Tocilizumab in Giant Cell Arteritis: A Multicentre Retrospective Study of 34 Patients

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ABSTRACT. ***Objective.*** To report the efficacy and safety of tocilizumab (TCZ) for giant cell arteritis (GCA).
Methods. A retrospective multicenter study that included 34 patients receiving TCZ for GCA.
Results. TCZ was effective in all but 6 patients, who still had mild symptoms. Mean glucocorticoid dose was tapered. One patient died and 3 patients had to stop TCZ because of severe adverse events. Twenty-three patients stopped treatment; 8 of these experienced relapses after a mean of 3.5 ± 1.3 months.
Conclusion. TCZ is effective in GCA. However, side effects occur. Whether this treatment has only a suspensive effect remains to be determined. (J Rheumatol First Release May 15 2016; doi:10.3899/jrheum.151252)

Key Indexing Terms:
GIANT CELL ARTERITIS
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Giant cell arteritis (GCA) is a vasculitis of large- and medium-sized arteries affecting people older than 50 years. Despite improvement in identifying the pathogenesis of the disease, glucocorticoid therapy remains the mainstay of treatment and is responsible for side effects in as many as 86% of patients[1]. Trials with methotrexate (MTX) as a steroid-sparing agent have given conflicting results[2], and other immunosuppressant and tumor necrosis factor-α blockers have failed to help with treatment strategies[3].

Interleukin 6 (IL-6) level is associated with GCA disease activity[4] and is responsible for macrophage activation and Th17 cell differentiation[5]. Thus, IL-6 inhibition with tocilizumab (TCZ), an anti–IL-6 receptor antibody, might be of therapeutic benefit. Case series and open-label studies

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have reported the efficacy of TCZ for symptoms and inflammatory markers[6,7]. However, side effects can occur and in some cases, because of the persistence of vasculitis with treatment, TCZ might not definitely cure GCA but instead have only a suspensive effect on disease evolution[8].

Here, we evaluated the off-label experience with TCZ for GCA in France.

MATERIALS AND METHODS

Patient selection. We performed in 2015 a retrospective survey of cases of GCA treated with TCZ. In total, 1200 rheumatologists and internists were asked to supply medical records for any patients with GCA who had received at least 1 infusion of TCZ. Patients were recruited through calls from the French Vasculitis Study Group, the Groupe français pour l'étude de l'artérite à cellules géantes, and the Club rhumatismes et inflammation. Patients were included if they had GCA according to the American College of Rheumatology (ACR) classification criteria[9] or imaging evidence (positron emission tomography or ultrasonography) of vasculitis and symptoms suggestive of GCA, and active disease requiring inappropriate use of glucocorticoids according to medical judgment at the time of initiation of anti-IL-6 therapy or as add-on therapy. Because of the observational, retrospective design of the study and the anonymization of information, approval from the local ethics committee was not required.

Assessment of vasculitis and anti–IL-6 treatment. The medical records of all patients were reviewed. A database was created to include patient characteristics and description of the vasculitis and treatment. Reasons for TCZ introduction and previous and concomitant therapies for GCA were recorded. Treatment outcome, side effects, and evolution after TCZ withdrawal were noted.

Statistical analysis. Data were compared by Wilcoxon signed-rank test for paired values, and statistical analysis involved use of GraphPad Prism 6. $P < 0.05$ was considered statistically significant.

