Tocilizumab in patients with Takayasu arteritis: a retrospective study and literature review

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ABSTRACT

Objective. *To assess the efficacy of tocilizumab (TCZ) in patients with Takayasu arteritis (TA).*

Methods. *Multicentre open-label retrospective study.*

Results. *Eight patients (all women) with a mean age of 34±16 years, median 36 years (range: 7–57) were assessed. The main clinical features at TCZ therapy onset were: constitutional symptoms (n=4), fever (n=3), headache (n=2), chest pain (n=1), abdominal pain (n=1), mesenteric ischaemia (n=1), myalgia involving the lower limbs (n=1), cerebral vascular insufficiency (n=1), malaise (n=1), upper limb claudication (n=1) and nodular scleritis (n=1). Besides corticosteroids and before TCZ treatment onset, 7 of 8 patients had also received several conventional immunosuppressive and/or biologic agents. Seven patients experienced marked clinical improvement in the first 3 months after the onset of TCZ therapy. After a median follow-up of 15.5 [interquartile range-IQR: 12–24] months, 7 patients were asymptomatic. The median C-reactive protein decreased from 3.09 [IQR: 0.5–12] to 0.15 [IQR: 0.1–0.5] mg/dL (p=0.018), and median erythrocyte sedimentation rate from 40 [IQ range: 28–72] to 3 [IQR: 2–5] mm/1st hour (p=0.012). The median dose of prednisone was also tapered from 42.5 [IQR: 25–50] to 2.5 [IQR: 0–7.5] mg/day (p=0.011). However, TCZ had to be discontinued in 1 patient because she developed a systemic lupus erythematosus, and in another patient due to inefficiency. TCZ dose was reduced in a patient because of mild thrombocytopenia.*

Conclusion. *TCZ appears to be effective in the management of patients with TA, in particular in patients refractory to corticosteroids and/or conventional immunosuppressive drugs.*

Introduction

Takayasu arteritis (TA) is a large-vessel vasculitis (1) characterised by a chronic granulomatous, inflammatory and stenotic disease, mainly affecting the aorta and its major branches (2, 3). Surgical series from the US have demonstrated that among the most frequent causes of aortitis is focal isolated idiopathic aortitis of the aortic root and arch. Other frequent underlying conditions of aortitis are giant cell arteritis (GCA) in Europe and North America (4-7), and TA in East Asia, Africa and South-America (8, 9). In some cases, aortitis, in particular in patients with classic cardiovascular risk factors such as hypertension (10), may be associated with severe complications, such as aneurysms, dissection and rupture of the aortic wall, and a prompt diagnosis and treatment is essential in these patients (11-14). TA also is responsible for aneurysms, although these occur far less often than stenoses and occlusions: In this regard, TA, aortic aneurysms have been reported in up to 45% of patients (10).

First-line therapy for TA includes high dose corticosteroids (15-19), although, in most cases, conventional synthetic immunosuppressive drugs are required to get adequate control of the disease or as corticosteroid sparing agents. According to Kötter *et al.* (20), between 46–84% of patients with TA require a second drug to achieve remission and successfully taper corticosteroids. In these cases, methotrexate (MTX), azathioprine (AZA), cyclophosphamide (CYP) and mycophenolate mofetil (MM) have been the immunosuppressive agents most frequently used, usually with a limited efficacy and often leading to severe side effects (21-26).

A better understanding of the pathogenesis of large-vessel vasculitis has allowed the use of biologic therapy, al-

though with discordant results (27-51). Several proinflammatory cytokines are involved in the pathogenesis of large-vessel vasculitis, such as TNF-α and interleukin-6 (IL-6), which are considered to be important mediators of the inflammatory processes in the vascular wall (52-56). IL-6 exerts pleiotropic effects on the body and it is responsible for the synthesis of C-reactive protein (CRP) in the liver and also activates B cells, increasing antibody production and stimulating angiogenesis. Moreover, IL-6 may induce vascular endothelial growth factor (VEGF), a potent angiogenic factor that promotes the migration and proliferation of endothelial cell, inducing vascular permeability and mediating inflammation (2, 57-60). IL-6 has a close implication in large-vessel vasculitis, given that it is overexpressed in the vessel walls of patients with active disease, and IL-6 serum levels correlate with disease activity (2, 57-59).

Taking this into account, we aimed to assess the efficacy and side-effect profile of tocilizumab (TCZ) in patients with TA, in most cases refractory to other therapies, in a preliminary multicentre study. Moreover, a literature review of the published reports of TA treated with TCZ was performed.

