Case report

One-year clinical and radiological evolution of a patient with refractory Takayasu's arteritis under treatment with tocilizumab

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ABSTRACT

A 28-year-old patient with Takayasu's arteritis (TA) failed to respond to high doses of prednisone in combination with methotrexate, pulses of cyclophosphamide and methylprednisolone, azathioprine, mycophenolate mofetil, adalimumab and monthly infusions of infliximab 5 mg/kg. After the beginning of tocilizumab therapy (4-8 mg/kg at monthly infusions), an impressive improvement in clinical and laboratory parameters of disease activity occurred, allowing the reduction of prednisone dose from 30 to 5 mg/day. However, after the 8th dose the patient developed symptoms of vertebrobasilar insufficiency, despite maintaining a good clinical condition and normal values of inflammatory markers. Angio-computed tomography repeated at one year of therapy showed reduction in aortic wall thickness, but also narrowing of the luminal diameters of the right subclavian, renal arteries, and left vertebral artery. Therefore, despite a significant clinical and laboratory improvement, vascular disease may progress in aortic branches in TA patients under tocilizumab therapy.

Introduction

The treatment of Takayasu's arteritis (TA) frequently represents a challenge to the rheumatologist. Recently, case reports have suggested efficacy of tocilizumab (TCZ; an anti-interleukin-6 receptor monoclonal antibody) in the treatment of TA (1, 2). Nishimoto *et al*. (1) reported a striking clinical and laboratory improvement, disappearance of syncope episodes, and reduction in the thickening of the aortic wall during TCZ therapy. Seitz *et al*. (2) observed disappearance of claudication and improvement of aortic abnormalities on magnetic resonance angiography (MRA) within three months of beginning of TCZ infusions (despite a rapid reduction of systemic corticosteroids) in two patients. However, both patients had to stop TCZ infusions after 4 and 8 months of therapy for different reasons (2). In the present study, we report a case of severe and refractory TA treated with tocilizumab during one year whose evolution differs in some aspects from the cases previously described.

In July 2004, a 22-year-old Caucasian female was admitted to the Hospital Nossa Senhora da Conceição (HNSC) presenting fever, weakness, arthralgias, weight loss, cervicalgia, hypertension and night sweating. Radial pulses were absent and the erythrocyte sedimentation rate (ESR) was 135 mm/h. MRA showed bilateral irregularities in the caliber of the subclavian and axillary arteries (with significant stenosis of the right subclavian artery), confirming the diagnosis of TA. Treatment with 60 mg/day of prednisone and oral methotrexate (MTX; 7.5 mg/week) was begun. After an initial good response, disease activity increased despite the use of 40 mg/day of prednisone and an escalating dose of MTX. Ten months later, the patient was referred to the Rheumatology Service of the HNSC presenting ESR of 107 mm/h and C-reactive protein (CRP) of 42 mg/L. MTX was interrupted; treatment with monthly pulses of intravenous cyclophosphamide (up to 1500 mg/month) plus methylprednisolone (1000 mg) was begun and continued for 9 months, with only modest results. Mycophenolate mofetil (up to 3000 mg/day) and azathioprine (200 mg/day) were ineffective. In August 2006, treatment with bi-monthly infusions of infliximab

Table I. Evolution of clinical and laboratory parameters during one year of tocilizumab therapy.

Date*	TCZ dose (mg/kg)	PRED dose (mg)	ESR (mm/h)	CRP (mg/L)	Serum Fibrinogen (mg/dL)	general health (VAS)	Pain (VAS)	Disease activity patient (VAS)	HAQ score	Physical functioning score (SF-36)	Mental Health score (SF-36)
24/May/2010		30	28	16							
06/Jul/2010		30	42	44	540						
30/Jul/2010		30				30	72	75	2.25	25	36
18/Aug/2010	1. 8.0	30	70	66	705	20	74	77	1.87	10	32
15/Sep/2010	2. 4.0	30	10	<3	288	80	0	11	0.75	50	80
15/Oct/2010	3. 6.0	30	8	13	341	90	7	5	0.0	60	88
12/Nov/2010	4. 6.0	20	2	<3	–	95	0	0	0.25	90	88
15/Dec/2010	5. 6.0	10	2	<3	220	90	0	0	0.25	85	80
21/Jan/2011	6. 6.0	7.5	10	15	290	80	3	0	0.0	90	92
18/Feb/2011	7. 8.0	10	2	<3	218	70	12	5	0.25	80	84
18/Mar/2011	8. 6.0	10	5	<3	203	50	37	8	0.37	90	48
19/Apr/2011	–	5	5	<3	229	80	0	0	0.37	80	52
06/Jun/2011	9. 4.5	5	17	8	353	95	3	0	0.25	85	88
11/Jul/2011	10. 4.5	25	4	<3	231	90	0	0	0.25	80	72
08/Aug/2011**	11. 4.5	30	2	<3	184	85	0	0	0.5	80	76

