Treatment of Refractory Takayasu Arteritis with Tocilizumab: 7 Italian Patients from a Single Referral Center

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ABSTRACT. ***Objective.*** The aim of our study was to evaluate the safety and the efficacy of tocilizumab (TCZ) for refractory Takayasu arteritis (TA).

Methods. We retrospectively assessed the outcome of blocking interleukin (IL)-6 with TCZ in 7 consecutive patients with refractory TA using a combination of clinical and imaging assessment.

Results. During a median followup visit at 14 months, 4 patients taking TCZ [including 2 non-responders to tumor necrosis factor (TNF) inhibitors] achieved clinical response, suggesting a non-redundant role for IL-6 in TA. Inflammatory markers normalized in all patients treated with TCZ. However, vascular progression occurred in 4 patients, suggesting the involvement of other inflammatory pathways and confirming the limitations of erythrocyte sedimentation rate and C-reactive protein for disease activity assessment while taking TCZ. Three patients experienced adverse events and 2 suspended TCZ.

Conclusion. TCZ may be effective in a subset of patients with refractory TA, even in cases of unresponsiveness to TNF inhibitors. Inflammatory markers are not valid markers of TA activity on TCZ. Further studies are needed to confirm these preliminary observations. (J Rheumatol First Release Nov 1 2013; doi:10.3899/jrheum.130536)

Key Indexing Terms:
TAKAYASU ARTERITIS TOCILIZUMAB INTERLEUKIN 6 VASCULITIS

Takayasu arteritis (TA) is a rare, idiopathic, chronic-relapsing inflammatory disease typically affecting young women, with considerable morbidity and mortality[1,2]. Patchy granulomatous panarteritis of the aorta and its major branches is typical of TA and may result in local pain, stenosis, occlusion, and aneurysm formation[1]. Systemic inflammatory reaction with constitutional symptoms and acute-phase response often accompany active disease[1]. Activated dendritic cells, T cells, B cells, macrophages, and multinucleated giant cells infiltrate vascular lesions[1,3]. Interleukin 6 (IL-6), a pivotal pleiotropic inflammatory cytokine with both local and systemic effects[4], is strongly expressed in TA aortic tissue, and serum IL-6 levels are elevated in TA, particularly during active phases[5,6,7].

The first goal of TA therapy is preventing the progression of vascular lesions. Medical therapy is the cornerstone of TA, although controlled clinical trials are lacking because of the rarity of TA[1]; some cases warrant revascularization procedures[2,8]. Medical therapy is based on corticosteroids, but most patients require steroid-sparing immunosuppressive agents[1]. Nonetheless, many patients with TA are refractory to combined steroids and immunosuppressive agents[2,8,9,10].

Previous observations suggest that tocilizumab (TCZ), a humanized anti-IL-6 receptor antibody, may be an option in this setting[11,12,13,14,15,16]. However, a recent report describes a patient with TA treated with TCZ who experienced radiological vascular progression despite good clinical response, normalization of symptoms of active disease and inflammatory markers[14].

The aim of our study was to evaluate the safety and the efficacy of TCZ for refractory TA.

MATERIALS AND METHODS

We retrospectively reviewed the treatment of the 62 patients with TA followed at our center between 2004 and 2012: 9 were treated with steroids only and 31 with both steroids and immunosuppressive agents. We proposed a biological therapy only to refractory patients [i.e., failing to obtain or maintain quiescent disease with prednisone (PD) ≤ 7.5 mg/day and at least 1 immunosuppressive drug]: 22 patients with TA received tumor necrosis factor (TNF) inhibitors and 7 received TCZ (8 mg/kg monthly). All of the patients taking TCZ met the American College Rheumatology classification criteria of TA and were entered in our study. Screening for latent tuberculosis was performed according to local guidelines.

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All of the patients gave informed consent to treatment and study participation.

Patients with TA treated with TCZ underwent bimonthly assessment where symptoms, physical examination, biochemistry, and treatment changes were recorded. All patients underwent a thorough imaging evaluation with both magnetic resonance angiography (MRA) and vascular ultrasonography (US) at baseline and at the end of followup. Imaging was also repeated yearly or when disease flared (whenever possible with both MRA and US). US evaluations assessed carotid, subclavian, abdominal, and femoral areas, while MRI was focused on thoracoabdominal or cervicothoracic regions according to disease involvement. Followup ended at the suspension of TCZ, or at the time of the last visit for patients still on TCZ.

