ESC HEART FAILURE
ESC Heart Failure 2019; **6**: 894–897
Published online 11 July 2019 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12487

CASE REPORT

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

Toshiyuki Yano[1]*, Arata Osanami[1], Masaki Shimizu[1], Satoshi Katano[2], Nobutaka Nagano[1], Hidemichi Kouzu[1], Masayuki Koyama[1,3], Atsuko Muranaka[1], Ryo Harada[4], Hirosato Doi[4,5], Nobuyoshi Kawaharada[4] and Tetsuji Miura[1]

[1]*Department of Cardiovascular, Renal and Metabolic Medicine, Sapporo Medical University School of Medicine, South-1, West-16, Chuo-ku, Sapporo 060-8543, Japan;* [2]*Division of Rehabilitation, Sapporo Medical University Hospital, Sapporo, Japan;* [3]*Department of Public Health, Sapporo Medical University School of Medicine, Sapporo, Japan;* [4]*Department of Cardiovascular Surgery, Sapporo Medical University School of Medicine, Sapporo, Japan;* [5]*Department of Cardiovascular Surgery, Sapporo Cardio Vascular Clinic, Sapporo Heart Center, Sapporo, Japan*

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

Received: 21 March 2019; Revised: 17 May 2019; Accepted: 1 June 2019
**Correspondence to: Toshiyuki Yano, Department of Cardiovascular, Renal and Metabolic Medicine, Sapporo Medical University School of Medicine, South-1, West-16, Chuo-ku, Sapporo 060-8543, Japan. Tel: +81 11 611 2111 ext. 3225; Fax: +81 11 644 7958. Email: tyano@sapmed.ac.jp*

