Utility and safety of tocilizumab in Takayasu arteritis with severe heart failure and muscle wasting

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Abstract

Takayasu arteritis (TA) is a large vessel vasculitis of unknown aetiology characterized by chronic inflammatory changes of the aorta and its major branches. We report the active TA case who had severe heart failure due to acute myocardial infarction and aortic regurgitation. Bentall procedure was successfully performed, but he had severely depressed left ventricular function and muscle wasting together with vascular inflammation. The treatment with tocilizumab, an interleukin-6 receptor monoclonal antibody, in addition to prednisolone and standard heart failure therapy led to prompt remission of TA activity and improvement of left ventricular function and muscle wasting. Taken together with possible involvement of interleukin-6 in the pathogenesis of heart failure and muscle wasting, inhibition of interleukin-6 receptor signalling by tocilizumab may be a safe and reasonable approach in the treatment of active TA with heart failure and muscle wasting.

Keywords Takayasu arteritis; Tocilizumab; Interleukin-6; Heart failure; Aortic regurgitation; Sarcopenia

Introduction

Takayasu arteritis (TA) is a large vessel vasculitis of unknown aetiology characterized by chronic inflammatory changes of the aorta and its major branches, resulting in various vascular complications.1 Treatment of TA consists of two strategies: immunosuppressive therapy for inflammation control and management of vascular diseases including control of blood pressure and surgical or interventional procedures. Glucocorticosteroids have been widely used as a first-line therapy to relieve systemic and regional inflammation in TA. However, to induce remission of active TA, a relatively high dose of glucocorticosteroid for a long term is often needed, which is associated with risk of major side effects of the steroids. Recently, favourable effects of tocilizumab (TCZ), an interleukin-6 (IL-6) receptor monoclonal antibody, on glucocorticoid-free remission rates in patients with large vessel vasculitis have been reported.2

Case report

A 65-year-old man who had received percutaneous coronary intervention for acute myocardial infarction was transferred to our institute for treatment of refractory heart failure. Transthoracic echocardiography showed severe aortic regurgitation with dilatation of the sinus of Valsalva and left ventricular ejection fraction (LVEF) of 32% with severe hypokinesis of anteroseptal and apical walls. In computed tomography angiography, the aortic root was dilated, and there were dilated and stenotic changes in both common carotid arteries and their branches (Figure 1A) together with delayed enhancement of the thickened vascular wall (Figure 1B,C), being consistent with the findings of active TA. Blood tests on the admission revealed a C-reactive protein (CRP) of 11.2 mg/dL, and a prominent elevation of NT-proBNP level (14 662 pg/mL). Because his heart failure worsened in spite of
intensive medical therapy, the aortic regurgitation was surgically corrected with Bentall procedure on Day 3 after the admission. Histological analyses of resected aortic tissues at the time of surgery showed massive infiltration of lymphocytes and giant cells mainly in the media and adventitia with destruction of the media (Figure 1D), typical findings of TA.

One week after the surgery, body mass index of the patient was 14.8 kg/m², and dual-energy X-ray absorptiometry scan revealed a prominent reduction of appendicular skeletal muscle mass index (ASMI: 3.43 kg/m², cut-off value of ASMI defined as ≤6.87 for Japanese men in the diagnosis of sarcopenia³). Repeated echocardiography showed impaired left ventricular systolic function (LVEF: 17.9%) with left ventricular dilatation (left ventricular end-diastolic volume (LVEDV): 207 mL) under continuous infusion of milrinone at a dose of 0.3 μg/kg/min. ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography imaging revealed strong ¹⁸F-FDG uptake at the left main coronary artery (Figure 1E) and its disappearance after the treatment with prednisolone and tocilizumab (F).