Study endpoints were efficacy and safety of TCZ in TA. TCZ efficacy was evaluated according to (1) satisfaction of response criteria and reduction of disease activity, as defined by acute-phase reactants and the US National Institutes of Health (NIH) criteria[9]; (2) capability of PD tapering in the absence of relapse; (3) radiological vascular evolution; and (4) need of revascularization procedures.

We defined complete response as the absence of imaging progression and of features of active disease[17] while taking a PD daily dose of ≤ 7.5 mg for at least 6 months; partial response occurred if clinical improvement allowed a daily reduction of steroid by at least 50%[17]. Relapsing disease was defined as the loss of complete response, as defined above[17].

For each patient we analyzed the course of every vascular lesion along with the serial imaging studies performed during followup. Lesions were classified as thickening (i.e., wall thickness > 1 mm), stenoses (i.e., diameter reduction > 50%), occlusions (diameter reduction > 99%), and ectasias/aneurysms. Lesions were classified as worsened during followup if the patient needed revascularization procedures or if imaging documented an increase of wall thickness or a worsening stenosis.

Statistics. Given the small size of our sample, scalar variables were evaluated using a non-normal distribution and were summarized using medians and interquartile ranges (IQR). Wilcoxon test was used for comparison between these variables.

RESULTS

Patient characteristics. Seven female patients with TA treated with TCZ were included in our study. Their median age at TA diagnosis was 24 years (IQR 23–30). Prior to TCZ, the median duration of illness was 66 months (IQR 17–82), and the median number of immunosuppressive agents (other than prednisone) was 4 (IQR 2–6; Tables 1 and 2). Other agents that patients had previously received included methotrexate (all patients), azathioprine (n = 4), cyclosporine (n = 3), cyclophosphamide (n = 2), mycophenolate mofetil (n = 2), and sirolimus (n = 2). Four patients had also been previously treated with biologic agents: infliximab (all patients), adalimumab (n = 3), and anakinra and rituximab (n = 1). At baseline, all patients had active disease according to the NIH criteria. The median followup on TCZ was 14 months (IQR 10-33). During followup, all patients received concurrent immunosuppressive therapy (1 patient changed immunosuppressive regime; data available from the authors).

Efficacy evaluation. Complete response was achieved in 3 patients (without subsequent relapse) and 1 achieved partial response. Three patients satisfied the disease activity criteria at the end of followup and suspended TCZ for suboptimal disease control. Inflammatory markers normalized in all patients: median erythrocyte sedimentation rate (ESR) reduced from 34 mm/h (IQR 31–40) to 4.0 mm/h (IQR 2.0–15; p = 0.028); median C-reactive protein (CRP) declined from 13 mg/l (IQR 12–14) to 2.0 mg/l (IQR 1.0–6.0; p = 0.043; Table 2). During followup, PD dose showed a consistent, although nonsignificant, reduction; platelet count and acute phase signs on serum protein electrophoresis, which are regulated by IL-6, abated (Table 2).

At imaging evaluation, 3 patients (the ones that achieved complete response) showed improvement or stabilization of all vascular lesions without any disease progression (Table 1 and Figure 1). Two other subjects showed a single worsening lesion, and the remaining 2 developed at least 1 new lesion. For each patient, a median value of 30% of all vascular lesions improved during followup, 50% remained stable, and 10% worsened or appeared. No revascularization procedures were needed during followup.

Adverse outcomes. During followup 3 patients experienced adverse reactions: 2 had recurrent respiratory infections (1 of them had recurrent pneumonia and suspended TCZ), another subject experienced a severe maculopapular rash that subsided after TCZ suspension. Transaminase levels increased during followup (Table 2), without cases of relevant liver toxicity.

DISCUSSION

To our knowledge, only 12 adult patients with TA and treated with TCZ have been reported in the literature. We describe the first cohort consisting exclusively of patients with TA taking TCZ with regular morphological imaging followup. Four of 7 patients (including 2 nonresponders to TNF inhibitors) significantly improved, confirming preliminary observations of possible TCZ efficacy for refractory TA[11,12,13,14,15,16].

