DEAR EDITOR, Takayasu’s arteritis (TAK) is a systemic vasculitis with a relapse rate of up to 70%, especially during the course of glucocorticoid (GC) tapering. Combination of GC-sparing agents early in the treatment is the general management principle in clinical practice. Conventional synthetic disease modifying anti-rheumatic drugs (cs-DMARDs) are effective in most cases. However, some TAK patients are refractory to all currently available cs-DMARDs. For these refractory patients, biologics including tocilizumab (TCZ) and TNF-inhibitor are recommended as alternatives based on the EULAR recommendations [1]. Nonetheless, there are still some patients who fail to respond to biologics. Tofacitinib, a Janus kinase (JAK) inhibitor, was demonstrated in an animal model of large vessel vasculitis by Zhang et al. recently to be effective in inhibiting vessel inflammation [2]. Therefore, we hypothesized that tofacitinib may be effective in treating TAK and we investigated the efficacy and safety of tofacitinib in five refractory Chinese TAK patients.

From August 2018, five consecutive patients with refractory TAK were treated with tofacitinib at a dose of 5 mg twice daily. All patients failed to achieve remission despite standard therapy including glucocorticoid, cs-DMARDs and biologics (i.e. TCZ). The patients had evidence of active disease including fever, carotidynia, myalgia, arthralgia, aggravated hypertension, iritis and persistent elevated inflammatory biomarkers when being treated with tofacitinib. In four patients, reduction of prednisone dosage to <15 mg daily was unsuccessful and pulse methylprednisolone therapy failed in one patient. These patients were followed at baseline, 1 month, then every 3 months after they were treated with tofacitinib to evaluate the efficacy and safety of the therapy. Their clinical symptoms, signs, laboratory tests and serial vascular Doppler imaging examinations were carried out as evidence for comprehensive disease activity evaluation at each follow-up visit (Table 1).

The demographic data, baseline clinical manifestations, angiographic involvements and medication history of these patients are shown in Table 1. The follow-up time of these five patients ranged from 6 months to 18 months. Patient 1 was followed-up for over 18 months. In patients 1, 3, 4 and 5, clinical symptoms suggesting active disease, including fever, carotidynia, myalgia, arthralgia and iritis disappeared after 4 weeks treatment with tofacitinib. Two observations were made in the process. Firstly, the ESR and high-sensitive CRP (hs-CRP) returned to normal range in patients 1, 3, 4 and 5. Secondly, the improvement and stabilizations of artery stenosis and mural thickness were observed by vascular Doppler in patients 1, 3 and 4 (Supplementary Table S1, available at Rheumatology online). Reduction of prednisone dosage from 15 mg to 10 mg daily in patient 1 and from 27.5 mg to 10 mg daily in patient 5 were successful. In patients 3, 4 and 5, dosage of prednisone was maintained at 10 mg or 15 mg daily during their use of tofacitinib. Our target maintenance dosage of prednisone is 10 mg daily in concord with the recommendation of EULAR [3]. Further medication adjustment of patients with persistent remission would be discussed with patients after comprehensive angiography evaluation, considering both high-cost and side-effect of immunosuppressive agents. The usage of tofacitinib in patient 1 was continued for >18 months with sustained inactive disease. No adverse event was observed during the follow-up period. In particular, complete blood counts, renal and liver function remained within normal range, and no patient developed bacterial or viral infection (such as herpes zoster).

The treatment of TAK is a big challenge due to high relapse rate. Although high dosage corticosteroid can always control recurrence or flare, maintenance therapy is very challenging. EULAR recommends early administration of a GC-sparing drug in TAK [3]. Efficacy of cs-DMARDs (including methotrexate, LEF, mycophenolate mofetil, azathioprine, CYC) and TNF inhibitors in TAK were reported only in retrospective case series and uncontrolled studies. Although the TCZ trial failed to meet the primary endpoint, signals for efficacy were seen and long-term extension data published recently indicate GC-sparing effect [4]. There is no high-quality evidence showing superiority of biologics over cs-DMARDs in TAK. cs-DMARD was recommended to be combined with corticosteroid as the initial therapy when the diagnosis of TAK was made, and biologicals (TNF-inhibitor or TCZ) were used as the second line agents in relapsing patients [1].

