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Concise report

Tocilizumab: a novel therapy for patients with large-vessel vasculitis

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Abstract

Objective. Treatment of large-vessel vasculitis (LVV) remains challenging. Patients usually respond to glucocorticoid (GC) therapy, but often relapse on tapering of the GC dose or after GC withdrawal. In addition, GCs are fraught with numerous adverse events. The aim of this study was to assess the efficacy and safety of the anti-IL-6 receptor (IL-6R) antibody tocilizumab (TCZ) in patients with LVV.

Methods. Four patients with active LVV (two with GCA and two with Takayasu arteritis) received monthly TCZ infusions (8 mg/kg bodyweight) for 6 consecutive months. Two patients were treatment naïve, while two had relapsing disease. Disease activity and drug tolerability were assessed clinically and by laboratory tests at study entry and subsequently every month for 6 months of TCZ treatment, while an [^{18}F]fluorodeoxyglucose PET (PET/CT) scan was performed before and after treatment. In addition, a semi-quantitative clinical evaluation was performed at baseline and at 3 and 6 months using the Indian Takayasu activity score and the Kerr indices. After TCZ, MTX was used as maintenance therapy.

Results. All patients treated with TCZ therapy had a satisfactory clinical and laboratory response, while PET/CT findings significantly improved in all cases. No serious adverse events were noted. Only one patient had a transient increase in liver enzymes.

Conclusions. In this small group of patients with LVV, treatment with TCZ was effective and well tolerated. Further, larger studies are required to confirm our findings.

Key words: interleukin-6, tocilizumab, large-vessel vasculitis, Takayasu arteritis, giant cell arteritis

Introduction

GCA and Takayasu arteritis (TA) are primary systemic vasculitides involving the aorta and its major branches [1]. Glucocorticoids (GCs) are the mainstay of treatment of GCA and TA, but a sizeable number of patients relapse upon tapering of the GC dose or discontinuation of GC therapy. MTX has shown some efficacy as steroid-sparing agent in relapsing patients in both conditions, but the entity of the benefit was rather modest, at least in GCA [2, 3]. There is some evidence that biologic agents, especially TNF-α inhibitors, might be efficacious in patients with GCA and TA who are relapsing [4, 5]. However, in a randomized controlled trial, the anti-TNF-α mAb infliximab did not appear to confer a significant benefit in patients with newly diagnosed GCA over and above that provided by GC alone [6]. Therefore, there is a need to develop novel, effective therapeutic strategies.

IL-6 is a key player in the pathogenesis of numerous inflammatory disorders, including GCA and TA [7]. Emerging data suggest that blockade of the soluble IL-6 receptor (s-IL-6R) with the mAb tocilizumab (TCZ) might be beneficial for patients with refractory TA and GCA [8]. The aim of this pilot study was to determine the efficacy and safety of TCZ in a small population of patients with large-vessel vasculitis (LVV).

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CLINICAL SCIENCE

Patients and methods

From June 2010 to January 2011, we enrolled four patients with LVV (two with TA and two with GCA). Patients were diagnosed according to ACR classification criteria for TA [9] and GCA [10], respectively. One patient (Case 3) did not fulfil the criteria for either GCA or TA, but was diagnosed with TA on the basis of constitutional manifestations, absence of cranial features, raised inflammatory markers and evidence of active LVV on PET/CT. Two patients were entirely treatment naïve, while two had relapsing disease upon tapering of the GC dose. Of those two patients with relapsing disease, one had failed MTX, and another had failed two TNF-α inhibitors tried sequentially after MTX. All patients received monthly TCZ (8 mg/kg/bodyweight) infusions for the study period of 6 months. Disease activity and drug tolerability were assessed clinically and by laboratory tests at study entry and subsequently every month during the 6 months of treatment with TCZ, while a PET/CT scan was performed before and after treatment.