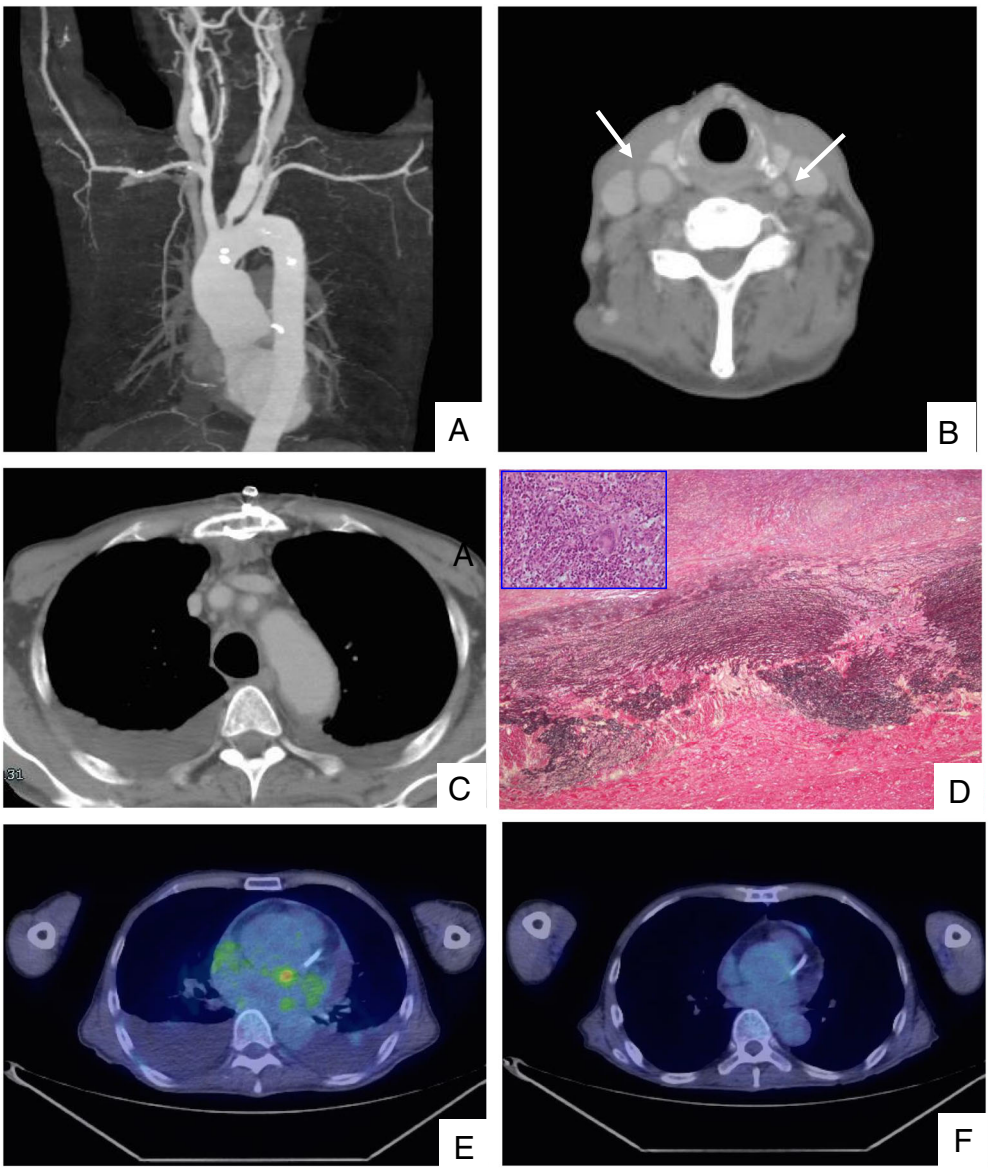
Introduction

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

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) ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography showing strong ^{18}F-FDG uptake in the left main coronary artery (E) and its disappearance after the treatment with prednisolone and tocilizumab (F).



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/m^2, and dual-energy X-ray absorptiometry scan revealed a prominent reduction of appendicular skeletal muscle mass index (ASMI: 3.43 kg/m^2, cut-off value of ASMI defined as ≤6.87 for Japanese men in the diagnosis of sarcopenia[3]). 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. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography images revealed strong uptake of ^{18}F-FDG at the left main coronary artery (*Figure 1E*). CRP

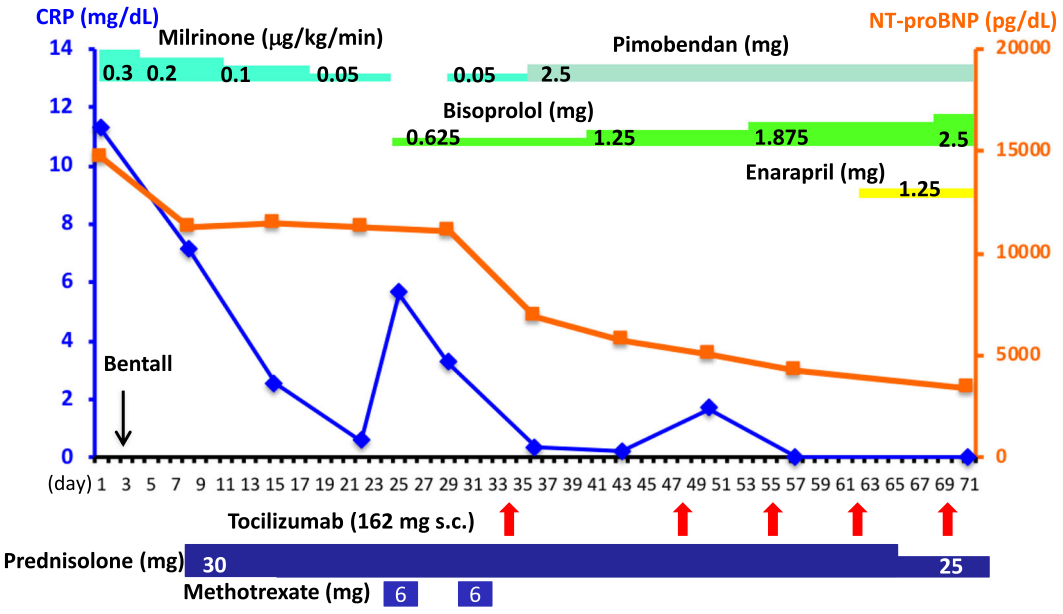
level was still elevated (10.1 mg/dL) and serum pentraxin-3 (PTX3) level, a marker of TA activity independent of IL-6 level,[4] was high (7.2 ng/mL, normal range: 0.73–5.49). Treatment with 30 mg of prednisolone per day was commenced in addition to standard heart failure therapy. CRP level gradually 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 ^{18}F-FDG at the left main coronary artery was undetected (*Figure 1F*). 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/m^2). 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.[1] 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,[1] 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.[5] 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.[2] 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[6] and patients with rheumatoid arthritis.[7] 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 ^{18}F-FDG uptake at the left main coronary, without cardiovascular complications. Because 18% of patients with active TA have left ventricular systolic dysfunction,[8] 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.[9,10] One of the