Our results indicate a dichotomy between the action of TCZ on the levels of liver-borne acute-phase reactants and its ability to induce and maintain clinical remission. This was not documented in all patients; 3 patients suspended TCZ for suboptimal disease control and 1 patient who had partial response underwent radiological vascular progression, although confined to a single vascular site (Table 1). The selection of a cohort with a high number of previously unsuccessful agents and long disease duration (potentially with a particularly refractory disease) could partially contribute to limit the efficacy of the treatment. Moreover, the imaging modality we have relied on has a very high sensitivity in detecting morphological vascular progression and could further justify the higher rates of imaging progression compared with previous reports[11,12,13,15,16].

Vascular histological inflammation or even imaging progression, despite clinically silent TA, is well known[10,18] and has frequently been reported for patients on TCZ[14,15,19]. All our vascular-worsening patients needed imaging data to

Table 1. Patient characteristics.

Patient	Age at Disease Onset, yrs	Disease Duration, mo	Before TCZ Therapy: Pervious Immuno-suppressive Agents	PD, mg/day	ESR, mm/h	CRP, mg/l	At the End of Followup: PD, mg/day	ESR, mm/h	CRP, mg/l	Improved Lesions	Stable Lesions	Worsened Lesions	New Lesions	Active Disease (NIH Criteria*)	Months on TCZ	Response	Cause of TCZ Withdrawal
1	24	101	MTX, MMF, AZA, IFX	10	76	10	10	15	< 1	4	5	2	2	Yes	17		Persistence of TA activity, vascular progression
2	23	66	MTX, ADA, IFX, CYC, sirolimus	7.5	34	13	3.75	14	< 1	1	4	1	0	No	36	PR	
3	30	17	AZA, MTX	15	31	13	10	4	1	1	5	1	3	Yes	9		Relapse at PD tapering and vascular progression
4	27	67	AZA, IFX, CTX, MTX, ADA, AKR, RTX, CYC	15	32	12	25	2	6	3	6	1	0	Yes	10		Relapse at PD tapering
5	39	17	MTX	8.8	8	12	0	2	1	6	2	0	0	No	33	CR	
6	19	50	MMF, CTX, minocycline, MTX	5.0	38	14	5.0	2	< 4	1	10	0	0	No	14	CR	Cutaneous rash
7	24	82	AZA, CYC, MTX, sirolimus, IFX, ADA	15	40	35	6.2	2	4	2	2	0	0	No	12	CR	Relapsing sinusitis and pneumonia

TCZ: tocilizumab; PD: prednisone daily dose; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CR: complete response; PR: partial response; AZA: azathioprine; MTX: methotrexate; MMF: mycophenolate mofetil; CYC: cyclosporine; CTX: cyclophosphamide; IFX: infliximab; ADA: adalimumab; AKR: anakinra; RTX: rituximab.

Table 2. Laboratory variables and average prednisone daily dose (PD) at the beginning and at the end of followup (median values and IQR of 7 patients).

	At Beginning of Followup	At End of Followup	p
PD (mg/day)	10 (7.5–15)	6.2 (3.7–10)	0.174
ESR (mm/h)	34 (31–40)	4.0 (2.0–15)	0.028
CRP (mg/l)	13 (12–14)	2.0 (1.0–6.0)	0.043
Number of vascular lesions	8 (6–11)	7 (5–10)	0.496
Leukocyte count ($\times 10^9$ cells/l)	9.25 (9.10–12.60)	9.01 (6.78–9.71)	0.091
Neutrophils ($\times 10^9$ cells/l)	5.53 (5.23–7.46)	5.60 (2.43–6.64)	0.091
Lymphocytes ($\times 10^9$ cells/l)	2.99 (2.30–3.52)	2.63 (2.26–2.94)	0.075
Monocytes ($\times 10^6$ cells/l)	680 (400–820)	680 (380–1020)	0.917
Eosinophils ($\times 10^6$ cells/l)	120 (110–150)	110 (80–140)	0.173
Basophils ($\times 10^6$ cells/l)	20 (10–40)	10 (10–40)	0.715
Hemoglobin (g/dl)	10.5 (10.2–11.4)	11.0 (10.6–11.5)	0.237
Platelets ($\times 10^9$/l)	370 (345–386)	277 (252–326)	0.018
Aspartate aminotransferase (Units/l)	17 (14–22)	25 (15–31)	0.028
Alanine aminotransferase (Units/l)	18 (13–27)	40 (16–54)	0.043
Serum protein (g/l)	73.9 (73.5–79.0)	71.7 (71.0–72.7)	0.028
Serum albumin (g/l)	39.8 (39.4–41.2)	41.6 (39.4–44.4)	0.116
Serum α1-globulin (g/l)	3.9 (2.8–4.3)	2.8 (2.4–3.0)	0.046
Serum α2-globulin (g/l)	8.3 (8.0–10.5)	6.0 (5.1–7.3)	0.028
Serum ß-globulin (g/l)	8.5 (7.5–9.6)	8.3 (6.8–9.7)	0.046
Serum γ-globulin (g/l)	13.7 (10.5–14.9)	12.7 (9.6–14.4)	0.028

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IQR: interquartile range.

