Case report

Rescue treatment with Tocilizumab for Takayasu arteritis resistant to TNF-α blockers

C. Salvarani[1], L. Magnani[1], M. Catanoso[1], N. Pipitone[1], A. Versari[2], L. Dardani[1], L. Pulsatelli[3], R. Meliconi[4], L. Boiardi[1]

[1]Rheumatology Unit, and [2]Nuclear Medicine Unit, Azienda Ospedaliera ASMN, IRCCS, Reggio Emilia, Italy; [3]Laboratory of Immunorheumatology and Tissue Regeneration, Istituto Ortopedico Rizzoli, Bologna, Italy; [4]Rheumatology Unit, Istituto Ortopedico Rizzoli and University of Bologna, Bologna, Italy.

Carlo Salvarani, MD
Luca Magnani, MD
Mariagrazia Catanoso, MD
Nicolò Pipitone, MD, PhD
Lucia Dardani, MD
Luigi Boiardi, MD, PhD
Annibale Versari, MD
Lia Pulsatelli, BSc
Riccardo Meliconi, MD

Please address correspondence to:
Dr Carlo Salvarani,
Servizio di Reumatologia,
Azienda Ospedaliera ASMN, IRCCS,
Viale Risorgimento 80,
42100 Reggio Emilia, Italy.
E-mail: salvarani.carlo@asmn.re.it

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ABSTRACT

Anti-TNF-α therapy has successfully been used to treat Takayasu arteritis (TA) refractory to conventional immunosuppressive treatment. However, some patients fail to respond even to TNF-α blockers. Interleukin-6 (IL-6) is a key player in the pathogenesis of TA. Preliminary data also suggest efficacy of the IL-6 receptor inhibitor tocilizumab in patients with large-vessel vasculitis. We report a patient with TA refractory to multiple conventional immunosuppressive agents and two TNF-α blockers successfully treated with monthly tocilizumab infusions (8 mg/kg body weight) for 6 consecutive months. Clinical indices of disease activity, inflammatory markers, and ^{18}F-fluorodeoxyglucose positron emission/computerised tomography findings normalised, while the prednisone dosage could be tapered. Serum IL-6 and soluble IL-6 receptor (sIL-6R) levels raised during tocilizumab treatment consistent with the mode of action of tocilizumab. Tocilizumab holds promise for patients with refractory TA. Larger studies are required to confirm our findings.

Introduction

Takayasu arteritis (TA) is a chronic granulomatous vasculitis mainly involving the aorta and its branches. Glucocorticoids and immunosuppressants are the mainstay of treatment, but relapses are common when treatment is tapered. Open-label studies have shown efficacy of anti-TNF-α therapy in refractory TA (1, 2). However, some patients may incur relapses and develop new vascular lesions even on anti-TNF-α therapy.

Serum interleukin-6 (IL-6) levels are elevated in TA and correlate with disease activity (3-5). In addition, high expression of IL-6 in the aortic tissue from patients with TA has been reported (6). These findings suggest that IL-6 may contribute to the pathogenesis of TA. Consistent with this hypothesis, pilot studies have demonstrated efficacy of the anti-interleukin-6-receptor (IL-6R) monoclonal antibody tocilizumab (TCZ) in patients with large-vessel vasculitis including TA (7-9).

Herein, we report compassionate treatment with TCZ of a patient with TA refractory to prednisone, traditional immunosuppressants, and two TNF-α blockers.

Case report

In July 2007, a 25-year-old female presented with myalgia, arthralgia, headache, fever (37.8°C), and carotidodynia. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated at 41 mm/1st h and 12.8 mg/dl (normal values: ESR <30 mm/1st h and CRP <0.5 mg/dl), respectively. ^{18}F-Fluorodeoxyglucose positron emission/computerised tomography (PET/CT) showed vascular uptake compatible with active vasculitis. TA was diagnosed and prednisone 50 mg/day started. However, the patient relapsed repeatedly upon tapering of the prednisone dose and was unable to reduce the dose below 12.5–15 mg/day over three years. Sequential therapy with methotrexate (20 mg/week), infliximab (5 mg/kg every 6 weeks for 12 months) and adalimumab (40 mg every 2 weeks for 13 months) failed to control disease activity. Both TNF-α inhibitors were given with mycophenolate mofetil at 2g/day. In August 2010, 10 months after starting adalimumab, while on prednisone 10 mg/day, the patient developed abdominal and bilateral arm claudication, arthralgia, myalgia, and fatigue. Physical examination disclosed an abdominal bruit.