A semi-quantitative clinical evaluation was performed at baseline and at 3 and 6 months using the Indian Takayasu activity score (ITAS) [11] and the Kerr [12] indices. The ITAS lists constitutional and organ manifestations with particular emphasis on cardiovascular features as well as inflammatory markers (ESR and CRP) and physician's global opinion. A score is generated on the basis of present (=1) or absent (=0) manifestations, and disease is considered active if one or more organ system scores positive [11]. The Kerr index assesses four items: constitutional manifestations, raised ESR, manifestations of vascular ischaemia and angiographic features indicative of vasculitis. Disease is defined as active in the presence of at least two new or worsened items [12].

For the purpose of this study, PET/CT was used instead of angiography to document vascular involvement. Vascular [^{18}F]fluorodeoxyglucose (FDG) uptake at PET/CT was expressed as standardized uptake value (SUV) relative to liver uptake. Vascular uptake was graded using a four-point scale [13] 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 two or more large vessels showed grade 2 FDG uptake or higher.

The primary end point of this open-label uncontrolled trial was the achievement of complete remission defined as normalization of all outcome measures (clinical indices, inflammatory markers and PET/CT findings). The secondary end points were decrease in GC dosage and attainment of partial remission defined as normalization of clinical indices and laboratory parameters but not of PET/CT findings.

Laboratory tests included ESR, CRP, IL-6 and the s-IL-6R. Serum IL-6 and s-IL-6R levels were measured using commercial sandwich ELISA (R&D Systems, USA) following the manufacturer's instructions. All patients gave informed consent before receiving TCZ treatment. The study was approved by the local Ethics Committee (Comitato etico Provinciale di Reggio Emilia).

Case reports

Table 1 shows clinical and laboratory findings and large-vessel FDG uptake before and after TCZ therapy.

Patient 1

A 21-year-old lady was referred to us because of myalgia, fever (37.5°C) and headache. On admission, she had bilateral carotid bruits (3/6), ESR and CRP were elevated, while PET/CT showed vascular uptake compatible with active vasculitis. TA was diagnosed and prednisone 50 mg/day tapering was commenced. However, the patient relapsed repeatedly upon tapering of the prednisone dose and was unable to reduce the dose $<$12.5 mg/day over 3 years despite MTX (15 mg/week) therapy. PET/CT before TCZ therapy showed high vascular uptake in multiple arteries. TCZ therapy was commenced 1 year after TA had been diagnosed.

After six TCZ infusions, clinical manifestations resolved, ESR and CRP normalized, while a repeat PET/CT showed a marked decrease in vascular FDG uptake. Prednisone was tapered off by the end of the TCZ cycle and MTX 15 mg/week was started as maintenance therapy. At 7-month follow-up, the patient remained asymptomatic and both Kerr and ITAS indices were negative, although ESR rose to 33 mm/first hour and CRP to 1.7 mg/dl (normal values $<$ 0.5).

Patient 2

A 40-year-old lady presented in June 2010 with recent onset of weight loss $>$2 kg, myalgia, arthralgia, fever and carotidodynia. Physical examination revealed a 3/6 right subclavian bruit. Past medical history disclosed renal artery stenosis with related renovascular hypertension treated with right nephrectomy. Inflammatory markers were raised, while PET/CT showed increased FDG vascular uptake in numerous large vessels (Fig. 1).

TA was diagnosed. Due to the patient's reluctance to take GC, TCZ was started 3 months later as monotherapy. After the first TCZ infusion, inflammatory markers normalized and the patient reported feeling much better in herself. A repeat PET/CT performed at the end of the TCZ course showed markedly decreased vascular FDG uptake. After TCZ withdrawal, MTX 20 mg/weekly was prescribed as maintenance therapy. At 10-month follow-up, the patient remained asymptomatic, Kerr and ITAS indices were negative and inflammatory markers were within limits. No further manifestations of vascular ischaemia occurred.