Figure 1  (A) 3D computed tomography angiography showing aortic root dilatation and dilated and stenotic changes of both common carotid arteries and their branches. (B, C) Axial computed tomography images showing wall thickening with enhancement of right (B) and left (B, C) common carotid arteries. (D) Histological findings of surgically resected aortic tissue showing massive infiltration of lymphocytes and giant cells mainly in the media and adventitia with destruction of the media. Images of Elastica von Gieson staining (original magnification ×100) and haematoxylin and eosin staining (inset, original magnification ×400) are shown. (E, F) ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography imaging showing strong ¹⁸F-FDG uptake in the left main coronary artery (E) and its disappearance after the treatment with prednisolone and tocilizumab (F).
level was still elevated (10.1 mg/dL) and serum pentraxin-3 (PTX3) level, a marker of TA activity independent of IL-6 level, was high (7.2 ng/mL, normal range: 0.73–5.49). Treatment with 30 mg of prednisolone per day was commenced in addition to standard heart failure therapy. CRP level gradually lowered over a period of 2 weeks, but its level rose again 18 days after the commencement of prednisolone treatment (Figure 2). After a short-term administration of methotrexate, TCZ was added to 30 mg of prednisolone per day. TCZ was initially scheduled to administer every 14 days, but it changed to every 7 days because of re-elevation of CRP 16 days after the initial dose of TCZ. Four weeks later, CRP and PTX3 levels were reduced to levels within normal ranges, and the uptake of 18F-FDG at the left main coronary artery was undetected (Figure 1). Follow-up examinations showed reverse left ventricular remodelling (LVEF: 35.1%, LVEDV: 110 mL), reduction in NT-proBNP level (Figure 2), and increase in ASMI (4.09 kg/m2). Considering the favourable responses to TCZ, we reduced prednisolone dose to 25 mg/day, and he was transferred to an affiliated hospital for rehabilitation. Further improvement in left ventricular function was observed 6 months after the discharge from our hospital (LVEF: 45.0%, LVEDV: 101 mL).

Discussion

A glucocorticosteroid is a cornerstone drug in the treatment of TA, but a number of patients experience relapse episodes during its tapering or after its discontinuation. Combination of an immunosuppressant with a glucocorticosteroid is an approach to prevent relapse of TA and/or to successfully taper the dose of glucocorticosteroid, but it is accompanied by immunosuppression-related side effects. As an alternative approach, molecular-targeted agents have been applied for the treatment of TA. Blocking of TNF-α receptor signalling seemed to be effective in a series of active and relapsed TA cases, but a detrimental effect of anti-TNF-α therapy on major cardiovascular events in patients with symptomatic heart failure (New York Heart Association Functional Class III or IV) was observed. Protective effect of TCZ on giant cell arteritis was recently shown by a randomized control trial that compared addition of TCZ to prednisolone with prednisolone alone. Intriguingly, TCZ, an inhibitor of IL-6 receptor signalling, does not appear to share such a side effect of TNF-α receptor inhibitors on heart failure patients. There are case reports that left ventricular dysfunction was not worsened or rather improved after TCZ treatment in patients with TA and patients with rheumatoid arthritis. In our case, addition of TCZ with prednisolone led to prompt remission of TA activity, as shown by a reduction in both PTX3 level and 18F-FDG uptake at the left main coronary, without cardiovascular complications. Because 18% of patients with active TA have left ventricular systolic dysfunction, inhibition of IL-6 receptor signalling by TCZ may be a reasonable approach in the treatment of active TA.

Skeletal muscle wasting, causing physical disability, is frequently observed in patients with chronic heart failure (CHF) and systemic inflammatory diseases. One of the
possible mechanisms of the skeletal muscle wasting is up-regulation of IL-6 level. The association between serum IL-6 level and ASMI has been shown in patients with CHF. While physiological production of IL-6 induces proliferation of satellite cells and myotube regeneration, persistent elevation of IL-6 level activates several protein degradation pathways and disturbs myocyte regeneration, leading to muscle atrophy. Furthermore, a recent study showed that levels of appendicular skeletal muscle mass, assessed by a dual-energy X-ray absorptiometry scan, were higher in patients with rheumatoid arthritis who received TCZ than in those who did not receive TCZ. Importantly, long-term administration of glucocorticosteroid induces muscle atrophy, although the glucocorticosteroid potentially suppresses skeletal muscle wasting due to inflammation. Nevertheless, detailed analysis is needed to determine the long-term effect of IL-6 inhibition on body composition including skeletal muscle mass in patients with TA and/or CHF.

**Conflict of interest**

None declared.

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