Review

Tocilizumab in refractory aortitis: a study on 16 patients and literature review

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ABSTRACT

Objective. *Non-infectious aortitis is often refractory to standard immunosuppressive therapy. Since IL-6 has been implicated in the pathogenesis of aortitis, we assessed the efficacy of the anti-IL6 receptor monoconal antibody tocilizumab (TCZ) in a series of patients with refractory non-infectious aortitis.*

Methods. *Review of 16 patients (14 women/2 men) with refractory aortitis diagnosed by imaging (CT angiography, MR angiography, and/or PET) that were treated with TCZ.*

Results. *The mean age±SD was 51.4±20.1 years. The underlying conditions were: Takayasu arteritis (TakA) (n=7 cases), giant cell arteritis (GCA) (n=7), relapsing polychondritis (RP) (n=1), and aortitis associated with retroperitoneal fibrosis (n=1). TCZ was the first biologic drug used in all patients with GCA and in the patient with aortitis associated with retroperitoneal fibrosis but in only 2 of 7 TakA patients. In the remaining cases anti-TNF inhibitors were prescribed before TCZ (standard dose was 8 mg/kg/iv/4 weeks). After a mean±SD follow-up of 11.8±6.6 months most patients experienced clinical improvement, showing reduction of erythrocyte sedimentation rate from 43±36 mm/1st h to 5±4 mm/1st h at last visit. At TCZ onset, 25% of patients had fever and 19% polymyalgia rheumatica. These manifestations disappeared after 3 months of TCZ therapy. A corticosteroid sparing effect was also achieved (from 27.3±17.6 mg/day of prednisone at TCZ onset to 4.2±3.8 mg/day at last visit). TCZ had to be discontinued in a patient because of severe neutropenia.*

Conclusion. *TCZ appears to be effective and relatively safe in patients with inflammatory aortitis refractory to corticosteroids or to other biologic immunosuppressive drugs.*

Introduction

Aortitis encompasses a wide spectrum of infectious and non-infectious pathologic conditions characterised by inflammation of the aortic wall. In some cases it may be associated with severe complications such as aneurysms, dissection and rupture of the aorta (1-4). Giant cell arteritis (GCA) and Takayasu arteritis (TakA) including in the category of large-vessel vasculitides are probably the most frequent causes of non-infectious aortitis. Nevertheless, non-infectious aortitis may present as an isolated entity or be associated with other well defined conditions (2, 5- 8). First-line treatment in non-infectious aortitis includes the use of corticosteroids, usually at high doses (9-12). Other therapies are often required to achieve control of the disease or as corticosteroid sparing agents. Different synthetic traditional immunosuppressive drugs such as methotrexate (MTX), azathioprine or cyclophosphamide have been used for this purpose (13-18). However, the efficacy of these drugs to control the activity of the disease is often insufficient and they are frequently associated with potential severe side effects.

In patients with large-vessel vasculitis, especially in GCA, a number of studies have shown the presence of abnormal production of pro-inflammatory cytokines, such as interleukin-1 (IL-1),

IL-6, IL-18, tumour necrosis factor-α (TNF-α) or interferon-γ, by T lymphocytes and macrophages (19-35). Due to this, several studies were performed to determine the efficacy of anti-TNF drugs on large-vessel vasculitides. Regrettably, in most cases, evidence supporting the use of anti-TNF-α inhibitors in aortitis refractory to corticosteroids is weak (36-40).

IL-6 is another pro-inflammatory pivotal cytokine that has been implicated in the pathogenesis of aortitis (26, 35, 41-43). Since tocilizumab (TCZ) is a humanised monoclonal anti-IL6 receptor (IL-6R) antibody, the use of this monoclonal antibody was described in some case reports and small series. The analysis of these reports suggests a potential efficacy of TCZ therapy in the treatment of aortitis, mainly in the setting of GCA and TakA (40, 43, 44-49). To further investigate into the potential efficacy of anti-IL6-R blockade in patients with large-vessel vasculitis, we assessed a series of patients with non-infectious aortitis refractory to corticosteroids and in some cases to anti-TNF-α inhibitors.

Patients and methods

Patient population

We conducted an interventional case series, open-label, multicentre study on 16 patients diagnosed as having non-infectious aortitis, either idiopathic or in the setting of well-defined autoimmune or inflammatory conditions. In all of them, TCZ therapy was given because patients were refractory to corticosteroids and standard synthetic immunosuppressive drugs and in some cases to other biologic agents.

Patients were diagnosed as having aortitis between January 1999 and December 2012 at the Rheumatology or Autoimmune units of 11 centres from Spain. The diagnosis of aortitis was based on imaging techniques (computed tomography-CT angiography, magnetic resonance-MR angiography, helical CT or 18F-fluorodeoxyglucose positron emission CT (FDG PET/CT) scan.

Six of the 7 patients that fulfilled the ACR classification criteria for GCA (50) also had a positive temporal artery biopsy. All 7 patients diagnosed with TakA fulfilled the 1990 ACR criteria for the classification for this vasculitis (51). A patient with aortitis was diagnosed as having relapsing polychondritis according to the criteria proposed by Michet *et al*. (52). Another patient with aortitis also fulfilled definitions for retroperitoneal fibrosis (53). Polymyalgia rheumatica (PMR) in the setting of GCA was diagnosed according to the criteria proposed by Chuang *et al*. (54). In most cases management started with corticosteroids. In a second phase, synthetic traditional immunosuppressive drugs and in some cases biologic therapy was given.