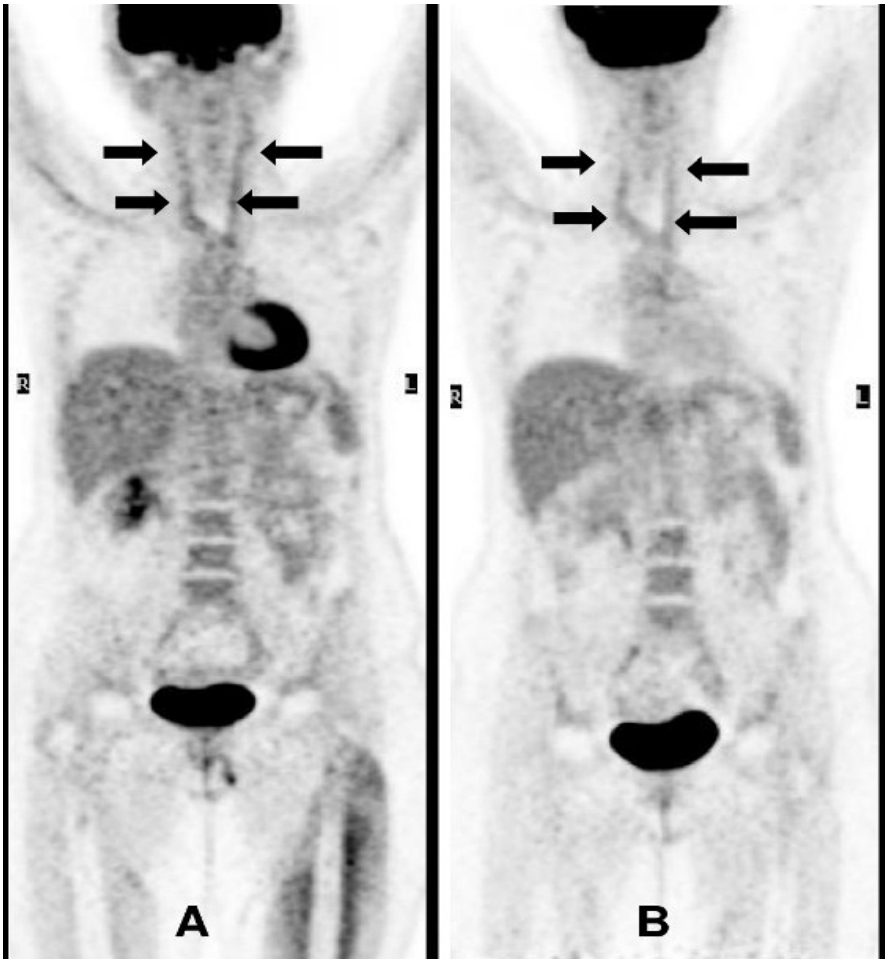

Fig. 1. FDG PET: Coronal image before (**A**) and after (**B**) tocilizumab.
A: Abnormal FDG uptake in the brachiocephalic artery and in the right and left carotid arteries (arrows). **B**: In the same areas (arrows) the FDG uptake decreased more than 30%.

Abdominal angiography demonstrated a new stenosis of the coeliac artery. Ultrasonography demonstrated an inflammatory halo in both common carotid and subclavian arteries.

TCZ (8 mg/kg/body weight) infusions every 4 weeks for 6 months were started without increasing the prednisone dosage. Mycophenolate mofetil therapy was continued at 2g/day.