Patients and methods

Patients and study protocol

We conducted a retrospective, open-label, multicentre study on 8 patients diagnosed with TA who were treated with TCZ. Before the onset of this biologic therapy all the patients had received high dose corticosteroids, and 7 of them traditional synthetic and/or biologic immunosuppressive drugs. In 7 of the 8 cases TCZ was given because of lack of efficacy to other therapies. Patients were diagnosed with TA between January 1999 and December 2014 at the Rheumatology or Autoimmune Units of 7 referrals centres. TA diagnosis was based on the American College of Rheumatology (ACR) criteria in all the cases (61). The involvement of the aorta and/or its major branches was confirmed by imaging techniques [computed tomography-angiography (CT-A), magnetic resonance imaging-angiography (MRI-A), helical CT-scan or ^{18}F-flourodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) scan]. In all patients an imaging procedure was performed before starting TCZ therapy, and then during the follow-up. In all cases, typical clinical and/or laboratory features were also present.

Treatment was generally in accordance with the usual pharmacological escalation, starting on corticosteroids, later synthetic classical immunosuppressive drugs and finally, biologic therapy. Before the onset of TCZ, malignancy or systemic infections, including hepatitis B or hepatitis C virus infection, were ruled out. According to the national guidelines, latent tuberculosis was excluded by tuberculin skin testing, and/or serum quantiferon test and chest radiographs. In patients with latent tuberculosis, prophylaxis with isoniazid was initiated at least 4 weeks before the onset of the biologic agent and it was maintained at least 9 months. Written informed consent was requested and obtained from all the patients before the use of TCZ.

Clinical definitions and laboratory data

Fever was defined as a temperature ≥38ºC, and *constitutional symptoms* as asthenia and/or anorexia or weight loss greater than 5% of the normal body weight during the last 6 months.

Data on routine laboratory markers of disease activity, including full blood cell count, erythrocyte sedimentation rate (ESR), serum CRP, as well as liver and renal function tests were collected. Anaemia was defined as a haemoglobin level ≤11 g/dL. The ESR was considered to be increased when it was higher than 20 or 25 mm/1st hour for men or women, respectively. Serum CRP was considered elevated when it was higher than 0.5 mg/dL.

Clinical improvement was established by the assessment of signs and symptoms of disease activity, ability to taper corticosteroids, and serial imaging before and during TCZ therapy. Remission was defined as the absence of any clinical signs or symptoms of active disease. For each patient we assessed the vascular lesions by serial imaging studies performed over the extended follow-up. Vascular improvement during the follow-up was defined to be present if imaging techniques disclosed a decrease of wall thickness, an improvement of the stenotic lesions or a decreased FDG-uptake.

Data collection

Data were first reviewed and then analysed in an attempt to assess the following information: clinical and laboratory data at the time of the onset of TCZ therapy, diagnostic procedure, therapies used in the management of TA, including those given to the patients before the onset of the biologic drug, response to TCZ, and adverse events during the treatment with this agent. This information was extracted from the clinical records by each investigator, reviewed for confirmation of the diagnosis, and stored in a computerised file according to a protocol established beforehand and agreed by the researchers. To minimise entry error all the data were double-checked.

Statistical analysis

Statistical analysis was conducted using STATISTICA software (StatSoft Inc. Tulsa, Oklahoma, USA). Results were expressed as mean ± standard deviation (SD) or as median and interquartile range [IQR] and range as appropriate. Besides clinical features, the effect of the biologic therapy on ESR and CRP and daily prednisone dose was assessed. Comparisons were performed between baseline and 1st, 3rd, 6th and 12th months, using the Wilcoxon´s signed rank test. Furthermore, clinical and laboratory data obtained at last visit were also analysed.

Results

Eight patients (all women) with TA who received treatment with TCZ were assessed. The mean±SD age at the onset of this biologic therapy was 34±16 years; median: 36 [IQR;16–46] (range: 7–57) years. The median [IQR] time from TA diagnosis to TCZ onset was 11 [IQR: 6–50] months, (range: 1–168 months).

Table I summarises the main features of the patients included in this series at the time of TCZ onset. When biologic

Table I. Main features before and after the onset of Tocilizumab therapy in patients with refractory Takayasu arteritis.