Before biologic treatment, evidence of malignancy or systemic infection was excluded including hepatitis B or hepatitis C. According to national guidelines in all patients receiving biologic drugs latent tuberculosis was excluded by a tuberculin skin testing (PPD) and/or quantiferon and chest radiograph. In patients with latent tuberculosis prophylaxis with isoniazid was initiated at least 4 weeks before the onset of the biologic therapy. Overall, prophylaxis with isoniazid was maintained for 9 months. Since TCZ is an off-label indication in non infectious aortitis, written informed consent was requested and obtained from all patients.

Data collection and clinical definitions

Clinical and laboratory data were extracted from the clinical records according to a specifically designed protocol that was designed beforehand. They were stored in a computerised file. To minimise entry error, all the data were double-checked. The following data were assessed: clinical, laboratory, diagnosis, treatment, prognosis and adverse events. Fever was defined as a temperature >38ºC, and constitutional syndrome as asthenia and/or anorexia and weight loss of at least 4 kg.

Data on routine laboratory markers of disease activity, including full blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, liver enzymes levels, creatinine serum level, proteinuria and hematuria were collected. The ESR was considered to be increased when it was higher than 20 or 25 mm/1st hour for men or women, respectively. We defined high CRP value when it was higher than 0.5 mg/dL.

Statistical analysis

Statistical analysis was performed using the software STATISTICA (StatSoft Inc. Tulsa, Oklahoma, USA). Results were expressed as mean±SD for variables with normal distribution, or as median, range or [25th-75th interquartile range (IQR)] when they were not normally distributed.

All of the following variables were compared: clinical manifestations, ESR, CRP, and daily prednisone dose. Comparisons of these variables were made between baseline and 3, 6 and 12 months after initiation of treatment. Comparison of continuous variables was performed using the Wilcoxon test.

Results

We studied 16 patients (14 women and 2 men) with non-infectious aortitis. The mean-age ± SD was 51.4±20.1 years (range: 7–77 years). Table I summarises the main features of the patients included in this series. Aortitis was associated to the following underlying conditions: TakA (n=7 patients), GCA (n=7), relapsing polychondritis (n=1), and aortitis with retroperitoneal fibrosis (n=1).

As discussed *Methods*, the diagnosis of aortitis was made by imaging techniques such as FDG PET/CT scan, MR angiography, and/or CT angiography. In the patient with aortitis and retroperitoneal fibrosis the diagnosis was performed by a retroperitoneal biopsy.

In 15 cases TCZ therapy was given due to aortitis refractory to standard synthetic immunosuppressive drugs and in some cases to other biologic agents. The patient with aortitis and retroperitoneal fibrosis started with TCZ without having previously received conventional immunosuppressive drugs because he was also diagnosed of secondary amyloidosis (Fig. 1).

The median duration of aortitis before TCZ onset was 12 months [IQR: 7-45]. TCZ was prescribed as monotherapy (6 cases) or combined with other traditional synthetic immunosuppressive drugs, usually MTX (7 cases), mycophenolate mofetil (2 cases), and aza-

Table I. Main features of 16 patients before and after tocilizumab therapy.

Case	Age/ Sex	Underlying disease	Diagnosis of aortitis	Previous traditional immunosuppressive drugs to TCZ	Prednisone dose (at TCZ onset) mg/d	Prednisone dose (at last visit) mg/d	CRP /ESR (at TCZ onset)	CRP /ESR (at last visit)	Follow-up with TCZ (months)	Serious side effects due to TCZ
1	7/F	TakA	MRI-A, echocardiogram	MTX, CYP, MM, ETN, IFX	30	0	12/72	< 0.1/5	24	None
2	57/F	TakA	MRI-A	CYP	45	5	3.3/99	0.2/2	18	None
3	26/F	TakA	CT-A, PET/CT	MTX, AZA, IFX	50	7.5	2.8/33	<0.1/2	12	None
4	16/F	TakA	MRI-A, PET/CT	MTX, ADA	50	7.5	0.5/14	0.1/7	12	None
5	45/F	TakA	PET/CT	MTX, AZA, MM, IFX	25	0	<0.1/28	< 0.1/3	13	None
6	41/F	TakA	MRI-A, PET/CT	MTX, ADA, IFX	40	10	3.7/29	<0.1/10	3	None
7	46/F	TakA	CT, PET/CT	CyA	25	5	14.9/5	0.2/5	4	Thrombocytopenia
8	77/F	GCA	PET/CT	MTX	10	2.5	3.7/120	1.7/7	5	None
9	59/F	GCA	CT	MTX	60	5	<0.1/2	<0.1/2	16	None
10	65/F	GCA	PET/CT	MTX	17.5	0	<0.1/3	<0.1/2	20	Severe neutropenia
11	67/F	GCA	PET/CT	MTX	10	0	1.9/44	<0.1/2	6	Pneumonia
12	74/F	GCA	PET/CT	MTX	0	0	0.8/46	<0.1/4	11	None
13	64/F	GCA	PET/CT	MTX	15	10	0.1/ND	<0.1/ND	3	Hypotension
14	53/M	GCA	MRI-A, PET/CT	MTX	30	10	25.6/43	5.4/17	5	None
15	50/F	RP	CT	MTX, CyA, LFN, CYP, IFX	30	5	0.9/13	<0.1/13	20	None
16	75/M	RF	CT-A	None	0	0	ND/98	ND/ND	17	None

TCZ: tocilizumab; TakA: Takayasu arteritis; GCA: giant cell arteritis; RP: relapsing polychondritis; RF: retroperitoneal fibrosis; AZA: azathioprine; CyA: cyclosporine A; CYP: cyclophosphamide; LFN: leflunomide; MM: mycophenolate mofetil; MTX: methotrexate; ADA: adalimumab; ETN: etanercept; IFX: infliximab; RTX: rituximab; CRP: C-reactive protein (mg/dL); ESR: erythrocyte sedimentation rate in 1st hour; CT: computed tomography; CT-A: computed tomography angiography; MRI-A: magnetic resonance angiography; PET: positron emission tomography; ND: Not described.