Tofacitinib is a JAK/signal transducer and activator (STAT)-dependent pathway inhibitor. It might be effective in treating autoimmune disease by suppressing the pathogenic Th1, Th2 and Th17 cells, activated dendritic cells and B cells [5]. Zhang et al. researchers had demonstrated in a mouse model of GCA that tofacitinib could suppress innate and adaptive immunity in the
TABLE 1 Clinical manifestations in patients receiving tofacitinib with refractory Takayasu’s arteritis at baseline and during follow-up

|                      | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|----------------------|-----------|-----------|-----------|-----------|-----------|
| **Gender**           | Female    | Female    | Female    | Female    | Female    |
| **At baseline**      |           |           |           |           |           |
| **Age – years**      | 29        | 23        | 19        | 22        | 17        |
| **Disease duration – months** | 51        | 66        | 4         | 18        | 23        |
| **Symptoms and/or signs suggesting active disease** | Fever | Aggravated hypertension | Fever, carotidin, arthralgia, myalgia | Carotidin | Iritis (New occurrence of stenosis and vessel thickness of left CCA) |
| **Vessel lesions**   |           |           |           |           |           |
| **Stenosis**         | Rt-CCA, Rt-SCA, Lt-SCA, Lt-AxA | Rt-CCA, Lt-CCA, Lt-SCA, Lt-VA, BCT, Ao-Arch, Tho-Ao, Abd-Ao, SMA, IMA, CA, Lt-RA | Lt-CCA, Rt-CCA, Lt-SCA | Lt-SCA | Lt-CCA |
| **Occlusion**        | Rt-CCA, Lt-CCA, Lt-SCA, Lt-VA, BCT, Ao-Arch, Tho-Ao, Abd-Ao, SMA, IMA, CA, Lt-RA | — | — | — | — |
| **Thickened vessel wall** | Rt-CCA, Lt-CCA, Lt-SCA, Lt-VA, BCT, Ao-Arch, Tho-Ao, Abd-Ao, SMA, IMA, CA, Lt-RA | Lt-SCA | Lt-CCA, Lt-CCA, Lt-SCA, Lt-VA, BCT, Ao-Arch, Tho-Ao, Abd-Ao, SMA, IMA, CA, Lt-RA | Lt-CCA | — |
| **Numano’ angiographic classification** | V | V | Ila | I | I |
| **Pulse methylprednisolone therapy treatment before tofacitinib** | Yes | No | No | No | No |
| **Immunosuppressant drugs before tofacitinib** | MTX, CYC, AZA, MMF, LEF, tacrolimus, tocilizumab | MTX, MMF, LEF, tocilizumab | CYC, tocilizumab | MMF, MTX, AZA | MMF, MTX, tocilizumab |
| **Prednisone – mg/day** | 15 | 15 | 15 | 10 | 27.5 |
| **ESR – mm/1st hr**  | 90 | 29 | 82 | 70 | 16 |
| **Hs-CRP – mg/l**    | 91.8 | 22.2 | 180.1 | 129.25 | 19.2 |
| **During follow-up** |           |           |           |           |           |
| **Prednisone – mg/day** |           |           |           |           |           |
| **Last visit**       | 10 | 15 | 15 | 10 | 10 |
| **ESR – mm/1st hr**  |           |           |           |           |           |
| 1 month              | 34 | 32 | 74 | 40 | 2 |
| 3 months             | 18 | 21 | 31 | 8 | 3 |
| 6 months             | 8 | 27 | 16 | 2a | 6p |
| 12 months            | 4 | — | — | — | — |
| 18 months            | 5a | — | — | — | — |
| **Hs-CRP – mg/l**    |           |           |           |           |           |
| 1 month              | 18.4 | 35.5 | 56.7 | 17.46 | 0.07 |
| 3 months             | 10.2 | 34.2 | 6.3 | 0.97 | 4.08 |
| 6 months             | 1.2 | 38.8 | 0.8 | <1.2a | 0.3a |

(continued)
vessel wall. The production of IFN-gamma, IL-17 and IL-21 was decreased. In addition, adventitia microvascular angiogenesis was suppressed and the hyperplastic intima growth was relieved. The amount of tissue-resident memory T cells in the vessel wall was also reduced by tofacitinib in their study [2]. Recently, two patients with refractory TAK were reported with good response to tofacitinib [6, 7], while two other patients were resistant to it [8]. These case reports demonstrated signals for possible efficacy of tofacitinib in some refractory TAK patients.

The result of our observation is promising, but a prospective clinical trial is required to further investigate the efficacy and safety of tofacitinib in the treatment of refractory TAK. The major limitations of this report are lack of repeated examination of CT angiography, relative short follow-up period, and no reduction of glucocorticoid dosage in three patients.

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**Supplementary data**

Supplementary data are available at Rheumatology online.

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