Case	Age/Sex	Previous traditional or biologic immunosup-pressive drugs	Clinical features at TCZ onset	CRP/ESR (at TCZ onset)	CRP/ESR (at last visit)	Haemoglobin value (at TCZ onset) g/dL	Haemoglobin value (at last visit) g/dL	Pred. dose (at TCZ onset) mg/d	Pred. dose (at last visit) mg/d	Imaging technique before TCZ therapy	Imaging technique after TCZ therapy	Follow-up with TCZ months	Outcome at the last visit	Adverse events during TCZ therapy
1	7/F	MTX*, CYP*, MM, ETN*, IFX*	Cerebrovascular insufficiency, chest pain	12/72	<0.1/5	10.4	12.4	30	0	MRI-A, echocardiogram: affection of aortic root, aortic arch, brachiocephalic trunk, carotid and subclavian arteries.	PET/CT, TC-A: improvement, although there are affection of aortic root and pulmonary artery	24	Clinical	None remission
2	57/F	CYP*	Fever, abdominal pain, constitutional symptoms	3.3/99	0.2/2	9.6	12.5	45	5	MRI-A : affection of abdominal aorta, iliac arteries, superior mesenteric artery, splenic artery and renal arteries	MRI-A: important improvement	18	Clinical remission	None
3	26/F	MTX*, AZA, IFX*	Constitutional symptoms	2.8/33	<0.1/2	11.5	11.6	50	7.5	MRI-A, PET/CT: afection of aortic arch, carotid arteries, innominate trunk and subclavian arteries	MRI-A: slight improvement	12	Clinical improvement	None
4	16/F	MTX*, ADA*	Mesenteric angina	0.5/14	0.1/7	10.8	10.7	50	7.5	MRI-A, PET/CT: thoracic and abdominal aorta, supraortic vessels, carotid arteries and coeliac trunk	MRI-A: important improvement	12	Clinical remission	None
5	45/F	MTX*, AZA*, MM, IFX*	Fever, myalgia in the lower limbs, headache	<0.1/28	<0.1/3	13.1	12.4	25	0	PET/CT: FDG uptake in abdominal aorta and pulmonary bifurcation	PET/CT: without FDG uptake	13	Clinical remission	None
6	41/F	MTX†, ADA*, IFX*	Constitutional symptoms, fever	3.7/29	0.5/NR	11.8	11.5	40	0	MRI-A, PET/CT: involvement of aortic arch, ascending and descending aorta, carotid arteries, left subclavian artery	PET/CT: important reduction of FDG uptake	24	Clinical remission	SLE
7	31/F	None	Constitutional symptoms, headache, claudication of upper limbs	2.9/50	1.4/7	10.7	13.1	60	15	CT-A , US: involvement of axillary and subclavian arteries	US, PET/CT: involvement of axillary arteries and right subclavian artery and FDG uptake in aortic arch	6	No improvement	None
8	46/F	CyA*	Malaise, nodular scleritis	14.9/47	0.2/NR	12.5	14.6	25	0	CT, PET/CT: aneurysm in aortic arch and ascending aorta with FDG uptake in aortic arch	PET/CT: without FDG uptake	21	Clinical remission	Thrombo. cytopenia

ADA: adalimumab; AZA: azathioprine; CRP: C-reactive protein (mg/dL); CT: computed tomography; CT-A: computed tomography angiography; CyA: cyclosporine A; CYP: cyclophosphamide; ESR: erythrocyte sedimentation rate in 1st hour; Pred.: prednisone; ETN: etanercept; FDG: fluorodeoxiglucose; IFX: infliximab; MM: Mycophenolate mofetil; MRI-A: magnetic resonance angiography; MTX: methotrexate; NR: Not reported; PET: positron emission tomography; SLE: systemic lupus erythematosus; US: ultrasonography. *Withdrawn due to lack of efficacy. †Discontinued because of improvement.

therapy was started the most common clinical manifestations were constitutional symptoms (n=4) and fever (n=3). Most patients had elevation of CRP (n=6) and/or ESR (n=6). Besides corticosteroids and before TCZ onset, 7 patients had received several conventional immunosuppressive agents, and 5 had also been treated with anti-TNF-α drugs (see Table I).

Since TCZ was prescribed in most cases due to failure to achieve remission with other therapies, at the onset of TCZ therapy most patients were receiving a dose of prednisone less than 1 mg/kg/day. Nevertheless, in these cases prednisone dose was initially higher. In this regard, it is important to keep in mind that 7 of the 8 patients had been in treatment with immunosuppressive drugs as corticosteroid-sparing agents.