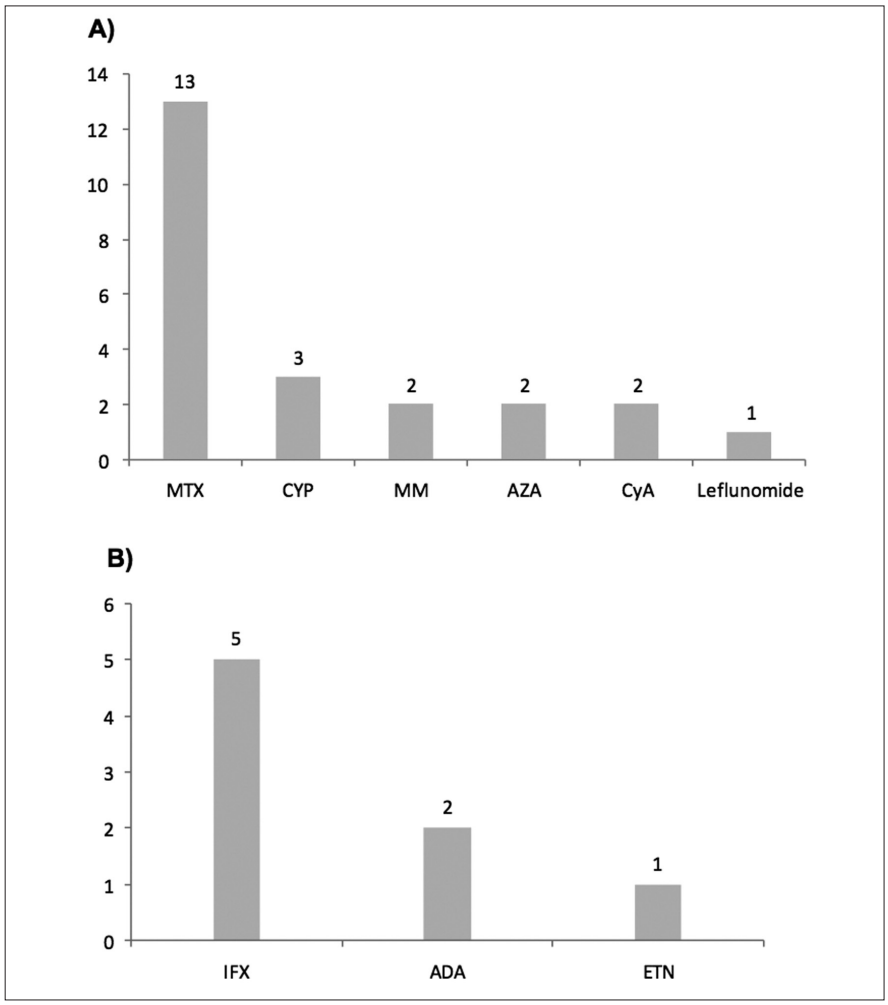

Fig. 1. Previous treatment with **A**) traditional immunosuppressive drugs and **B**) biologic drugs in 16 patients receiving tocilizumab therapy due to refractory non-infectious aortitis.

thioprine (1 case). The initial TCZ dose was 8 mg/kg every 4 weeks in 15 cases and every 2 weeks in 1 case. Maintenance TCZ dose ranged between 4-8 mg/kg every 2 or every 4 weeks.

Most patients experienced improvement of clinical manifestations and laboratory parameters following TCZ therapy. This improvement was evident at the first available measure assessed at month 3. This response to TCZ was maintained over time (Fig. 2). An imaging technique was usually performed after TCZ onset to confirm improvement of the disease (Fig. 3 corresponding to case 14 in Table I).

Specific subtypes of aortitis – Takayasu arteritis

At TCZ onset, the 7 patients with TakA (corresponding to cases 1–7 of Table I) showed the following clinical manifestations: constitutional syndrome (n=2), fever (n=3), chest pain (n=1), abdominal pain (n=1), myalgia in the lower limbs (n=1), headache (n=1), transient ischaemic attacks (n=1), malaise (n=1) and nodular scleritis (n=1). All of them had received treatment with several traditional immunosuppressive drugs such as MTX (n=5), cyclophosphamide (n=2), azathioprine (n=2), mycophenolate mofetil (n=2) and cyclosporine A (n=1). Since they were refractory to

