Original Article

Long-term treatment with tocilizumab in giant cell arteritis: efficacy and safety in a monocentric cohort of patients

Francesca Regola [1,2], Elisabetta Cerudelli[3], Giovanni Bosio[3],
Laura Andreoli[1,2], Angela Tincani[1,2], Franco Franceschini[1,2] and
Paola Toniati[1]

Abstract

Objective The efficacy of tocilizumab (TCZ) in GCA is supported by two randomized controlled studies, in which TCZ allowed remission to be achieved after 52 weeks of treatment. However, after discontinuation of treatment, half of the patients relapsed. The aim of this study was to analyse the efficacy and safety of long-term treatment with TCZ and the role of fluorodeoxyglucose (FDG)-PET/CT scanning in the follow-up of these patients.

Methods We collected the clinical data of a monocentric cohort of GCA patients retrospectively.

Results Thirty-two patients were treated with TCZ [25 males and 7 females; age = 74 (59–81) years]. Most of them achieved and maintained clinical remission (1 month: 69%; 3 months: 91%; 6 months: 96%; 12 months: 100%), with serological and FDG-PET/CT scan improvement and a reduction of concomitant glucocorticoid therapy. Nineteen patients were treated for >52 weeks, and in 13 of them a dose tapering was performed, whereas in 2 cases TCZ was suspended for disease remission. Only two patients relapsed: one during TCZ tapering and one after TCZ discontinuation. Ten cases of mild infections and a case of urinary sepsis were reported; in patients treated for >1 year there was no increase in the incidence of side effects compared with patients treated for <12 months.

Conclusion In our cohort of patients, we confirmed the efficacy of TCZ in the induction and maintenance of remission of GCA, demonstrating an important steroid-sparing effect and a good safety profile. Long-term treatment seems to prevent relapse of the disease, suggesting that TCZ treatment can be continued for >52 weeks with efficacy and safety.

Key words: giant cell arteritis, tocilizumab, fluorodeoxyglucose-PET/CT, large vessel vasculitis

CLINICAL SCIENCE

Introduction

GCA is an idiopathic large vessel vasculitis that usually occurs in patients older than 50 years of age, with markedly increased incidence in the eighth and ninth decades of life [1]. It preferentially involves the extracranial branches of the carotid artery, including the superficial temporal artery, but the whole aorta and its major branches can also be affected.

Tocilizumab (TCZ), a humanized monoclonal antibody blocker of IL-6 signalling, has been approved for the treatment of GCA. In the GiACTA trial, a multicentre phase III study, TCZ was demonstrated to be superior to placebo for the achievement of sustained remission after 52 weeks of treatment [2]. Despite these promising data, several questions about the use of TCZ in GCA remain unanswered. For example, the duration of treatment is still matter of debate, because data from the long-term follow-up of the GiACTA patients showed that

[1]Rheumatology and Clinical Immunology Unit, ASST Spedali Civili di Brescia, [2]Department of Clinical and Experimental Sciences, University of Brescia and [3]Nuclear Medicine Unit, ASST Spedali Civili di Brescia, Brescia, Italy

Correspondence to: Francesca Regola, Department of Clinical and Experimental Sciences, Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Piazzale Spedali Civili, 1, 25123 Brescia, Italy. E-mail: regola.francesca@gmail.com

half of the patients relapsed after discontinuation of treatment [3]. Moreover, more information on long-term safety is needed, particularly in real-world patients, who can be different from patients enrolled in randomized controlled trial.

It is also well known that monitoring disease activity is difficult in GCA patients receiving TCZ, mainly because of the limited reliability of acute phase reactants, owing to suppression of CRP synthesis in the liver by TCZ. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) integrated with CT is a very useful imaging technique to support the diagnosis of large vessel GCA (LV-GCA), but its use in the monitoring of GCA is still a subject of study [4].

We report a case series of 32 patients with GCA treated with TCZ and followed up in the last 8 years in our centre, in order to analyse the long-term efficacy and safety of this drug in GCA patients in a real clinical setting. We also evaluated the usefulness of FDG-PET/CT in disease activity assessment in the follow-up of these patients.

Methods

Patients

We performed a retrospective observational study on 32 patients with GCA treated with TCZ between 2013 and 2019 in our centre. The study was approved by the local institutional ethics committee and conducted in accordance with the Declaration of Helsinki.

Patients who were enrolled in the study were older than 50 years of age, met the ACR criteria for GCA [5] or had a positive biopsy of the temporal artery or evidence of large vessel vasculitis at FDG-PET/CT scan.

Clinical and laboratory data of all patients were collected from clinical charts at the diagnosis, at the beginning of TCZ treatment, after 1 month of therapy and every 3 months of follow-up. Laboratory data included ESR, CRP, complete blood count, serum protein electrophoresis and renal and liver function tests.