RESULTS

In total, 34 patients (27 women; mean age 70.5 ± 8.2 yrs) were included and received TCZ between 2011 and 2015. The main clinical data are in Table 1A and Table 1B. A flowchart of the therapy experience is shown in Figure 1. The mean treatment time was 6.4 ± 4.5 months and median followup after initiation of TCZ therapy 13 months (range 1-48). Diagnosis of GCA was based on the ACR criteria (30 patients) and/or an abnormal temporal artery biopsy (24 patients) and/or imaging abnormalities suggestive of GCA (11 patients). Disease was treated with glucocorticoids for all patients (patients 3, 24, and 33 received intravenous methylprednisolone pulses), and another immunosuppressant was added before TCZ treatment for 20 (59%; MTX for 18 patients, infliximab for 3, and adalimumab, anakinra, dapsone, azathioprine, and leflunomide for 1 each). At TCZ introduction, patients had been treated for a mean duration of 18 months (range 0–107 mos) and the mean glucocorticoid dose was 26.3 ± 13.8 mg/day. The reasons for TCZ introduction included unacceptable glucocorticoid side effects (n = 31); severity of disease (scalp necrosis and retinal central artery occlusion, 1 each); and as a steroid-sparing agent in 1 patient with diabetes, hypertension, and obesity. Treatment was introduced in 9 patients during the early disease stage (< 3 mos) and for 25, the disease had evolved for > 3 months. Patients received a monthly 8-mg/kg dose of TCZ, and the dose was reduced for 1 patient because of transient neutropenia.

TCZ treatment was associated with marked improvement in clinical symptoms in patients within 1 or 2 months except for 6 who still had mild symptoms: asthenia (n = 2), peripheral joint pain (n = 2), polymyalgia rheumatica, and headaches (n = 1 each). This improvement was concomitant with reduced mean C-reactive protein level, from 40.4 ± 45.6 to 1.5 ± 1.8 mg/l ($p < 0.0001$) and a tapering of glucocorticoids from 26.3 ± 13.8 to 10.3 ± 8.3 mg/day ($p < 0.0001$), although none of them completely discontinued glucocorticoid therapy (Figure 2). Visual impairment in the patient with retinal central artery occlusion was not reversed despite treatment.

Six patients had side effects that were possibly related to TCZ treatment. Three patients had neutropenia. In 2 cases, neutropenia was moderate and transient and the TCZ dose was reduced in one. In 1 patient, treatment was stopped after 10 months, and neutropenia (< 500/mm^3) resolved rapidly. Two patients experienced infectious complications: tuberculous pericarditis in 1 and fatal septic shock in another. A final patient who concomitantly received MTX experienced liver cytolysis (transaminase level > 10 times the upper limit of normal) that resolved after discontinuation of both TCZ and MTX. No other cause for liver impairment was identified and MTX alone was reintroduced without increase in transaminase level.

Treatment was stopped in 23 patients after a mean treatment duration of 5.6 ± 2.9 months: 3 patients because of side effects and 20 as planned; 8/23 (34.8) experienced a disease flare that occurred after a mean of 3.5 ± 1.3 months. However, none of the relapses occurred in the 7 patients who received TCZ in the early phase of the disease (< 3 months). The relapses occurred in patients with disease for ≥ 3 months before TCZ treatment. TCZ was started again in 5 of the 8 patients, with good clinical and biological response. Therefore, with a median followup of 13 months, 15/34 patients (44.1%) were receiving treatment at the end of the study, corresponding to 23 patient-years of therapy.

DISCUSSION

In this study, we confirm the efficacy of TCZ for treating GCA[6,7]. Indeed, all patients showed clinical improvement even though 6 still had minor clinical symptoms, and levels of biological markers were always reduced (a direct effect of IL-6 receptor blockade), which allowed for a progressive glucocorticoid tapering.

Six patients had side effects that may have been related to treatment. Infectious complications may also have been due to glucocorticoids. Ongoing randomized control trials such as GiACTA (NCT01791153) are required to properly determine the risk of infection in TCZ therapy in this population of older adults also receiving high-dose glucocor-

Table 1A. Demographic data, giant cell arteritis (GCA) diagnosis, and reason for tocilizumab (TCZ) treatment in 34 patients.