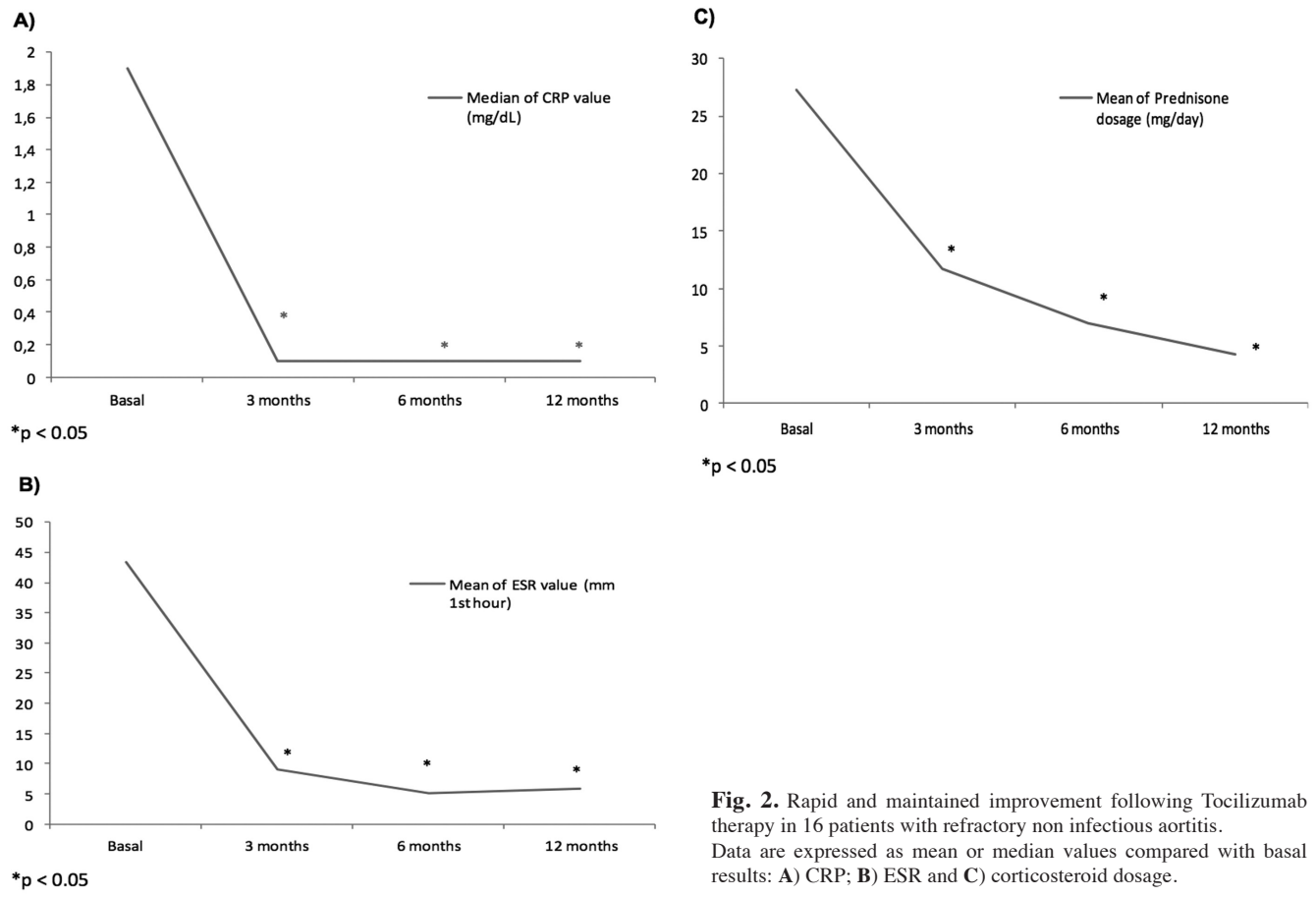

Fig. 2. Rapid and maintained improvement following Tocilizumab therapy in 16 patients with refractory non infectious aortitis.
Data are expressed as mean or median values compared with basal results: **A**) CRP; **B**) ESR and **C**) corticosteroid dosage.

these drugs, five of the seven patients were initially treated with TNF-α inhibitors. One patient undergoing treatment with adalimumab and another with etanercept were switched to infliximab. Finally, all the five patients on anti-TNF-inhibitors had to be changed to TCZ due to lack of response to anti-TNF-α inhibitors. In addition, two patients treated with non-biologic agents were also changed to TCZ. After 3 months of therapy with TCZ, 3 patients were asymptomatic, 3 patients had substantial improvement and only 1 had not experienced any improvement. Further improvement following TCZ therapy was achieved. In this regard, at last available visit, 6 patients were asymptomatic and 1 patient had mild asthenia. Moreover, in all them the dose of corticosteroids was reduced; and in 2 of them it was discontinued (cases 1 and 5). During the follow-up, imaging techniques also showed improvement in the 6 patients in whom they were performed. With respect to this, in 4 of them there was an improvement of MR angiography. In the other 2 patients there was a significant decrease in FDG PET/CT uptake following TCZ therapy.

– *Giant cell arteritis*

The main features of the 7 patients with GCA (corresponding to cases 8–14 of Table I) at TCZ onset were the following: PMR (n=3), constitutional syndrome (n=2), jaw claudication (n=1), headache (n=1), scapular pain (n=1), intermittent claudication of the lower extremities (n=1), and chest pain (n=1). Besides corticosteroids and before TCZ therapy, all the patients with GCA had received MTX. TCZ was started because of lack of efficacy of MTX. After 3 months on TCZ therapy, 5 patients were asymptomatic; 1 patient had mild asthenia and another patient persisted with intermittent claudication of the lower extremities. Laboratory parameters also improved. At last available visit, corticosteroid dose was reduced in all GCA patients. In 3 of them corticosteroids were completely discontinued.