Patient number 8 had been diagnosed with polychondritis and MAGIC syndrome (mouth and genital ulcers with inflamed cartilage) 18 years before the diagnosis of TA. At that time she started treatment with cyclosporine. She developed malaise and persistent elevation of CRP and ESR several years later. A CT-scan disclosed aortic aneurysms with severe dilatation of aortic arch, and she was finally diagnosed with TA. Patient number 7 was a 31-year-old woman diagnosed with TA and pulmonary hypertension. Considering the possible rapid effect of TCZ and the fewer side effects, this biologic agent was started along with high-dose prednisone (initial prednisone dose: 60 mg/day).

Patient number 4 had normal inflammatory markers at the onset of TCZ therapy but presented with mesenteric angina. Imaging techniques (MRI-A and PET/CT scan) disclosed involvement of the thoracic and abdominal aorta, as well as supraortic vessels, carotid arteries and celiac trunk despite the fact that she had received treatment with corticosteroids, MTX and ADA. For this reason TCZ therapy was started.

A patient who underwent treatment with adalimumab (ADA) and another who was treated with etanercept were switched to infliximab (IFX) before TCZ onset. All the patients on anti-TNF-α agents or using conventional immunosuppressive agents had to be changed to TCZ because of lack of response. Regardless of corticosteroid use, TCZ was prescribed as monotherapy (n=4) or combined with MM (n=2), AZA (n=1) and MTX (n=1). The initial intravenous TCZ dose was 8 mg/kg every 4 weeks in 7 cases and every 2 weeks in 1 case. The maintenance dose ranged from 4–8 mg/kg/4 weeks.

Seven patients achieved rapid and maintained clinical improvement. TCZ also yielded a significant improvement of laboratory parameters (Table I). This effect was already observed at month 1 (Fig. 1A-B). Three months after TCZ onset, 3 patients were asymptomatic, 4 patients had substantial clinical improvement and only 1 remained symptomatic. In this regard, at last visit, after a median follow-up of 15.5 [IQR: 12–24] months (range: 6–24 months), 7 patients (87.5%) were asymptomatic and 1 had mild asthenia and upper limb claudication. Moreover, serum CRP levels decreased from 3.09 [IQR: 0.5–12] (range: 0.1–14.9) to 0.15 [IQR: 0.1–0.5] (range: 0.1–1.4) mg/dL (p=0.018) and ESR values from 40 [IQR: 28–72] (range: 14–99) to 3 [IQR: 2–5] (range: 2–7) mm/1st hour (p=0.012). The value of haemoglobin showed a trend to improve over time [from 11.15 [IQR: 10.4–12.5] (range: 9.6–13.1) to 12.4 [IQR: 11.5–13.1] (range: 10.7–14.6) g/dL (p=0.18)] (Fig. 1C). Noteworthy, at last visit, the median dose of prednisone had also been reduced from 42.5 [IQR: 25–50] (range: 25–60) to 2.5 [IQR: 0–7.5] (range: 0–15) mg/day (p=0.011). Corticosteroids were successfully tapered in all patients (Fig. 1D) and discontinued in 4 of them. During the follow-up, imaging procedures showed an important clinical improvement in 5 patients (Table I). One of our patients had to withdraw TCZ because she developed a photosensitive rash on her face, back and arms. At that time the blood cell count showed 2380 leukocytes/mL and 560 lymphocytes/mm^3. Also, C3 complement fraction dropped to values below the normal limit (73 mg/dL) and the antinuclear antibodies turned out to be positive (1/80 by indirect immunofluorescence) with negative anti-dsDNA. In addition, a skin biopsy unveiled pathological features compatible with systemic lupus erythematosus. However, a PET/CT scan performed before the withdrawal of TCZ disclosed an important reduction of FDG uptake. In another patient, the dose had to be reduced due to a mild thrombocytopenia. On the other hand, regarding patient 7 of Table I, although this patient experienced a marked reduction in CRP and ESR as well as an increase of haemoglobin levels, the patient continued with persistent asthenia and upper limb claudication. A PET/CT scan performed after 6 months of TCZ therapy still showed increased FDG uptake in the aortic arch, right subclavian and axillary arteries. Because of that TCZ therapy was discontinued and CYP was started.

Discussion

The results from this retrospective observational study indicate that TCZ leads to a rapid and maintained clinical and laboratory parameter improvement in patients with TA that in most cases have been refractory to corticosteroids and/or other immunosuppressive agents.