*Date refers to the day of infusion, when applicable (in these cases, the respective lab exams where done within 5 days before the referred date).
**The patient increased the prednisone dose despite the medical recommendation to reduce the dose to 20 mg/day. At the last contact (30th November 2011), the patient was asymptomatic under treatment with oral MTX 12.5 mg/week, prednisone 15 mg/day and monthly infusions of tocilizumab 7 mg/kg.
TCZ: tocilizumab; PRED: prednisone; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analogue scale, HAQ: Health Assessment Questionnaire; SF-36: 36-Item Short Form Health Survey.

Table II. Comparison of angio-CT before and at one year of monthly therapy with tocilizumab*.

Vascular area under exam	Angio-CT of 21/Jul/2010		Angio-CT of 07/Aug/2011	
	Largest wall thickness (mm)	Smallest luminal diameter (mm)	Largest wall thickness (mm)	Smallest luminal diameter (mm)
Right renal artery	–	2.84	–	2.31
Left renal artery	–	4.86	–	2.62
Aorta at the level of the left renal vein	2.86	12.07	2.05	11.06
Aorta 3 cm below the emergence of the coeliac trunk	3.21	11.76	1.71	11.40
Coeliac trunk	–	4.86	–	6.15
Descending aorta at the level of the carina cartilage	3.62	19.60	3.05	21.68
Aortic arch	3.44	28.85	1.92	30.26
Ascending aorta at the level of the carina cartilage	4.10	28.95	1.92	30.50
Right subclavian artery (proximal region)	–	8.70	–	8.95
Right subclavian artery (distal to the emergence of the internal mammary artery)	–	2.10	–	1.00
Left subclavian artery (proximal region)	2.40	8.62	2.80	8.39
Left subclavian artery (distal to the emergence of the vertebral artery)	–	2.69	–	4.25
Right vertebral artery (proximal region)	–	2.71	–	2.43
Left vertebral artery (proximal region)	–	2.66	–	2.24

*Angio-CT scans were performed using 4-mm slices. A second radiologist, blinded to the results of the first examiner, evaluated the luminal diameters (LDs) of the aortic branches. The variation of LDs were scored as "reduced", "equal" or "increased" in relation to the first angio-CT. There was good agreement between the examiners (weighted Kappa = 0.61). Both radiologists agreed on the observation of reduction of the LDs of the renal arteries, left vertebral artery, and right subclavian artery.

300 mg (3.5 mg/kg/dose) and injectable MTX (up to 25 mg/week) was initiated. The disease remained active during 2007 and 2008, with the use a relatively high dose of prednisone (≥30 mg/day, sometimes >120 mg/day) and CRP values sometimes >30 mg/l. On February 2009 the disease flared up and was controlled with pulse steroid therapy. Applications of MTX were interrupted due to intolerance and elevation of hepatic transaminases. In November 2009, treatment with infliximab was briefly interrupted for a trial of adalimumab (2 applications), which was poorly tolerated. Therapy with infliximab was reintroduced two months later and dose was augmented to 5 mg/kg at monthly intervals, without consistent effect. In June 2010 the patient had elevated inflammatory markers (Table I) and symptoms of malaise, pain in upper extremities, and arthralgias indicating high disease activity while still receiving monthly high dose infliximab and prednisone ≥30 mg/day.

After approval of the study by the ethics research committee and signing of a written informed consent, treatment with monthly tocilizumab 8 mg/kg/dose was started. Four weeks later, an impressive

improvement in parameters of disease activity, quality of life, and disability was observed (Table I). Considering the elevation of hepatic transaminases, the second dosing was reduced to 4 mg/kg. The third dose was adjusted to 6 mg/kg due to an elevation of CPR. A progressive reduction in the dose of prednisone was allowed. The patient considered herself "cured" in November 2010 and was able to live alone, without support of her parents. A higher dose of tocilizumab (8 mg/kg) was tried again on 18th February 2011, but the patient felt unwell and asked for reduction of the dose (Table I). No severe infections or serious adverse events were observed during the treatment.