– *Relapsing polychondritis*

A 50-year-old woman with relapsing polychondritis (case 15 of Table I) persisted with asthenia, deafness, profuse sweating, fever, abdominal pain and keratitis despite of treatment with corticosteroids, MTX, cyclosporine, leflunomide and cyclophosphamide. Because of that she was initially treated with infliximab at a dose of 5 mg/kg at 0, 2 and then every 6 weeks without improvement. Therefore, she was switched to TCZ 8 mg/kg/4 weeks showing complete clinical-laboratory improvement at month 3. Corticosteroid dose was also reduced. A CT angiography showed a significant decrease in the intimal thickness.

– *Aortitis associated with retroperitoneal fibrosis*

A 75-year-old man with retroperitoneal fibrosis and nephrotic syndrome due to AA amyloid deposition started with constitutional syndrome and musculoskeletal pain more intense in the dorsal region (case 16 of Table I). A CT angio-

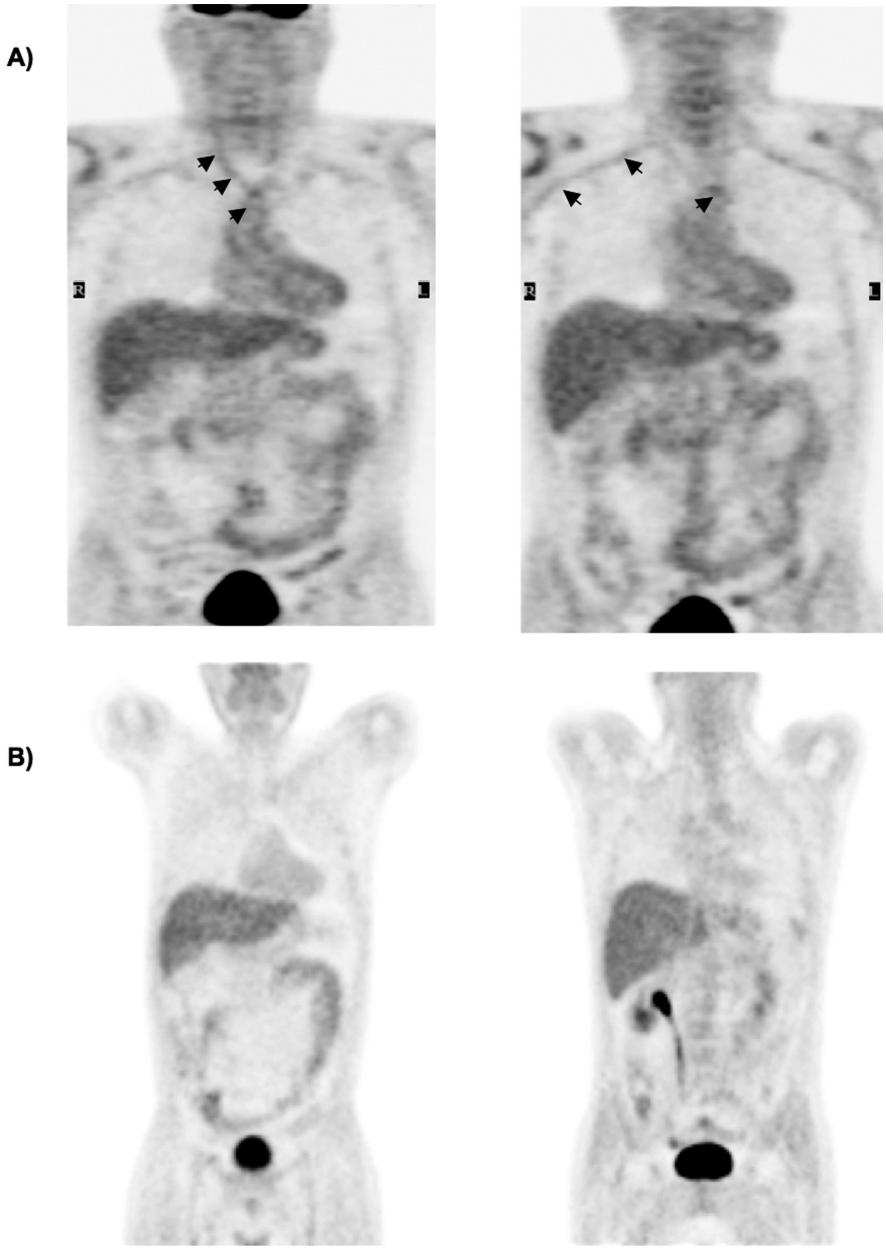

Fig. 3. A) PET scan of a patient with GCA (case 14 from Table I) showing an increased FDG uptake in the ascending aorta, aortic arch, descending aorta, carotid, subclavian, axillary and brachial arteries suggestive of active vasculitis. **B**) The same patient 4 months after the onset of treatment with tocilizumab. Marked reduction of mural diffuse uptake of large vessels and their main branches was seen (Courtesy of Dr. Narváez. Department of Radiology, Hospital Universitari de Bellvitge).

graphy showed mild aortic but intense periaortic inflammation. A retroperitoneal biopsy showed severe fibrosis and inflammatory cells that supported a diagnosis of periaortitis. Improvement following TCZ therapy was observed.