Corticosteroids are widely used as first-line drugs in TA but relapses are common when they are tapered. For this reason and to prevent their side effects, MTX, AZA, CYP and MM have been used in these patients (21-26). On the other hand, TNF-α and IL-6 are very important mediators of the inflammatory processes in the vascular wall and at a systemic level. Several investigators have reported the use of anti-TNF-α agents in patients with refractory TA with different results (27, 30, 32, 43-45). The presence of non-specific polyclonal hypergammaglobulinemia, circulating antiendothelial antibodies and an increased levels of plasmablasts in the peripheral blood suggests a potential implication of B cells in TA (62, 63). Following this finding, several investigators have reported an improvement of clinical signs and symptoms in some patients with refractory TA treated with rituximab (62, 64, 65).

IL-6 is a cytokine involved in the pathogenesis of TA. It is expressed in TA tissue and its serum levels are raised in patients with this vasculitis correlating with the activity of the disease. Seko

Table II. Main reported series and case reports on the use of tocilizumab in patients with Takayasu arteritis.

Age/Sex	Biologic therapy, initial dose	Clinical features	Previous therapy	Imaging technique before biologic therapy	Imaging technique after biologic therapy	ESR before / after biologic therapy	CRP before/ after biologic therapy	Outcome	Author (Ref.)
40/M	TCZ, 8 mg/kg/month	Leakage of a graft of the thoracic aorta and ischaemic pain	GCs	MRI-A: aortitis	MRI-A: aortitis improvement	80/ 5	4.1/ <0.3	Clinical remission	Seitz (41)
27/ F	TCZ, 8 mg/kg/month	Malaise, claudication of lower and upper limbs	GCs, MTX, AZA, IFX	MRI-A: aortitis	MRI-A: aortitis improvement	40/ <3	5/ <0.3	Clinical remission	Seitz (41)
21/F	TCZ, 8 mg/kg/month	Myalgia, fever, headache, bilateral carotid bruits	GCs, MTX	PET/CT (FDG uptake): multiple arteries	PET/CT: decrease FDG uptake	45/3	4.02/ 0.06	Clinical remission	Salvarani (40)
40/F	TCZ, 8 mg/kg/month	Arthromyalgia, fever, weight loss, carotidynia, subclavian bruit	None	PET/CT (FDG uptake): multiple arteries	PET/CT: decrease FDG uptake	67/2	0.99/0.05	Clinical improvement	Salvarani (40)
54/M	TCZ, 8 mg/kg/month	Malaise, myalgia, weight loss	None	PET/CT (FDG uptake): numerous vessels	PET/CT: decrease aortic FDG uptake	84/2	4.8/0.01	Clinical remission	Salvarani (40)
25/F	TCZ, 8 mg/kg/month	Myalgia, arthralgia, headache, fever, claudication of upper limbs, abdominal bruit, fatigue, carotidynia	GCs, MTX, MM, IFX, ADA	PET/CT (FDG uptake): brachiocephalic, carotid arteries. Abdominal angiography: stenosis of celiac artery. US: carotid and subclavian involvement.	PET/CT: decrease FDG uptake	69/Normal (NV)	7.2/Normal (NV)	Clinical remission	Salvarani (51)
NR/NR	TCZ, 8 mg/kg/month	Claudication of upper limb, pulse deficit, pulmonary hypertension	GCs	Cross-sectional imaging (CT-A, MRI-A): pulmonary, carotid and subclavian artery stenosis	NR	15/3.6	0.8/0.03	Clinical remission	Unizony (42)
NR/NR	TCZ, 8 mg/kg/month	Claudication of lower limbs, pulselessness, hypertension	GCs	CT-A, MRI-A: aortic arch aneurysm and external iliac artery stenosis	NR	34/8.7	1.7/0.56	Clinical remission	Unizony (42)
20/F	TCZ, 4 mg/kg/week	Left cervical pain, left chest pain, syncope, weight loss	GCs, CyA, CYP, AZA, MM, MTX	Chest CT: aortitis, and stenosis of the left subclavian artery.	CT: reduction of aortitis stenosis	NR/NR	12.6/Normal (NV)	Clinical improvement	Nishimoto (39)
28/F	TCZ, 8 mg/kg/month	Arthralgia, cervicalgia, fever, weakness, sweats, weight loss, hypertension, radial pulselessness	GCs, MTX, CYP, MM, AZA, IFX, ADA	MRI-A: subclavian and axillary arteries involvement	CT-A: reduction of aortitis; stenosis progression in renal, subclavian and vertebral arteries	70/2	6.6/ <0.3	Clinical improvement	Bredemeier (47)
24/F	TCZ, 8 mg/kg/month	NR	GCs, MTX, MM, AZA, IFX	MRI-A and US: NR	MRI-A and US: NR	76/15	1/<0.1	Persistence of activity, vascular progression	Tombetti (49)