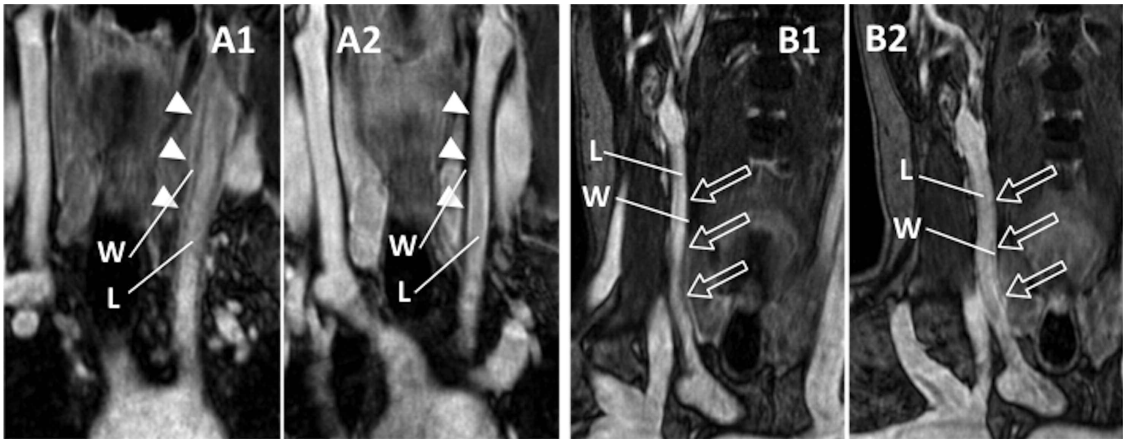

Figure 1. Magnetic resonance imaging followup in 2 patients. Case A: Radiological improvement with thinning (and loss of enhancement) of left carotid arterial wall (arrowheads; A1, October 2008; A2, January 2012). Case B: Radiologic new disease onset in right carotid artery with enhanced vessel wall thickening (arrows; B1, March 2009; B2, February 2011). L: lumen; W: vessel wall.

satisfy NIH activity criteria and showed progression without elevation of inflammatory markers.

These observations suggest that acute-phase reactants could not be valid biomarkers of disease activity during TCZ therapy and cannot be used to determine therapeutic changes. Consequently, disease activity indices including acute-phase reactants, such as NIH criteria, may be less accurate when applied to these patients. Therefore, we suggest that thorough morphological imaging be mandatory for the followup of these patients and for therapeutic decisions.

Silent vascular progression might depend on (1) local smoldering vessel inflammation quantitatively insufficient to induce a systemic reaction, or (2) local vessel inflammation recruiting pathways independent of IL-6. The 2 hypotheses are not mutually exclusive and noninflammatory factors could also play a role. Locally produced inflammatory proteins such as pentraxin-3 (a long pentraxin produced directly within the sites of arterial inflammation), whose production is not directly elicited by IL-6, have been shown to better detect TA activity than ESR and CRP[20].

Our study is a pilot study and carries major limitations. It is retrospective, uncontrolled, and it analyzes a very small cohort of refractory TA patients that have, in general, failed to respond to several other treatments. Another limitation is the radiological focus on vascular morphology without concurrent functional analysis with positron emission tomography.

Our study suggests that TCZ may be effective in a subset of refractory patients with TA, even in cases unresponsive to TNF inhibitors. However, 4 of the 7 patients experienced imaging progression, and only 2 subjects remained on TCZ at the 2-year followup. Further studies are needed to confirm these preliminary observations, with larger, randomized, and multicentric trials. ESR, CRP, and other acute-phase reactants abated in all patients treated with TCZ, suggesting a nonredundant role for IL-6, but they are not valid markers of TA activity on TCZ. Hence, rigorous morphological imaging assessment should be warranted in these patients.

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