Outcome

After a mean±SD follow-up of 11.8±6.6 months, only 4 patients had experienced side effects: 1) A 46-year-old woman with TakA developed a thrombocytopenia and because of that TCZ dose had to be reduced; 2) A 64-year-old woman with GCA suffered hypotension during the second infusion of TCZ; 3) A 67-year-old woman with GCA suffered a pneumonia; 4) A 65-year-old woman diagnosed with GCA (case 10 of Table I) developed severe neutropenia (351 neutrophils) after 20 months of TCZ therapy and, because of that, the drug was discontinued.

Discussion

Non-infectious aortitis is frequently associated with GCA and TakA (35). These two entities have similar pathological findings (55) and share common pathogenic pathways that differentiate them from other vasculitides. Cellular immune responses involving T cells, antigen-presenting cells, and macrophages are relevant elements in GCA and TakA pathogenesis (35). However, they differ in the age at clinical onset and vascular involvement (12, 56).

GCA is a vasculitis quite common in European countries and North America involving vessels of medium and large caliber characterised by the granulomatous involvement of the aorta and its major branches with a predilection for the cranial arteries of people over 50 years of age (12, 57-59). The most common serious complication of GCA is irreversible visual loss due to optic nerve ischaemia (57, 60). GCA is associated with the upregulation of multiple proinflammatory cytokines, such as IL-6, secreted by several cell types, predominantly T-cells, macrophages, and endothelial cells (20, 61).

IL-6 plays a variety of pivotal biological functions depending on the target cell (61, 62). Thus, during physiological inflammatory responses, IL-6 participates in the synthesis of acute phase proteins, promotes the passage of acute to chronic inflammation, and facilitates development of adaptative immunity (61, 63). Moreover, IL-6 modulates activation, proliferation and differentiation of various T cell lines including CD8 T, Th17 and Treg cells. This proinflammatory cytokine also stimulates terminal differentiation of B cells and improves survival of plasma cells (61). Increased IL-6 serum levels have ben observed in patients with active GCA and a correlation of IL-6 with disease activity has also been observed (20). Also, temporal artery biopsies in GCA show an increase in the local expression of IL-6 (40-42).

TCZ is a humanised anti-IL6 receptor monoclonal antibody. This biologic agent has proved to be effective not only in rheumatoid arthritis, but also in patients with systemic inflammatory diseases such as Still's disease (40, 64-66).

Table II. Reported series and case reports on the use of tocilizumab in aortitis and/or its main branches associated with Giant Cell Arteritis.

Age / Sex	Clinical features	Previous therapy	Imaging technique before TCZ	Imaging technique after TCZ	ESR before / after TCZ	CRP before / after TCZ	Outcome	Ref.
64/M	Systemic manifestations	GCs, IFX, ETN	PET/CT (FDG uptake) in numerous vessels	PET/CT: decreased FDG uptake in the involved vessels	95/ 4	5.4/ 0.07	Clinical improvement	Salvarani (47)
63/M	Malaise, PMR, peripheral occlusive arterial disease	None	MRI-A: aortitis	MRI-A: resolved	91/ 2	0.6/ <0.03	Clinical remission	Seitz (48)
73/M	Malaise, PMR, jaw claudication	None	MRI-A: aortitis	MRI-A: resolved	100/ 2	0.6/ <0.03	Clinical remission	Seitz (48)
79/F	Malaise, PMR, amaurosis fugax	GCs, MTX	MRI-A: aortitis	MRI-A: resolved	44/ 8	0.1/ <0.03	Clinical remission	Seitz (48)
79/M	Fever, night sweats and weight loss	GCs, AZA	PET/CT: large-vessel vasculitis	PET/CT: no metabolic activity	ND/ND	16.8 /normal (NV)	Clinical remission	Beyer (44)
72/F	Weight loss, sweats, anorexia, uveitis, subungueal haemorrhages	GCs, AZA, MM	PET/CT (FDG uptake) in aorta, subclavian and carotid arteries	PET/CT: no metabolic activity	ND/ND	30.7/ Normal (NV)	Clinical remission	Beyer (44)
71/F	Systemic symptoms, headache, diplopia, night sweats, anorexia	GCs, MTX	MRI-A: subclavian and femoral artery involvement	ND	ND/ND	Elevated (NV)/ normal (NV)	Clinical remission	Beyer (44)
63/F	PMR, headache, fatigue, transient visual loss, anorexia, loss of weight	GCs, MTX, LFN, AZA	PET/CT (FDG uptake) in aorta, axillary, subclavian arteries	PET/CT: partial response with reduction in uptake in the abdominal aorta	ND/ND	7.8/0.1	Clinical remission	Christidis (45)
ND/ ND	PMR, headache, jaw and upper extremity claudication	GCs, CYM, IFX	CT-A, MRI-A: carotid, subclavian, aorta and iliac artery involvement	ND	64/7	5.1/0.07	Clinical remission	Unizony (49)
ND/ND	Headache, jaw claudication	GCs, MTX	CT-A, MRI-A: aortic involvement	ND	90/4.8	3.3/0.06	Clinical remission	Unizony (49)
72/F	Fever, headache, weight loss, weakness, pain of neck, shoulder and pelvic girdles, carotidynia	None	PET (FDG uptake): carotid, subclavian, thoracic and abdominal aorta.	PET/CT (decrease FDG uptake): carotid, subclavian arteries, thoracic and abdominal aorta	120/8	8.9/0.02	Clinical remission	Pazzola (43)

TCZ: tocilizumab; PMR: polymyalgia rheumatica; GCs: glucocorticosteroids; AZA: azathioprine; CyA: cyclosporine A; CYP: cyclophosphamide; LFN: leflunomide ; MM: Mycophenolate mofetil; MTX: methotrexate; ADA: adalimumab; ETN: etanercept; IFX: infliximab; RTX: rituximab; CRP: C-reactive protein (mg/dL); ESR: erythrocyte sedimentation rate in 1st hour; FDG: fluordeoxyglucose; CT: computed tomography; CT-A: computed tomography angiography; MRI-A: magnetic resonance angiography; PET: positron emission tomography; ND: not described; NV: no numerical value.