Patient 3

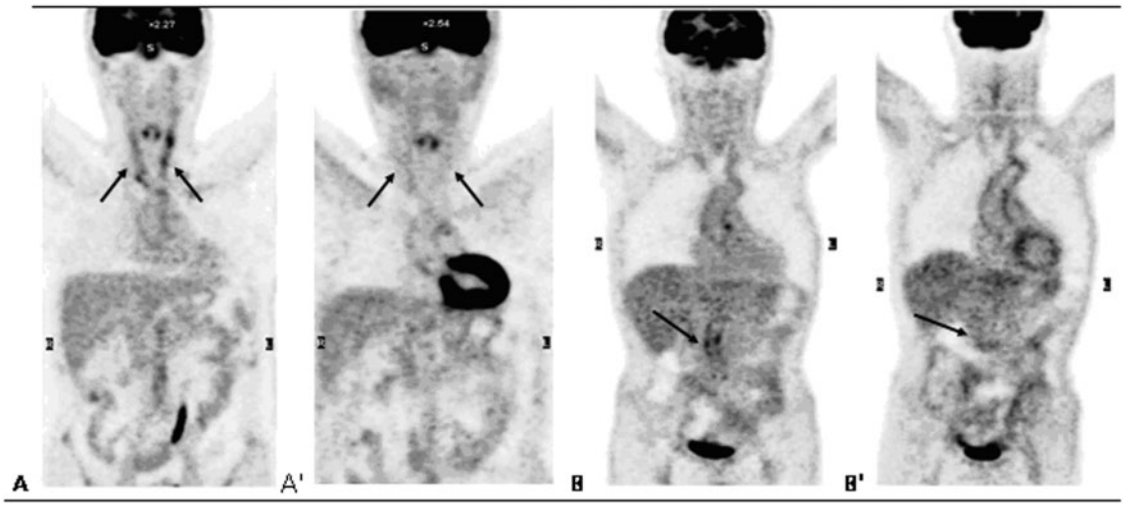
A 54-year-old gentleman was admitted because of new onset of weight loss (10 kg/3 months), myalgia and malaise in the absence of cranial signs and symptoms. ESR and CRP were elevated, while PET/CT showed increased FDG uptake in numerous large vessels. LVV (probable TA despite his age $>$40 years) was diagnosed and TCZ

Table 1 Clinical data, laboratory findings and large-vessel FDG uptake expressed as the ratio of vascular to liver SUV before and after TCZ therapy

Patient	ESR (mm/1 h)	CRP (mg/dl)	IL-6 (pg/ml)	s-IL6R (ng/ml)	ITAS	Kerr	Arch. A	As. A	DA	LS	RS	LC	RC	LF	RF	Ab. A
Patient 1 before TCZ	45	4.02	32.4	169.2	4	4	1.6 (3)		1.2 (2)	1.24 (3)	2.0 (3)	1.96 (3)				
Patient 1 after TCZ	3	0.06	66.9	1355.7	0	0	0.78 (1)		0.78 (1)	0.78 (1)	0.78 (1)	0.78 (1)				
Patient 2 before TCZ	67	0.99	0	250.1	3	4	1.6 (3)	1.1 (2)	1.05 (2)			1.35 (3)	2.1 (3)			
Patient 2 after TCZ	2	0.05	44.3	2109.8	0	0	0.72 (1)	0.72 (1)	0.72 (1)			0.72 (1)	0.72 (1)			
Patient 3 before TCZ	84	4.80	16.0	78.1	8	4	1.35 (3)	1.88 (3)	1.88 (3)							1.76 (3)
Patient 3 after TCZ	2	0.01	27.6	2265.1	0	1	0.92 (2)	1.0 (2)	0.92 (2)							0.0 (0)
Patient 4 before TCZ	95	5.42	ND	ND	3	4	0.90 (2)	1.35 (3)	0.90 (2)			1.2 (2)	1.2 (2)	1.1 (2)	1.1 (2)	
Patient 4 after TCZ	4	0.07	379.2	1838.7	0	1	0.75 (1)	0.75 (1)	0.75 (1)			0.75 (1)	0.75 (1)	0.75 (1)	0.75 (1)	