Demographic Data			GCA Diagnosis		Disease Length before TCZ, Mos	Reason for TCZ Treatment		
Pt.	Age/sex	TAB	ACR criteria	Imaging proof of vasculitis		GC side effects/dependence	Failure of other drugs	Disease severity
1	77/F	+	Yes		18	Yes		
2	74/F	+	Yes		9	Yes		
3	75/M	+	Yes		4	Yes		
4	66/F	+	Yes	US of TA	72	Yes	MTX	
5	65/F	+	Yes		6	Yes		
6	76/M	+	Yes		12	Yes	MTX	
7	78/F	+	Yes		11	Yes	MTX	
8	78/F	–	No	PET scan	107	Yes		
9	66/F	+	Yes		84	Yes		
10	68/M	+	Yes	PET scan	40	Yes	MTX, AZA, LEF	
11	63/F	+	Yes		36	Yes	MTX	
12	54/F	–	No	PET scan	7	Yes	IFX, MTX	
13	58/F	–	Yes	PET scan	27	Yes	MTX	
14	55/F	–	Yes		36	Yes	anakinra, dapsone, MTX	
15	63/F	–	Yes	PET scan	15	Yes		
16	73/F	+	Yes		22	Yes	IFX	
17	67/F	–	Yes		31	Yes		
18	76/F	+	Yes	PET scan	5	Yes		
19	72/F	+	Yes		11	Yes	MTX	
20	80/M	–	No	US of TA	3	Yes	MTX	
21	60/F	–	No	PET scan	10	Yes	MTX	
22	74/F	+	Yes		11	Yes	IFX, ADA	
23	63/F	+	Yes		17	Yes	MTX	
24	70/F	+	Yes	PET scan	5	Yes	MTX	
25	66/M	–	Yes		5	Yes		
26	76/F	+	Yes		2	Yes	MTX	
27	86/F	+	Yes		0	No		Yes
28	60/F	+	Yes	PET scan	2	Yes	MTX	
29	86/F	+	Yes		1	Yes	MTX	
30	78/F	+	Yes		1	Yes	MTX	
31	78/M	–	Yes		1	Yes	MTX	
32	66/F	+	Yes		1	Yes		
33	78/F	+	Yes		0	No		Yes
34	74/M	+	Yes		0	No		

ACR: American College of Rheumatology; AZA: azathioprine; MTX: methotrexate; TA: temporal artery; TAB: temporal artery biopsy; PET scan: positron emission tomography scanner; US: ultrasound; IFX: infliximab; ADA: adalimumab; LEF: leflunomide.

ticoids[10]. Three patients experienced neutropenia, which seemed to be more frequent in our cohort than in a population receiving TCZ for rheumatoid arthritis[11]. However, we could not identify any major safety concern in this retrospective study.

This is the first report, to our knowledge, on the evolution of disease after TCZ treatment withdrawal. Of note, patients with recent disease (< 3 mos) did not experience disease flare. None of these patients received glucocorticoid intravenous pulses. In contrast, 8/16 with a more chronic disease course (≥ 3 mos) before TCZ introduction experienced flares when treatment was withdrawn. Therefore, the place of TCZ in the treatment strategy of GCA is in question. Indeed, ongoing studies can confirm the steroid-sparing effect of TCZ, but its longterm effect is still unknown. Specifically studying disease evolution during the 6 months after treatment withdrawal is important. Another trial, HORTOCI (NCT01910038), might also help to better understand the effect of IL-6 blockade on blood lymphocytic populations. However, the treatment effect on temporal lymphocytes and macrophage infiltrates will not be assessed in these trials. Limited experience is available with other biological agents such as anakinra or rituximab as an alternative therapy for refractory GCA and it is insufficient to draw conclusions[12,13]. Therefore, TCZ seems to be the best therapeutic option for patients who experience side effects with glucocorticoids and who do not benefit from MTX therapy, or in patients with multiple relapses[14].

Our study has several limitations. Its retrospective design does not allow for definitive conclusions. For some patients at inclusion, TCZ was an add-on therapy, and treatment was also prescribed in the context of relapsing glucocorti-

Table 1B. Symptoms at tocilizumab (TCZ) introduction and discontinuation for 34 patients with giant cell arteritis (GCA).