Table III. Reported series and case reports on the use of Tocilizumab in aortitis and/or its main branches associated with Takayasu arteritis.

Age/ Sex	Clinical features	Previous therapy	Imaging technique before TCZ	Imaging technique after TCZ	ESR before / after TCZ	CRP before / after TCZ	Outcome	Ref.
40/M	Leakage of a graft of the thoracic aorta and ischaemic pain	GCs	MRI-A: aortitis	MRA: improvement in aortitis	80/ 5	0.4/ <0.03	Clinical remission	Seitz (48)
27/ F	Malaise, arms and legs claudication	GCs, MTX, AZA, IFX	MRI-A: aortitis	MRA: improvement in aortitis	40/ <3	0.5/ <0.03	Clinical remission	Seitz (48)
21/F	Myalgia, fever, headache, bilateral carotid bruits	GCs, MTX	PET/CT (FDG uptake): multiple arteries	PET/CT: decrease in FDG uptake	45/3	4.02/ 0.06	Clinical remission	Salvarani (47)
40/F	Arthro-myalgia, fever, weight loss, carotidynia, subclavian bruit	None	PET/CT (FDG uptake): multiple arteries	PET/CT: decrease in FDG uptake	67/2	0.99/0.05	Clinical improvement	Salvarani (47)
54/M	Malaise, myalgia, weight loss	None	PET/CT (FDG uptake): numerous vessels	PET/CT: decrease in FDG uptake in aorta	84/2	4.8/0.01	Clinical remission	Salvarani (47)
25/F	Myalgia, arthralgia, headache, fever, arm claudication, 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 in FDG uptake	69/Normal (NV)	7.2/Normal (NV)	Clinical remission	Salvarani (75)
ND/ND	Upper estremity claudication, pulse deficit, pulmonary hypertension	GCs	Cross-sectional imaging (CT-A, MR-A): pulmonary, carotid and subclavian artery stenosis	ND	15/3.6	0.8/0.03	Clinical remission	Unizony (49)
ND/ND	Lower extremity claudication, pulse deficit, hypertension	GCs	CT-A, MRI-A: aortic arch aneurysm and external iliac artery stenosis	ND	34/8.7	1.7/0.56	Clinical remission	Unizony (49)
20/F	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 in aortitis	ND/ND	12.6/Normal (NV)	Clinical improvement	Nishimoto (46)
28/F	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 in aortitis; progression of stenosis in renal, subclavian and vertebral artery.	70/2	6.6/ <0.3	Clinical improvement	Bredemeier (76)

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

Interestingly, several studies indicate that TCZ may be a useful therapy in patients with non-infectious aortitis. Table II and Table III show avaliable information on the use of TCZ in aortitis and/or its large branches in GCA and TakA. Of paticular interest is the case reported by Salvarani *et al*. (47); a patient with biopsy-proven GCA that had previously been diagnosed with spondyloarthritis, having been initially treated with infliximab and then with etanercept. Besides corticosteroids, MTX had been added to etanercept for one year without improvement. The patient experienced frequent relapses, including systemic manifestations, elevated acute phase reactants and inflammation of large vessels confirmed by PET/CT when prednisone dose was decreased below 12.5 mg/day. Thus, MTX and etanercept were changed to TCZ. One month after TCZ onset the patient achieved clinical, laboratory and PET/CT improvement and the dose of prednisone was successfully tapered (47). Seitz *et al*. (48) published five patients with GCA treated with TCZ (8 mg/kg). The patients experienced clinical improvement that correlated with improvement in imaging techniques. Because of that, corticosteroid dose was successfully reduced (48). Beyer *et al*. (44) reported 3 patients with GCA that received treatment with TCZ because of active disease associated with aortitis and/or femoral inflammation on PET. Rapid and maintained improvement was found in all patients following TCZ therapy, and corticosteroid dose was successfully tapered. Unizony *et al*. (49) described 7 patients with GCA refractory to corticosteroid therapy and immunosuppressive agents. For this reason, they started on TCZ 4-8 mg/kg every month. They got into remission and were able to taper corticosteroid dose. Recently, Pazzola *et al*. (43) described a woman diagnosed with GCA and PMR. She began with TCZ as monotherapy at a dose of 8 mg/Kg monthly. Clinical improvement and reduction of ESR and CRP was observed. Six months after the onset of TCZ the patient was asymptomatic and the image techniques showed markedly decreased of vascular FDG uptake in the affected vessels.

TakA is another large-vessel vascultis that involves the aorta, its large branches, and the proximal portions of renal, coronary and pulmonary arteries (67). Incidence of TakA is 1.2-2.6/million per year in western population and 100-times higher approximately in the countries of *The Silk Road* (56, 68, 69). This entity is more common in women between 20–40 years (9, 68). Clinically it is characterised by fever, weight loss, joint pain, claudication of affected limbs, decrease or loss of pulses, carotidynia, headache, amaurosis, diplopia, renal failure, cerebrovascular events, heart failure, acute myocardial infarction and aneurysms (70-74).