23/F	TCZ, 8 mg/kg/month	NR	GCs, MTX, ADA, IFX, CyA, sirolimus	MRI-A and US: NR	MRI-A and US: NR	34/14	1.3/<0.1	Clinical improvement	Tombetti (49)
30/F	TCZ, 8 mg/kg/month	NR	AZA, MTX	MRI-A and US: NR	MRI-A and US: NR	31/4	1.3/0.1	Relapse and vascular progression	Tombetti (49)
27/F	TCZ, 8 mg/kg/month	NR	GCs, AZA, IFX, CYP, MTX, ADA, anakinra, RTX, CyA	MRI-A and US: NR	MRI-A and US: NR	32/2	1.2/0.6	Relapse	Tombetti (49)
39/F	TCZ, 8 mg/kg/month	NR	GCs, MTX	MRI-A and US: NR	MRI-A and US: NR	8/2	3.5/0.4	Clinical remission	Tombetti (49)
19/F	TCZ, 8 mg/kg/month	NR	GCs, MM, CYP, minocycle, MTX	MRI-A and US: NR	MRI-A and US: NR	38/2	1.4/<0.4	Clinical remission	Tombetti (49)
24/F	TCZ, 8 mg/kg/month	NR	GCs, AZA, CyA, MTX, sirolimus, IFX, ADA	MRI-A and US: NR	MRI-A and US: NR	40/2	3.5/0.4	Clinical remission	Tombetti (49)
46/F	TCZ, 8 mg/kg/month	Axillary pain, dyspnea, weight loss	GCs, MTX	US: stenosis of right subclavian and left carotid arteries. MRI-A: aortitis. PET/CT: high diffuse vascular uptake	PET/CT: decrease vascular uptake	NR/NR	1.5/NR	Relapse	Abisror (46)
52/F	TCZ, 8 mg/kg/month	Asthenia, arthralgia	GCs, AZA	MRI-A: aortitis	PET/CT: decrease vascular uptake	NR/NR	NR/NR	Clinical improvement	Abisror (46)
65/F	TCZ, 8 mg/kg/month	NR	GCs, MTX, AZA, IFX	NR	PET/CT and MRI-A: decrease vascular uptake and decrease of aorta wall thickening	NR/NR	NR/NR	Clinical remission	Abisror (46)
46/M	TCZ, 8 mg/kg/month	Fever, headache, weight loss	GC, CYP	CT: abdominal aorta aneurysm	PET/CT: no improvement	NR/NR	NR/NR	Relapse	Abisror (46)
61/F	TCZ, 8 mg/kg/month	Fever, weight loss	GC, MTX	MRI-A: aortitis	NR	NR/NR	9.9/NR	Clinical remission	Abisror (46)
45/F	TCZ, 8 mg/kg/month	Headache, limb claudication	GCs, MTX, AZA, CYP, IFX, ADA	MRI: thoracic and abdominal aortitis	MRI: without any improvement	88/NR	3.6/NR	No improvement	Xenitidis (48)
21/F	TCZ, 8 mg/kg/month	Abdominal pain, diarrhoea	CYP, MTX, IFX	MRI: stenosis in the abdominal aorta, left renal artery, coeliac trunk and superior mesenteric artery	MRI: without any improvement	NR/NR	NR/NR	No improvement	Xenitidis (48)

ADA: adalimumab; AZA: azathioprine; CRP: C-reactive protein (mg/dL); CT: computed tomography; CT-A: computed tomography angiography; GCs: glucocorticosteroids; CyA: cyclosporine A; CYP: cyclophosphamide; ESR: erythrocyte sedimentation rate in 1st hour; FDG: fluorodeoxyglucose; IFX: infliximab; MM: mycophenolate mofetil; MRI: magnetic resonance imaging; MRI-A: magnetic resonance angiography; MTX: methotrexate; NV: no numerical value; NR: not reported; PET: positron emission tomography; RTX: rituximab; US: ultrasonography.-