Figure 2 Clinical course of this case. Tocilizumab was initially scheduled to administer every 14 days, but it changed to every 7 days because of re-elevation of C-reactive protein 16 days after the initial dose of tocilizumab.



DOI: 10.1002/ehf2.12487

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.[11] 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.[12] 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 received TCZ.[13] 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.

References

1. Isobe M. Takayasu arteritis revisited: current diagnosis and treatment. *Int J Cardiol* 2013; **168**: 3–10.
2. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, Brouwer E, Cid MC, Dasgupta B, Rech J, Salvarani C, Schett G, Schulze-Koops H, Spiera R, Unizony SH, Collinson N. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017; **377**: 317–328.
3. Sanada K, Miyachi M, Tanimoto M, Yamamoto K, Murakami H, Okumura S, Gando Y, Suzuki K, Tabata I, Higuchi M. A cross-sectional study of sarcopenia in Japanese men and women: reference values and association with cardiovascular risk factors. *Eur J Appl Physiol* 2010; **110**: 57–65.
4. Ishihara T, Haraguchi G, Tezuka D, Kamiishi T, Inagaki H, Isobe M. Diagnosis and assessment of Takayasu arteritis by multiple biomarkers. *Circ J* 2013; **77**: 477–483.
5. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Anti-TNF therapy against congestive heart failure investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-α, in patients with moderate-to-severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTA CH) trial. *Circulation* 2003; **107**: 3133–3140.
6. Schiavon F, Cuffaro S, Ometto F, Mojoli M, Ramonda R. Takayasu arteritis and NYHA III/IV idiopathic cardiomiopathy: tocilizumab proves effective and safe. *Joint Bone Spine* 2014; **81**: 278–279.
7. Suzuki A, Tamamura T, Okai T. Five-year administration of tocilizumab to a patient with rheumatoid arthritis complicated by severe chronic heart failure. *Nihon Rinsho Meneki Gakkai Kaishi* 2014; **37**: 488–492.
8. Lee GY, Jang SY, Ko SM, Kim EK, Lee SH, Han H, Choi SH, Kim YW, Choe YH, Kim DK. Cardiovascular manifestations of Takayasu arteritis and their relationship to the disease activity: analysis of 204 Korean patients at a single center. *Int J Cardiol* 2012; **159**: 14–20.
9. Suzuki T, Palus S, Springer J. Skeletal muscle wasting in chronic heart failure. *ESC Heart Fail* 2018; **5**: 1099–1107.
10. Springer J, Springer JI, Anker SD. Muscle wasting and sarcopenia in heart failure and beyond: update 2017. *ESC Heart Fail* 2017; **4**: 492–498.
11. Fülster S, Tacke M, Sandek A, Ebner N, Tschöpe C, Doehner W, Anker SD, von Haehling S. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *Eur Heart J* 2013; **34**: 512–519.
12. Belizário JE, Fontes-Oliveira CC, Borges JP, Kashiabara JA, Vannier E. Skeletal muscle wasting and renewal: a pivotal role of myokine IL-6. *Springerplus* 2016; **5**: 619.
13. Tournadre A, Pereira B, Dutheil F, Giraud C, Courteix D, Sapin V, Frayssac T, Mathieu S, Malochet-Guinamand S, Soubrier M. Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. *J Cachexia Sarcopenia Muscle* 2017; **8**: 639–646.