As occurs in the GCA, IL-6 is also expressed in TakA tissue. Furthermore, serum levels of IL-6 are elevated in patients with TakA correlating very well with disease activity. Therefore, pharmacological blockade of IL-6 is also a potential target to be considered in this kind of vasculitis. Nishimoto *et al*. (46) published in 2008 the case of a 20-year-old woman diagnosed with TakA five years before. She also had ulcerative colitis. The patient was treated with corticosteroids, immunosuppressive agents and leukapheresis. Despite this, the patient could not reduce the dose of prednisolone below 30 mg/day because the symptoms recurred. For this reason, TCZ was started achieving a disease remission, allowing to taper the dose of corticosteroids. Ulcerative colitis also improved.

Salvarani *et al*. (47) published a study on 3 patients with TakA who experienced important improvement following TCZ therapy. Also, this group (75) reported a 25-year-old woman with TakA that started treatment with prednisone. Then, the patient received MTX, mycophenolate mofetil, infliximab and adalimumab, but none of them managed to reach control the disease activity. Therefore, TCZ was started (8 mg/kg) every 4 weeks for 6 months. Clinical activity, inflammatory markers and PET/CT findings became normal, while prednisone dosage was successfully tapered. Seitz *et al*. reported 2 cases of TakA (48). One of them had only been treated with corticosteroids while the other had been treated with MTX, azathioprine and infliximab. Due to lack of response, TCZ was started in both cases. Following this procedure, complete clinical response with normalisation of CRP and ESR was observed. However, one of them relapsed after 8 months of treatment. Unizony *et al*. (49) also described 2 patients diagnosed of TakA and treated with TCZ with good response. In contrast, Bredemeier *et al*. (76) described a 28-year-old woman with TakA that suffered progression of vascular stenosis despite treatment with TCZ.

RP is a rare systemic disease characterised by recurrent inflammation and destruction of cartilaginous structures as well as other structures rich in proteoglicans such as eyes, heart, blood vessels, middle ear and kidneys (77-79). Little is known on the use of TCZ in patients with RP. With respect to this, Narshi and Allard (80) described a 43-year-old woman with RP and aortitis requiring emergency aortic valve replacement. The patient had poor response to conventional therapy. Because of that, infliximab was started in combination with oral MTX and deflazacort, but she suffered a relapse of the disease associated with elevation of the laboratory markers of inflammation. Adalimumab was then started showing improvement. However, since the patient developed a recurrence of the disease despite of increasing the corticosteroid dose and the frequency of adalimumab, she was switched to TCZ (8 mg/kg/ every 4 weeks). Following TCZ the patient achieved a rapid improvement with normalisation of CRP. Other authors such as Kawai *et al*. or more recently Wallace and Stone also published good results in RP patients treated with TCZ (81, 82). Wendling *et al*. (83) reported a 46-year-old woman with RP that had received treatment with prednisone, dapsone, several disease-modifying anti-rheumatic drugs, infliximab, etanercept and anakinra, achieving clinical remission with the last one. However, when anakinra was discontinued she suffered a relapse of symptoms. At that time, she refused to start again with subcutaneous injections and because of that iv infusions of TCZ (8 mg/kg/monthly) were given.

The patient experienced clinical improvement within the first week after the first infusion of TCZ. However, subsequently, no improvement was observed and the patient had to return to anakinra.

Idiopathic isolated aortitis is characterised by giant cells or lymphoplasmacytic inflammation of the aorta. Isolated aortitis generally manifests as an ascending aortic aneurysm and it is usually discovered incidentally within a pathological study of a sample of aortic wall after surgery (8). Pazzola *et al*. (43) described 57-year-old man with idiopathic aortitis and diabetes mellitus that received TCZ as monotherapy at the dose of 8 mg/kg monthly for 6 months. After 2 months of treatment the patient experienced clinical improvement with normalisation of inflammation markers. A PET/CT performed after 6 months of TCZ therapy did not disclose abnormal FDG uptake.

Some authors have included within the category of idiopathic aortitis to cases of chronic periaortitis, idiopathic retroperitoneal fibrosis (Ormond disease), inflammatory abdominal aortic aneurysm, perianeurysmal aortitis and idiopathic isolated abdominal periaortitis (2, 84- 90). We support this consideration and, because of that, we defined patient number 16 from our series (Table I) as aortitis associated with retroperitoneal fibrosis. Interestingly, a recent study conducted by Vaglio *et al*. supports the use of TCZ in patients with chronic periaortitis who are refractory or have contrainications for the use of corticosteroids (91). In this regard, according to the the results derived form this study, TCZ should be considered in cases of chronic periaortitis refractory to other immunosuppressive drugs. TCZ added to ongoing therapy with prednisone and MTX allowed prednisone withdrawal and induced resolution of symptoms, acute-phase reactant normalisation, and reduction in FDG PET uptake in one case (91). In another case of chronic periaortitis, TCZ in monotherapy induced sustained clinical and laboratory remission, FDG uptake disappearance, and chronic periaortitis shrinkage.

In conclusion, taking all these evidences together, TCZ appears to be a biologic agent effective and relatively safe in patients with inflammatory aortitis refractory to corticosteroids or to other biologic immunosuppressive drugs. However, additional studies including randomised controlled trials are needed to evaluate the long-term efficacy and safety of TCZ in patients with aortitis.

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