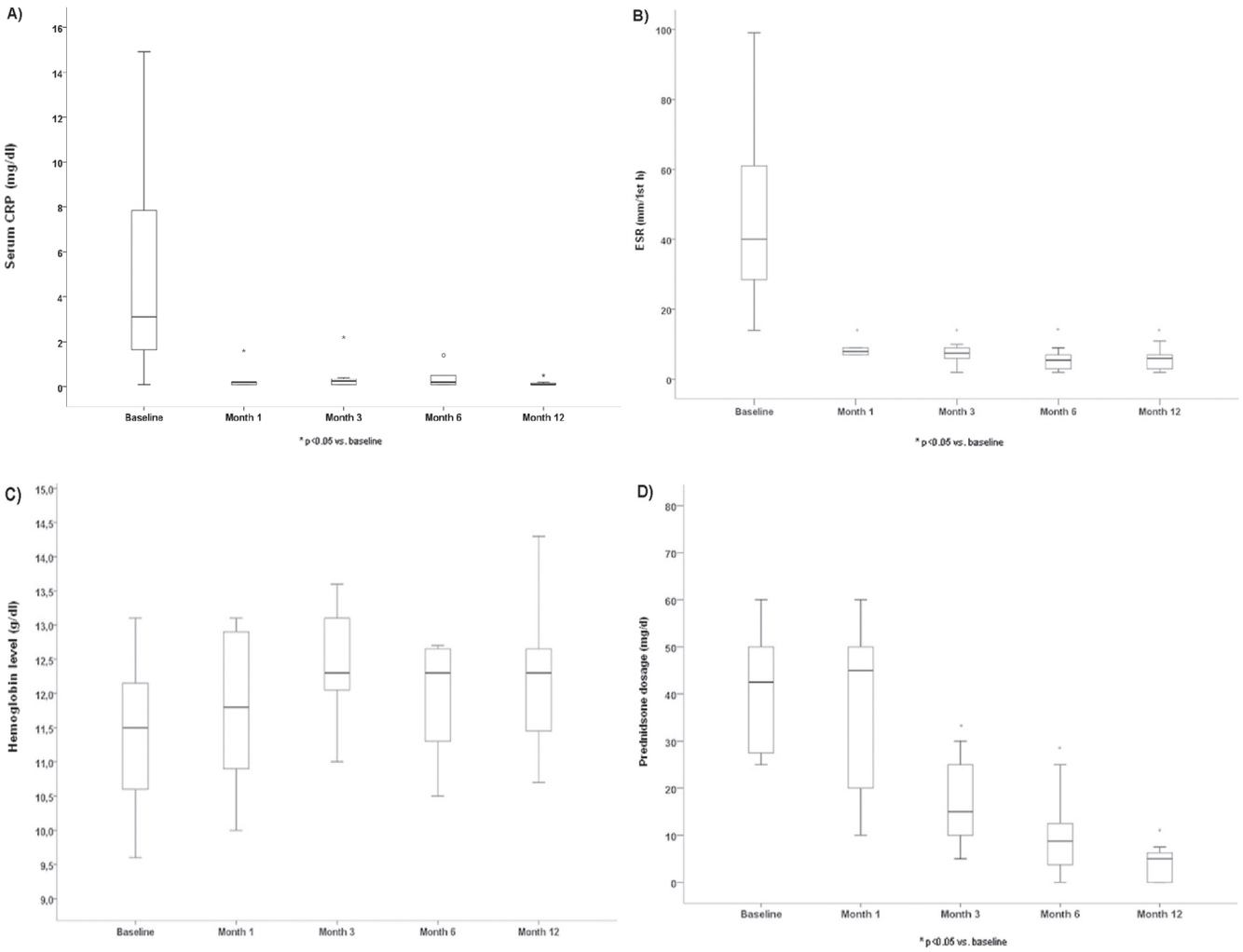

Fig. 1. Rapid improvement of laboratory abnormalities and reduction of corticosteroid dose following tocilizumab therapy in 8 patients with Takayasu arteritis (data expressed as median values; *p*-compared with baseline): **A**) serum C-reactive protein (CRP); **B**) erythrocyte sedimentation rate (ESR); **C**) haemoglobin; and **D**) corticosteroid dose. Bars represent 95% confidence intervals.

et al. (66), in samples of patients with aortic aneurysm and TA, performed a genetic amplification of cDNAs from the aortic tissue for cytokine transcripts obtaining strong bands for IL-6. Therefore, IL-6 receptor blockade may be an attractive therapeutic option in TA patients. In this regard, Alibaz-Oner *et al*. (67) have recently reported that IL-6 level is higher in active than in inactive TA patients, although differences did not reach statistical significance. TA is still an orphan disease with broad areas of pathogenesis that are poorly understood and it is possible that other local inflammatory pathways may cooperate in its pathogenic process (68). In this regard, locally-produced inflammatory molecules whose production is independent of IL-6, such as pentraxin-3, have been found to be useful to detect TA activity (69). Osman *et al*. (70) reported a systematically review and meta-analysis about the effectiveness and safety of biological drugs in patients with large-vessel vasculitis observing a potential benefit for TCZ in TA as well as in GCA.