Pt.	At TCZ Introduction				Tx Length, mos	At TCZ Discontinuation/Last Infusion			
	Clinical symptoms	CRP level, mg/l	GC, mg/day	MTX, mg/week		Clinical symptoms	CRP level, mg/l	GC, mg/day	MTX, mg/ week
1	Headache, asthenia, scalp tenderness, jaw claudication	3	30		21		0	5	
2	Headache, jaw claudication	9	20		6	Peripheral arthralgia	2	7	
3	Asthenia, visual symptoms	1	30		8		1	7	
4	Fever, asthenia, PMR, peripheral arthralgia	30	20		6	Asthenia	1	15	
5	Asthenia, weight loss, scalp tenderness	26	40		6	Asthenia	1	5	
6	Asthenia, weight loss, scalp tenderness	30	20	12.5	3		6	15	12.5
7	Asthenia, headache, scalp tenderness	15	40	12.5	3		3	2.5	12.5
8	PMR	60	30		6		1	5	
9	Asthenia	6	10		3		0	9	
10	Asthenia	35	20		18	Peripheral arthralgia	0	8	20
11	Asthenia, headache	45	20	17.5	6		0	5	15
12	Asthenia	19	20	25	12		1.1	5	25
13	Asthenia, headache	1.9	20	25	3		0	15	25
14	Headache	20	7	15	8	Headache	1	15	15
15	Asthenia, headache, PMR	8	14		5		1	4	
16	Asthenia, headache, PMR	184	3.3*		6		1	0.3*	
17	Asthenia, headache	31	20		12		1	5	
18	Asthenia, PMR	20	30		1		1	15	
19	Asthenia, headache	57	25	15	5		0	6.5	15
20	Asthenia, PMR	20	15	15	10		1	3	15
21	PMR, jaw claudication	20	20	20	4		0	12.5	20
22	Fever, PMR	94	8		6	PMR	1	7	
23	None	4	30	20	6		0	10	
24	Scalp tenderness, PMR	35	60	20	2		2	40	20
25	Asthenia, PMR	94	20		3		0.6	5	
26	Asthenia, PMR, visual symptoms	4	60	12.5	6		0.6	5	12.5
27	Scalp necrosis	100	20	12.5	3		5	15	12.5
28	Asthenia, headaches, jaw claudication	20	40	12.5	3		3	17.5	12.5
29	Asthenia, headaches	30	20	12.5	6		2	5	12.5
30	Asthenia, headache, jaw claudication	30	15	12.5	4		6	15	12.5
31	Asthenia, headache, jaw claudication	50	25	12.5	3		5	7.5	12.5
32	Asthenia, headache, jaw claudication	1	20		6		0	7	
33	Asthenia, headache, jaw claudication, visual symptoms	92	60		15		0	5	
34	Asthenia, loss of weight	180	40	12.5	2		4	35	12.5

* Patient received betamethasone. 0.75 mg betamethasone = 5 mg prednisone. GC: glucocorticoids; CRP: C-reactive protein; MTX: methotrexate; PMR: polymyalgia rheumatica.

coid-dependent disease. Medical staff in charge of the patient decided on treatment duration and/or discontinuation and this might explain part of the discrepancy. In addition, optimal dose of TCZ therapy has not been evaluated. Lastly, patients also received glucocorticoids with a daily dose of 10.3 ± 8.3 mg at the end of TCZ treatment. Therefore, we cannot exclude a significant effect of glucocorticoids on disease control. Nevertheless, this is the largest experience reported to date of TCZ for patients with GCA.

TCZ seems to be efficient for GCA. However, it has potential side effects and might have only a suspensive effect. Additional data from ongoing placebo-controlled trials is required to better evaluate the place of IL-6 blockade in GCA treatment.