FDG/CT uptake values expressed on a 0–3 scale are given within parentheses—for details, see manuscript. Normal values: ESR < 40 mm/h; CRP < 0.05 mg/dl; serum IL-6 < 4.5 pg/ml; serum s-IL-6R < 80.1 ng/ml; ITAS < 1; Kerr $\leqslant 1$. Arch. A: aortic arch; As. A: ascending aorta; DA: descending aorta; LS: left subclavian artery; RS: right subclavian artery; LC: left carotid artery; RC: right carotid artery; LF: left femoral artery; RF: right femoral artery; Ab. A: abdominal aorta; ND: not done.

Fig. 1 PET/CT scans of Patients 2 and 3 before (**A**, **B**) and after (**A′**, **B′**) TCZ therapy. Patient 2 (**A** and **A′**): bilateral Grade 3 carotid artery FDG uptake before TCZ (→) (**A**). After TCZ therapy, FDG uptake markedly decreases to Grade 1 (**A′**). Patient 3 (**B** and **B′**): Grade 3 FDG uptake in the abdominal aorta before TCZ (→) (**B**). Note the marked decrease to Grade 1 after TCZ therapy (**B′**).



infusions commenced 2 months after TA had been diagnosed. GCs were not prescribed because of the patient's reluctance to take them. The patient reported a fast improvement of his constitutional manifestations although myalgia did not resolve entirely, while inflammatory markers normalized. Increased liver enzymes were noted after the second infusion, which returned to below the upper normal limit just 2 weeks after the infusion. This patient subsequently received a half-dose of TCZ at the third infusion and the full dose of TCZ thereafter without any further elevation of liver enzymes. PET/CT demonstrated a significant reduction in vascular FDG uptake in the abdominal aorta, but only a modestly decreased uptake in the thoracic aorta.

Following TCZ therapy, the patient was started on MTX 20 mg/week. At 8-month follow-up, the patients remained in clinical and laboratory remission, Kerr and ITAS were normal and no new vascular lesions developed.

Patient 4

A 64-year-old man with biopsy-proven GCA of 3 years duration had frequent relapses characterized by systemic manifestations, raised inflammatory markers and active LVV on PET/CT upon decrease in the prednisone dose $<$12.5 mg/day. Past medical history revealed SpA treated initially with infliximab and subsequently with etanercept (ongoing at the time of onset of GCA manifestations). MTX was added to etanercept as steroid-sparing agent for 1 year without significant benefit.

At baseline assessment, ESR and CRP were raised, while PET/CT demonstrated increased FDG uptake in numerous vessels. Etanercept and MTX were withdrawn and TCZ was commenced 3 years after GCA had been diagnosed.

Four weeks after starting TCZ therapy, the patient reported a significant clinical improvement, while the prednisone dose was tapered starting after the 12th week to the current dose of 2.5 mg/day. ESR and CRP normalized, while a repeat PET/CT revealed decreased FDG uptake in the vessels involved. After TCZ withdrawal, MTX 15 mg/week was commenced while keeping unchanged background prednisone 2.5 mg/day. At 11-month follow-up, the patients described widespread aches and pains without evidence of vascular ischaemia. ESR and CRP rose to 84 mm/first hour and 3.7 mg/dl, respectively, while Kerr was 2 and ITAS 1.