Disease activity was assessed at baseline and at 6 months using the Indian Takayasu Activity Score (ITAS) (10) and the Kerr (11) indices. Laboratory tests including ESR, CRP, IL-6, and the soluble-IL-6R (sIL-6R) were performed before the 1st administration of TCZ (time 0) and subsequently every 4 weeks before the infusion of TCZ during the treatment period. Normal values for IL-6 and s-IL-6R were <4.5 pg/ml, and <80.1 ng/ml, respectively. PET/CT was performed before and after treatment. PET/CT vascular FDG uptake was expressed as Standardised Uptake Value (SUV) relative to liver uptake. Vascular uptake was also graded using a 4-point scale (12) ranging from 0 to 3, where 0=no uptake, 1=low-grade uptake (lower than liver uptake), 2=intermediate-grade uptake (similar to liver uptake), and 3=high-grade uptake (higher than liver uptake). Vasculitis was considered active if ≥2 large vessels showed ≥grade 2 FDG uptake.

The patient gave informed consent before receiving TCZ treatment. The treatment was approved by the local Ethics Committee.

Before treatment, Indian Takayasu Activity Score (ITAS) and Kerr indices were both 3. ESR and CRP were respectively 69 mm/1st hour and 7.2 mg/dl. Serum IL-6 was 27.724 pg/ml and sIL-6R levels 28.894 ng/ml. PET/CT showed high-grade vascular FDG uptake (grade 3) indicative of active vasculitis in the brachiocephalic artery, and right and left carotid arteries. SUV in these 3 large vessels was 1.30, 1.10, and 1.3, respectively.

After the second TCZ infusion, clinical manifestations resolved, while ESR and CRP normalised. Serum IL-6 and sIL-6R levels peaked after the 2nd infusion at 338.20 pg/ml and 175.070 ng/ml, respectively, and remained elevated throughout TCZ treatment (Fig. 1). After 6 infusions of TCZ, Kerr and ITAS indices decreased to 1 and 0, respectively. PET/CT showed a marked decrease in vascular FDG uptake with SUV in the brachiocephalic artery and in the right and left carotid arteries of 0.81, 0.74, and 0.81, respectively (Fig. 2).

Prednisone could be tapered to 5 mg/day. No safety issues emerged.

At 2 months of follow-up, the patient remains asymptomatic, Kerr and ITAS indices are unchanged and inflammatory markers are within limits. Figure 1 shows ESR, CRP, serum IL-6 and soluble IL-6 receptor (sIL-6R) values during TCZ treatment.

