockers, and tocilizumab (TCZ), a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody. Additionally, our case suggests that TOF in combination with MTX could be effective in TAK patients for tapering GCs and that the serum level of IL-6 may be a useful biological marker to assess the disease activity.

A 26-year-old man, diagnosed with TAK at the age of 24 years and treated with prednisolone (16 mg/day) in combination with infliximab (400 mg/8 weeks), cyclosporine (CyA, 200 mg/day), and azathioprine (AZA, 50 mg/day), was admitted to our hospital due to a relapse of the disease. He was...
treated with prednisolone (30 mg/day) in combination with TCZ (162 mg/week), followed by oral
cyclophosphamide (CPA, 100 mg/day) for the induction of remission. However, neither TCZ nor CPA
was effective in tapering prednisolone to less than 25 mg/day due to aggravation of his chest pain. A
CT scan revealed the worsening of arterial wall thickness, of both left common carotid artery and
descending aorta, with pleural effusion (figure 1A). In view of the inflammatory phenotype caused by
multiple cytokines through cytokine receptors and their downstream JAK/STAT signaling pathways,
we treated the patient with 10 mg/day of TOF in combination with 50 mg/day of prednisolone based
on the approval from the Okayama University Hospital Ethics Committee. His symptoms improved
following the dissipation of the thickened aorta and pericardial pleural effusion (figure 1B), despite
developing an infection twice (bacteremia of unknown origin and atheroma infection) (figure 1C).
Notably, MTX in combination with TOF was effective against chest pain and the elevated serum CRP
levels following prednisolone tapering to 20 mg/day (figure 1C), demonstrating the additive effects of
MTX and TOF in the maintenance of remission in TAK. After the commencement of MTX,
prednisolone was further tapered from 20 to 15 mg/day without relapse (figure 1C). Lastly, we
performed a multiplex measurement of serum inflammatory cytokines, and observed high levels of IL-
6, TNF-α, and IL-18 during high disease activity. After the commencement of treatment, only the IL-
6 level was decreased, suggesting a possible role of IL-6 as a biological marker of TAK (figure 1C).

A recent randomized, placebo-controlled, double-blind, parallel-group, comparative study
demonstrated that TCZ is effective in patients with refractory TAK, leading to clinical application.\textsuperscript{5}
However, 61% of TAK patients treated with TCZ relapse during tapering of GCs,\textsuperscript{5} indicating that
another therapeutic strategy needs to be established. Another recent study in mice suggests the clinical
effectiveness of TOF on large vessel vasculitis.\textsuperscript{6} Since TOF is approved only for treatment of
rheumatoid arthritis and ulcerative colitis in Japan, the off-label use of TOF in the present case was
approved by the Okayama University Hospital Ethics Committee and financially supported by the Okayama University Hospital. Our case indicates that TOF in combination with MTX is a possible treatment strategy in patients with refractory TAK, and the serum level of IL-6 may be a useful biological marker to assess the disease activity.

In conclusion, our report provides new clinical insight into the role of TOF for refractory TAK and expands the concept that TOF in combination with MTX may be effective in other autoinflammatory diseases caused by multiple cytokines.

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**Figure 1. CT scan images, clinical course and the serum levels of cytokines in the present case.**

(Figure 1A and 1B) The CT images show the left common carotid artery (red arrow), the descending aorta (yellow arrow) and pleural effusion (green arrow) before (A, Relapse) and 12 months after (B, 12 M) the commencement of tofacitinib (TOF). A: prednisolone (25 mg/day) + cyclophosphamide (100 mg/day), B: prednisolone (15 mg/day) + TOF (10 mg/day) + methotrexate (MTX, 10 mg/week).

(Figure 1C) Clinical course of the patient showing serum levels of CRP and inflammatory cytokines before and during 12 months of prednisolone and TOF treatment.
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(Figure 1C) Clinical course of the patient showing serum levels of CRP and inflammatory cytokines before and during 12 months of prednisolone and TOF treatment.

|          | Relapse | 3 M | 12 M |
|----------|---------|-----|------|
| IL-6 (pg/ml) | 93.76   | 5.49| 1.90 |
| IL-18 (pg/ml) | 108.04  | 85.51| 85.89|
| TNF-α (pg/ml) | 21.43   | 17.4 | 15.14|

39x29mm (600 x 600 DPI)