Tofacitinib for the treatment of refractory Takayasu's arteritis: description of 2 cases

Sirs,

Glucocorticoids (GCs) are the mainstay treatment for the induction of remission in Takayasu's arteritis (TAK) (1, 2), however a high relapse rate (93% within two years) is observed in patients treated with GCs alone. Traditional immunosuppressants (ISs) are usually associated to GCs as initial treatment for TAK (3), however, 54% of patients are refractory to ISs (4), and biological agents seem to be more effective than ISs at maintaining remission (1). Around 1/3 of patients treated with biologics flare (4), therefore the management of TAK remains challenging.

We herein report two cases of refractory TAK treated with the janus kinase (JAK) 1 and 3 inhibitor tofacitinib.

A 18-year-old female presented with dyspnea, fatigue and weight loss. Elevated blood pressure and elevated acute phase reactants were observed. MR angiography (MRA) showed vessel wall thickening and enhancement of the thoracic and abdominal aorta and epiaortic vessels, and occlusion of the left carotid and subclavian arteries and right renal artery. TAK was diagnosed and GCs (prednisone 1 mg/kg/day) and methotrexate (20 mg/week) were started. Percutaneous transluminal angioplasty of the right renal artery was performed.

Fourteen months later, low-grade fever recurred and inflammatory markers increased. MRA showed occlusion of the right renal artery and stenosis of the left renal artery. Rituximab with high-dose GCs were added.

Fourteen months later, constitutional symptoms and increased inflammatory markers occurred. PET/CT scanning showed an increased FDG uptake of the epiaortic vessels, thoracic and abdominal aorta. Rituximab was switched to adalimumab, and then 28 months later, to tocilizumab for the inefficacy of adalimumab.

After six months, because of persistent disease activity (constitutional symptoms and increased aortic FDG uptake) (Fig. 1) and worsening of left renal artery stenosis at ultrasonography tofacitinib 5 mg twice daily was started with prednisone 0.5 mg/kg/die.

At two months of follow-up, the uptake on PET/CT decreased (Fig. 1), but inflammatory markers increased and the patient became pulseless in both radial arteries. Tofacitinib was switched to infliximab.

In 2009, a 14-year-old female presented with constitutional symptoms and elevated acute-phase reactants. MRA showed vessel wall thickening with enhancement and stenosis of the thoracic and abdominal aorta. TAK was diagnosed and prednisone 1 mg/kg/day and methotrexate 15 mg/week were started.

Two years later, the disease was still active and infliximab was added. Twelve months later, the patient presented with elevated blood pressure and cardiac failure. MRA revealed bilateral occlusion of the renal arteries, which required aorto-renal bypass. Tocilizumab was started, in addition to methotrexate and high dose GCs. In the following years, the patient failed to respond to different therapies (azathioprine, mycophenolate mofetil, adalimumab, rituximab).

In 2018, while on infliximab, mycophenolate mofetil and low-dose prednisone, the patient presented with persistent constitutional symptoms, lower extremity claudication and elevated acute-phase reactants. A PET/CT scanning showed increased FDG uptake of the thoracic and abdominal aorta (Fig. 1). MRA showed persistent vessel wall thickening with enhancement and progression of the stenosis of the thoracic and abdominal aorta. Infliximab was switched to tofacitinib 5 mg twice daily. Seven months later, tofacitinib and mycophenolate mofetil were stopped for the persistence of constitutional symptoms, elevated inflammatory markers and increased left carotid and aortic FDG uptake at PET/CT scanning (Fig. 1). Cyclophosphamide pulses were started.

To our knowledge, no other cases of TAK treated with JAK inhibitors have been described in literature.