Discussion

Glucocorticoids are the mainstay of therapy of TA. However, although

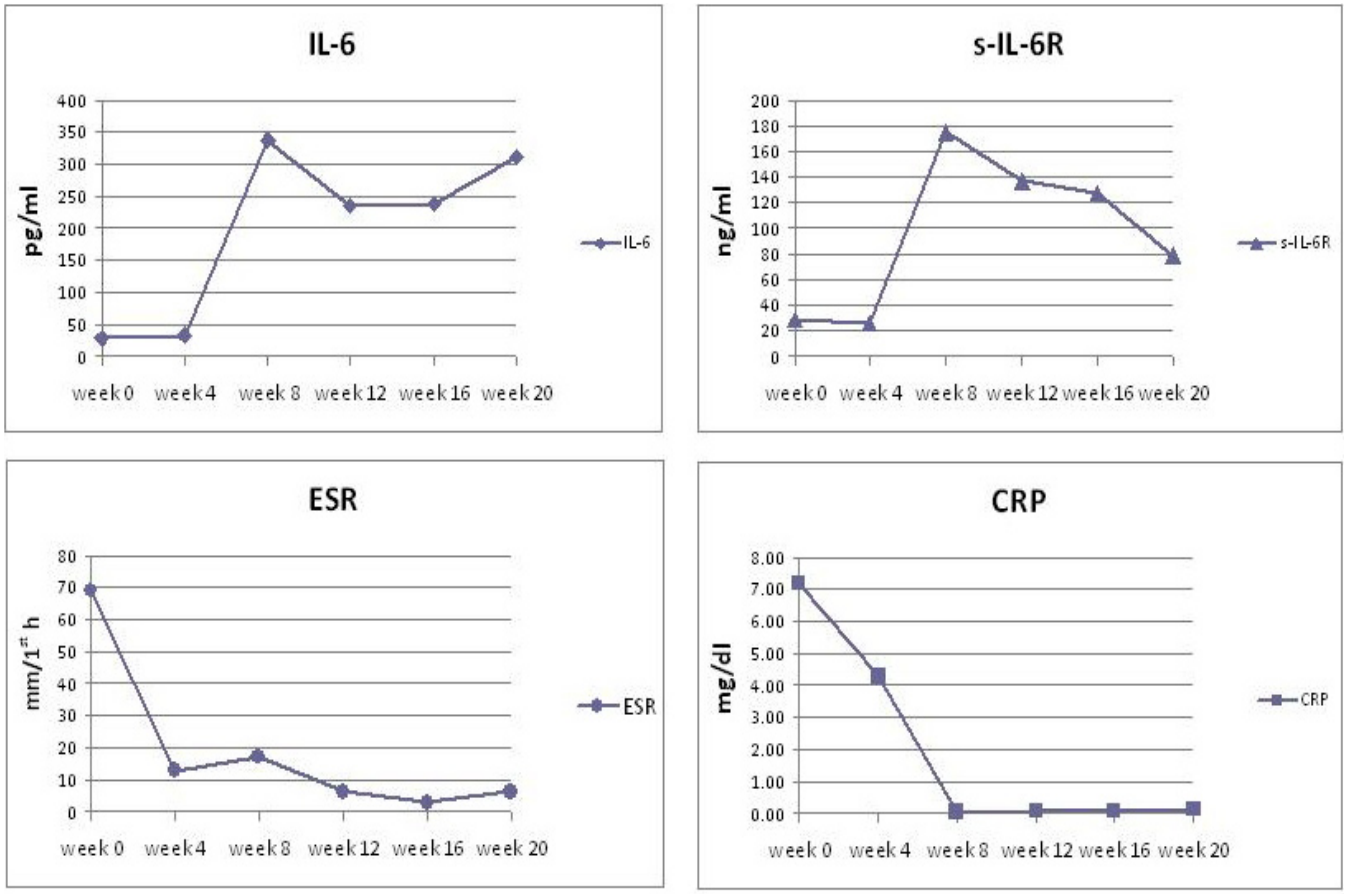

Fig. 2. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6), and IL-6 soluble receptor (sIL-6R) in the serum of a Takayasu arteritis patient during tocilizumab treatment. Laboratory tests performed before the 1st administration of tocilizimuab (time 0) and subsequently every 4 weeks before the infusion of tocilizumab.
Tocilizumab treatment increased the baseline serum levels of IL-6 and sIL-6R, that peaked after the 2nd infusion and remained elevated during the therapy, while ESR and CRP serum levels normalised.

virtually all patients respond to glucocorticoids, most of them suffer clinical relapses and may develop new vascular lesions upon dose tapering (13). To minimise glucocorticoid-related side effects and to attain disease control, traditional immunosuppressive agents, such as methotrexate, are required in most patients (14). However, only a minority of patients achieve long-term remission and are able to successfully taper or discontinue glucocorticoids. Anti-TNF-α therapy is effective in some, but by no means all patients with TA refractory to conventional treatment (1, 2).

To our knowledge, this is the first report on the efficacy of TCZ in a patient with TA refractory to traditional immunosuppressive agents and two TNF-α blockers. We rationale for using TCZ was twofold. First, IL-6 has been shown to play a pivotal pathogenetic role in TA (3-6). Second, previous reports have documented efficacy of IL-6 blockade in large-vessel vasculitis including three cases of TA refractory to conventional therapy (7-9). In line with these data, TCZ led to a complete response in our patient, with normalisation of clinical and laboratory parameters of disease activity and substantial improvement in imaging findings (15).

We also measured IL-6 and sIL-6R levels during TCZ treatment. At baseline, serum IL-6, and CRP levels were elevated in keeping with active disease. Previous observations have shown that long-term TCZ treatment reduced serum IL-6 levels in TA (9). This reduction was hypothesised to be due to IL-6R inhibition indirectly suppressing IL-6 production. In contrast, we found that TCZ treatment further increased serum levels of IL-6 and sIL-6R, which remained elevated throughout TCZ therapy. We hypothesise that this observed rise in serum IL-6 may be related to the inhibition of IL-6 clearance by IL-6R blockade, rather than to induction of IL-6 production, as conjectured by previous works (16, 17). In agreement with this notion, CRP serum levels normalised in our patient, suggesting that IL-6 signalling was inhibited and inflammation curbed. Similar findings have been observed in rheumatoid arthritis, Castleman disease, Crohn disease, and in collagen-induced arthritis, where TCZ administration resulted in marked increase in blood IL-6 and/or sIL-6R levels despite inhibiting inflammation (16, 17).