Discussion

IL-6 is a pleiotropic cytokine, which exerts powerful pro-inflammatory effects both locally and systemically [14]. The IL-6/s-IL-6R complex is likely to be a major player in the pathogenesis of LVV for several reasons. First, serum IL-6 levels have been shown to be raised in active GCA and TA patients and to correlate with disease activity [7]. Second, IL-6 is expressed in aortic tissue from patients with TA [1]. Third, IL-6 is specifically required for the TGF-β-induced differentiation of the pro-inflammatory Th17 cells, which have been demonstrated to be primed in active GCA [15]. Fourth, IL-6 can induce the production of acute-phase reactants and provoke constitutional manifestations, both of which are recognized features of the LVV [7]. Finally, as this and previous [8, 14] studies have revealed, s-IL-6R blockade by TCZ is effective in curbing inflammation and ameliorating clinical manifestations in patients with LVV. Taken together, these data strongly suggest that the IL-6/s-IL-6R complex plays a pivotal role in both GCA and TA LVV and that its blockade by TCZ is an effective therapeutic strategy.

All our patients treated with TCZ therapy had a satisfactory clinical and laboratory response, while PET/CT findings significantly improved in all cases. More specifically, three patients achieved the primary end point of complete response and one patient (Case 3) achieved partial remission. In the two refractory patients who were still taking GCs at study entry, GCs were tapered off or the dosage was gradually decreased to 2.5 mg/day by the end of the study period.

TCZ was well tolerated by all patients. In particular, no serious adverse events such as severe infections or infusion-related reactions occurred. Only one patient had a transient increase in liver enzymes after the second infusion. This patient was subsequently safely treated with TCZ without any further elevation of liver enzymes.

Both IL-6 and s-IL-6R serum levels rose in our patients following TCZ treatment despite the attainment of a response to therapy across the board (Table 1). While these findings seem at first to be hard to reconcile with the response to TCZ, they are in fact known to occur in patients treated with TCZ for other disorders [14]. The most likely explanation is that s-IL-6R elevation is due to an increase of residence time in plasma by the formation of TCZ/s-IL-6R ICs [14]. On the other hand, serum-free IL-6 might accumulate because the binding of TCZ to s-IL-6R inhibits the receptor-mediated clearance of IL-6 [14].

The results of our study are in agreement with those of previous reports. In the first published report, TCZ (4 mg/kg/weekly tapering) rapidly improved clinical manifestations and laboratory parameters, and partially reverted signs of vascular ischaemia in a patient with refractory TA [16]. TCZ (8 mg/kg/month) proved also effective in seven patients with LVV (five with GCA and two with TA) [8]. Of these patients, three were newly diagnosed, and four had a relapsing course upon tapering of the prednisone dose $<$7.5 mg/day. All patients achieved a rapid and complete clinical response and normalization of the acute-phase proteins, while the prednisone dosage could be reduced to a mean of 2.5 mg/day.

Our study has a number of strengths. All patients were carefully assessed clinically as well as by laboratory investigations and PET/CT imaging. In all patients, TCZ was able to consistently suppress disease activity as assessed by clinical, laboratory and metabolic imaging criteria. Clinical response and normalization of inflammatory markers were observed early after treatment onset, suggesting a rapid mode of action for TCZ. Importantly, TCZ proved effective both in treatment naïve and in relapsing patients. This suggests that TCZ may be a treatment option on its own for patients who have relative contraindications to GC therapy.

On the other hand, limitations of our study are the small sample size, the lack of patient-reported outcomes, the limited follow-up duration and the exclusion of patients with GCA characterized by cranial involvement. Therefore, our results should be taken with caution and not be extrapolated to GCA patients who present with cranial manifestations. In addition, it is unclear how the response achieved using TCZ should be best maintained over time.

In conclusion, TCZ appears to be a promising therapy for LVV. Since the cost of TCZ is considerably higher than that of GCs or of synthetic agents such as MTX, we feel that its use should be reserved to those patients who are refractory or have contraindications to conventional treatment. We propose that the much cheaper MTX may be used as maintenance therapy, but the insufficient follow-up duration of the study does not allow us to establish whether and to what extent this strategy is effective. Randomized controlled studies are required to investigate the efficacy and safety profile of TCZ in both GCA and TA.

Rheumatology key message

- TCZ holds promise as an effective and safe treatment for LVV.

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