Recently, Zhang *et al*. demonstrated that cytokine signalling dependent on JAK3 and JAK1 is critically important in chronic inflammation of medium and large arteries and that the JAK inhibitor tofacitinib effectively suppresses tissue-resident memory T cells and inhibits several processes relat-

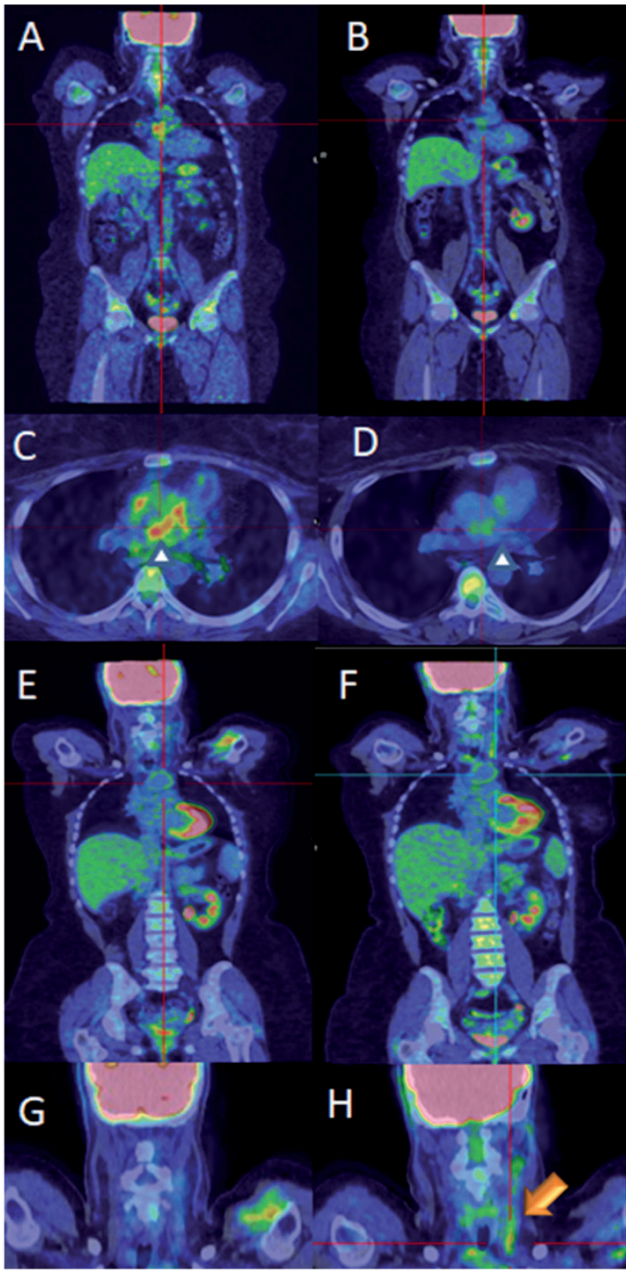

Fig. 1. PET/CT before and after tofacitinib.
Case 1. A,**C**: grade 3 FDG uptake at aortic arc (arrowhead) (6). ESR: 19 mm/1st hour, systemic symptoms, worsening of left renal artery stenosis.
B,**D**: after tofacitinib: grade 2 FDG uptake at aortic arc (arrowhead), ESR: 48 mm/1st hour, pulseless radial arteries (Kerr/NIH criteria =2) (7).
Case 2. E,**G**: grade 1 FDG uptake at aortic arch and common carotid artery. ESR: 40 mm/1st hour, constitutional symptoms, lower extremity claudication, progression of abdominal aorta stenosis.
F,**H**: after tofacitinib: grade 3 FDG uptake at left common carotid (arrow), ESR: 98 mm/1st hour, systemic symptoms, pulseless radial arteries (Kerr/NIH = 3).

ed to the inflammatory vascular damage (5). Tofacitinib failed to induce remission in our two patients, who were refractory to GCs and multiple ISs and biological agents. Moreover, the follow-up was relatively too short to evaluate the evolution of arterial lesions. Therefore, caution is required before considering tofacitinib ineffective for TAK, and only randomized controlled trials will ultimately define the efficacy and safety of JAK inhibitors in large-vessel vasculitis.

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