In conclusion, this case suggests the TCZ may be a useful therapeutic option for patients with TA refractory to the traditional immunosuppressive therapy and TNF-α blockers. A controlled trial to evaluate the efficacy and safety of TCZ in refractory TA is required.

References

1. HOFFMAN GS, MERKEL PA, BRASINGTON RD, LENSCHOW DJ, LIANG P: Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum* 2004; 50: 2296-304.
2. MOLLOY ES, LANGFORD CA, CLARK TM, GOTA CE, HOFFMAN GS: Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up. *Ann Rheum Dis* 2008; 67: 1567-9.
3. PARK MC, LEE SW, PARK YB, LEE SK: Serum cytokine profiles and their correlations with disease activity in Takayasu's arteritis. *Rheumatology* (Oxford) 2006; 45: 545-8.
4. NORIS M, DAINA E, GAMBA S, BONAZZOLA S, REMUZZI G: Interleukin-6 and RANTES in Takayasu arteritis: a guide for therapeutic decisions? *Circulation* 1999; 100: 55-60.
5. SALVARANI C, CANTINI F, BOIARDI L, HUNDER GG: Laboratory investigations useful in giant cell arteritis and Takayasu's arteritis. *Clin Exp Rheumatol* 2003; 21 (Suppl. 32): S23-8.
6. SEKO Y, SATO O, TAKAGI A *et al*.: Restricted usage of T-cell receptor Valpha-Vbeta genes in infiltrating cells in aortic tissue of patients with Takayasu's arteritis. *Circulation* 1996; 93: 1788-90.
7. SEITZ M, REICHENBACH S, BONEL HM, ADLER S, WERMELINGER F, VILLIGER PM: Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. *Swiss Med Wkly* 2011; 141: w13156.
8. BEYER C, AXMANN R, SAHINBEGOVIC E *et al*.: Anti-interleukin 6 receptor therapy as rescue treatment for giant cell arteritis. *Ann Rheum Dis* 2011; 70: 1874-5.
9. NISHIMOTO N, NAKAHARA H, YOSHIO-HOSHINO N, MIMA T: Successful treatment of a patient with Takayasu arteritis using a humanized anti-interleukin-6 receptor antibody. *Arthritis Rheum* 2008; 58: 1197-200.
10. MISHRA R, DANDA D, JAYASEELAN L, SIVAKUMAR R, LAWRENCE A, BACON PA: ITAS & DEI.TAK scores for clinical disease activity and damage extent in Takayasu's aortoarteritis (TA). *Rheumatology* (Oxford). 2008; 47.ii:101.
11. KERR GS, HALLAHAN CW, GIORDANO J *et al*.: Takayasu arteritis. *Ann Intern Med* 1994; 120: 919-29.
12. WALTER MA, MELZER RA, SCHINDLER C, MÜLLER-BRAND J, TYNDALL A, NITZSCHE EU: The value of [18F]FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease. *Eur J Nucl Med Mol Imaging* 2005; 32: 674-81.
13. MAKSIMOWICZ-MCKINNON K, HOFFMAN GS: Takayasu arteritis: what is the long-term prognosis? *Rheum Dis Clin North Am* 2007; 33: 777-86.
14. SALVARANI C, PIPITONE N: Treatment of large-vessel vasculitis: where do we stand? *Clin Exp Rheumatol* 2011; 29 (Suppl. 64):S3-5.
15. DIRESKENELI H, AYDIN SZ, MERKEL PA: Assessment of disease activity and progression in Takayasu's arteritis. *Clin Exp Rheumatol* 2011; 29 (Suppl. 64): S86-91. 2:
16. NISHIMOTO N, TERAO K, MIMA T, NAKAHARA H, TAKAGI N, KAKEHI T: Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood* 2008; 112: 3959-64.
17. UCHIYAMA Y, YOSHIDA H, KOIKE N *et al*.: Anti-IL-6 receptor antibody increases blood IL-6 level via the blockade of IL-6 clearance, but not via the induction of IL-6 production. *Int Immunopharmacol* 2008; 8: 1595-601.