Table II (39-42, 46-49, 51) shows the main series and case reports published in the literature on the use of TCZ in patients with TA. As occurred in our series, most patients achieved clinical and laboratory improvement and a reduction of vessel wall inflammation that was confirmed by imaging techniques, although relapses were also reported. With respect to this, some authors, such as Bredemeier *et al*. (47) and Xenitidis *et al*. (48), observed progression of vascular lesions in TA patients undergoing treatment with TCZ.

To the best of our knowledge, our series along with the recently published by Cañas *et al*. (71) constitutes the largest series of patients with refractory TA treated with TCZ. Noteworthy, we observed an improvement of clinical manifestations and laboratory parameters in most cases, which was already observed 4 weeks after the onset of this biologic agent. This improvement was maintained at 3, 6 and 12 months, leading to a normalisation of acute phase reactants in most patients. Regarding this issue, it is worth mentioning that Tombetti *et al*. (49) have suggested that inflammatory markers might be not completely valid to assess TA activity during TCZ treatment. They found that despite normalisation of laboratory parameters of inflammation after the onset of the biologic agent, some patients showed

vascular progression, similar findings we observed in the patient 7 of our series shown in Table I. In our series 6 patients did not show vascular progression. At this point, it is important to note that it is recommended using the same imaging technique both at baseline and during the follow-up, in order to compare the findings. Nonetheless, this is not always possible and often depends on the availability of the technique and on the delay estimated for the accomplishment of it. Imaging techniques allow studying the distribution of aortic involvement. They are also useful to disclose the activity of the disease (72-75). Angiography was the gold standard technique to evaluate the lumen of the vessels and to diagnose TA. However, since it is an invasive procedure, it has being replaced by angio-CT scan and MRI (72, 74, 75). In fact, angiography is now performed almost exclusively in cases of interventional therapeutic procedures. The contrast-enhanced multidetector-CT-angiography allows the exclusion of other aortic disorders that mimic acute aortitis, and it is used to assess the presence of stenosis, wall thickening, aneurysms and thrombosis. It is very helpful to detect wall calcifications, a well-known complication of long-standing aortitis (76). Nevertheless, it has the disadvantage of ionising radiation and the iodinated contrast, and it is possible that milder degrees of inflammation might not be apparent using this imaging technique (10, 77). MRI-angiography is recommended in patients who will need a follow-up. This imaging technique is very useful to assess the wall thickening, the presence of aneurysms or thrombus, and wall oedema (10, 72, 74, 78). Ultrasonography (US) is a non-invasive toll that can study the initial portions of the aorta, proximal carotid and subclavian arteries (2). FDG-PET/CT scan plays a major role as non-invasive tool for the diagnosis and management of patients with large vessel vasculitis by providing a metabolic functional image of the vessel wall inflammation before structural changes are seen (79-85). Previous studies have shown good results by the use of this tool in the evaluation of the aortic involvement in patients with large-vessel vasculitis (83-85). However, it is important emphasise that an increase in FDG uptake may be a feature of tissue vessel wall hypertrophy, repair and regeneration. Therefore, the validity of an increased FDG uptake equating to active disease is unproven.

It is also important to note that TCZ yielded a significant corticosteroid sparing effect in our patients. Thus, prednisone dosage was reduced significantly following TCZ therapy (Fig. 1D). This is especially true in the first 3 months after the onset of this biologic agent. This fact is of main importance in these patients to avoid high cumulative dose of prednisone that may lead to ominous adverse effects.

Regarding safety concerns, and although TCZ seems to be a relatively safe drug, one of our patients developed a systemic lupus erythematosus and, therefore, TCZ therapy was discontinued. On the other hand, another patient had to reduce the dose of TCZ because of mild thrombocytopenia. However, it is worth mentioning that in a former study in which we assessed the efficacy of TCZ in patients with refractory GCA we observed an increased risk of severe infections in elderly patients with GCA (59).

Although our study has potential limitations derived from its observational and retrospective nature, in view of our results and those previously reported, we feel that TCZ may be a potentially effective therapeutic option in patients with TA refractory to standard immunosuppressive drugs. However, there are many questions unanswered to date, such as the optimal duration of TCZ therapy or the long-term efficacy and side-effect profile of this biologic agent. For this reason, randomised controlled trials in patients with TA are needed to shed light on these questions.

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