On 19th April 2011 (the day scheduled for the 9th application) the medication was unavailable. Through a law suit against the state, the patient obtained two bottles of tocilizumab 200 mg and attended the visit for medication application on 6th June 2011. She still felt well and presented only minor elevations in ESR e CRP (Table I). However, she retrospectively reported the emergence of daily episodes of unilateral amaurosis followed by vertigo and syncope when performing light over head activities (hanging out clothes). The symptoms had begun on 23rd April 2011 (four days after the missed dose of tocilizumab). The diagnosis of vertebrobasilar insufficiency was made, and the prednisone dose was increased from 5 to 15 mg/day, oral MTX (7.5 mg/week) was initiated, and the patient was advised to avoid physical efforts that trigger episodes of syncope. After that, the syncope episodes did not recur, but the dose of prednisone was increased to 25 mg/day due to the persistence of episodes of vertigo. These episodes disappeared two weeks later.

The comparison of the results of angio-computed tomography (CT) before and one year after the beginning of tocilizumab therapy is shown in Table II. A reduction in the wall thickness and an increase in luminal diameters of the thoracic aorta was observed (Fig. 1A-B). However, there was a significant progression of stenosis in the renal arteries, in the right subclavian artery (Fig. 1C-D) and in the left vertebral artery (the latter possibly related to the vertebrobasilar insufficiency symptoms).

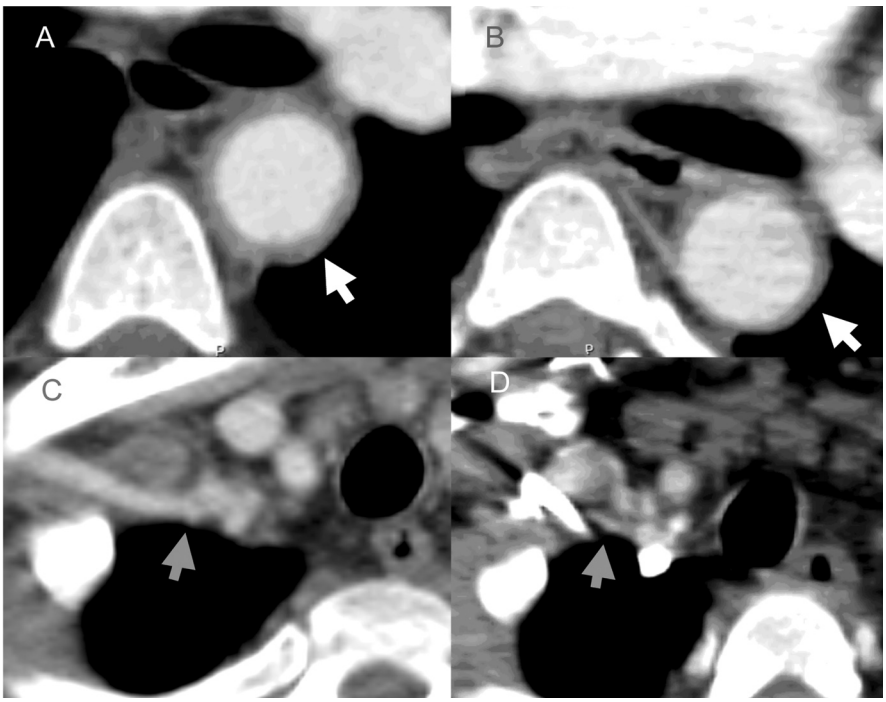

Fig. 1. Angio-computed tomography images of the descending aorta and right subclavian artery before (**A** and **C**, respectively) and after one year of tocilizumab therapy (**B** and **D**, respectively).

Contrast between the evolution of imaging studies, clinical symptoms and acute-phase reactants has been frequently reported in TA, with a substantial number of patients showing radiographic disease progression in the context of normal laboratory markers of inflammation (3, 4). Although our findings and those of previous reports (1, 2) showed a reduction in the thickness of the aortic wall during tocilizumab therapy, our results suggest that TA may progress in the aortic branches even when the disease seems to be controlled under this treatment. Nevertheless, the remarkable effect on clinical parameters and quality of life justifies the use of tocilizumab in TA refractory to anti-TNF therapy.

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