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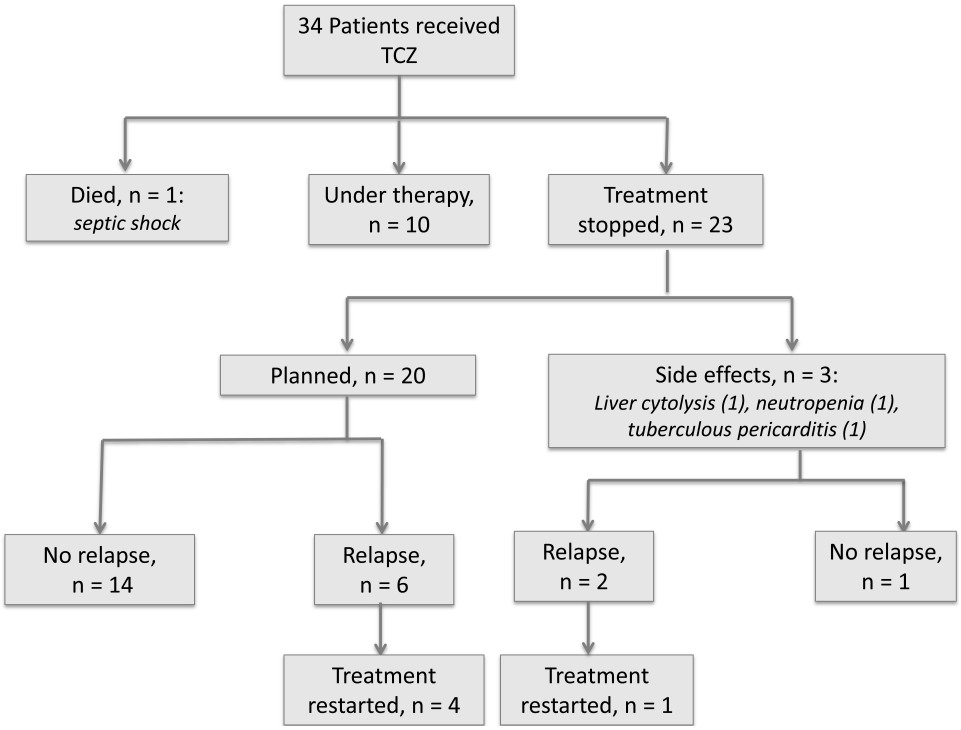

Figure 1. Tocilizumab (TCZ) therapy experience for 34 patients with giant cell arteritis.

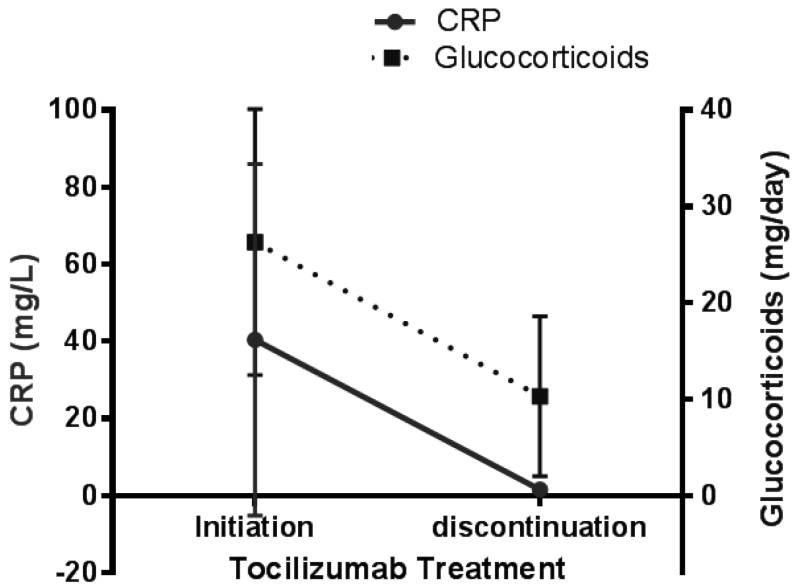

Figure 2. C-reactive protein (CRP) level and glucocorticoid treatment before tocilizumab therapy and at treatment discontinuation.

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