We also collected all the available radiological data prescribed during the follow-up of the patients according to clinical practice. In particular, the main imaging techniques used for the diagnosis of GCA and in the follow-up of these patients were Doppler ultrasound imaging, angio-CT, MRI and FDG-PET/CT scan. A retrospective qualitative and semi-quantitative analysis of the FDG-PET/CT scans was conducted by a nuclear medicine physician evaluating four segments of aorta (ascending, arch, descending and abdominal) and five branch arteries (innominate, carotids and subclavians). For the visual assessment, the PET vascular activity score was calculated [6]. For the semi-quantitative analysis, the maximum standardized uptake value (SUVmax) was measured, and the vessel-to-liver SUVmax was computed for every vessel mentioned above; the highest value of the ratio was representative of the disease. Both the PET vascular activity score and the vessel-to-liver SUVmax were calculated at different time points to compare disease activity.

The response to treatment was assessed by the physician at each visit, by evaluation of the improvement of clinical symptoms and signs of GCA and reduction of inflammatory markers. According to 2018 EULAR recommendations for the management of large vessel vasculitis [7], a patient was defined as being in remission in the case of absence of symptoms and signs of active vasculitis, with normalization of the acute phase reactants (CRP and ESR) and no evidence of progressive vessel narrowing or dilatation. Prolonged remission was defined if persistent for ≥6 months. Relapse was defined as the recurrence of signs or symptoms of GCA and/or worsening of radiological imaging.

TCZ was administered i.v. or s.c. at an initial dose of 8 mg/kg/4 weeks or 162 mg/week, respectively. In patients with good control of the disease, dose reduction was performed. TCZ tapering was determined by the clinician at the time of the visit and prescribed only if the patient fulfilled the definition of prolonged remission. The following tapering regimens were used. For patients treated with i.v. TCZ: from baseline to the 18th month, 8 mg/kg/4 weeks; from the 18th to the 24th month, 6 mg/kg/4 weeks or, alternatively, 8 mg/kg/5 weeks; from the 24th to the 30th month, 6 mg/kg/5 weeks; from the 30th to the 36th month, 4 mg/kg/6 weeks; from the 36th to the 48th month, 4 mg/kg/8 weeks; then discontinuation. For patients treated with s.c. TCZ: from baseline to the 18th month, 162 mg every 7 days; from the 18th to the 24th month, 162 mg every 10 days; from the 24th to the 30th month, 162 mg every 14 days; from the 30th to the 36th month, 162 mg every 18 days; from the 36th to the 48th month, 162 mg every 21 days; then discontinuation. If the disease relapsed during dose tapering or after treatment discontinuation, TCZ was resumed at the standard dose.

Statistical analysis

Data were described as the median (10th–90th percentile). The Mann–Whitney *U* test was used to compare continuous variables, whereas Fisher's exact test was applied for comparison between qualitative variables. Variations between baseline and different time points were evaluated using Wilcoxon's signed rank test. Pearson correlation and linear regression were used to evaluate the association between quantitative variables. Analysis was performed with the GraphPad statistical software package (GraphPad Software, Inc, CA, USA). A *P*-value of ≤0.05 was considered statistically significant.

Results

Baseline characteristics of patients before TCZ

We enrolled 32 patients with GCA and a median age of 74 (59–81) years (Table 1). Twenty-two patients fulfilled the 1990 ACR classification criteria for GCA, whereas 10 patients did not, but in all cases the diagnosis of vasculitis was supported by temporal artery biopsy or by imaging, as suggested in EULAR recommendations [7]. In particular, temporal artery biopsy was performed in 15 patients and was positive in 12 (80%) cases; in two cases, histological examination demostrated vasa vasorum vasculitis [8]. Twenty-six patients, presenting with constitutional or suggestive symptoms for large vessel vasculitis, were studied for extracranial involvement with PET scan, with pathological findings in 24 cases.

Based on vascular involvement, we divided patients into three group: 8 patients with only TA (C-GCA), 12 patients with an extracranial large vessel involvement (LV-GCA) and 12 patients with both cranial and extracranial vasculitis (LV-C-GCA).

Compared with patients who had cranial arteritis only (C-GCA), patients who had large vessel involvement (LV-GCA and LV-C-GCA) more frequently presented

TABLE 1 Main clinical features of patients at diagnosis (**A**) and at commencement of tocilizumab (**B**)

		Total GCA patients (*n* = 32)	LV-GCA patients (*n* = 12)	LV-C-GCA patients (*n* = 12)	C-GCA patients (*n* = 8)	*P*-value
A Sex	Female	25 (78)	10 (83)	9 (75)	6 (75)	0.858
	Male	7 (22)	2 (17)	3 (25)	2 (25)	0.858
Age at diagnosis, years		74 (59–81)	63 (56–81)	74 (67–77)	77 (72–82)	0.053
Time between symptom onset and diagnosis (months)		3 (0–10)	5 (2–23)	3 (0–8)	1 (0–3)	0.101
Clinical manifestations	Fever	11 (34)	6 (50)	5 (42)	0 (0)	0.055
	Fatigue	27 (84)	10 (83)	11 (92)	6 (75)	0.598
	Weight loss	13 (38)	8 (67)	4 (33)	0 (0)	0.009*
	PMR	12 (38)	3 (25)	5 (42)	4 (50)	0.491
	Temporal headache	19 (56)	0 (0)	11 (92)	8 (100)	<0.0001*
	Jaw claudication	9 (75)	0 (0)	5 (42)	4 (50)	0.021*
	Visual symptoms	9 (75)	0 (0)	2 (17)	7 (88)	<0.0001*
	Limb claudication	4 (13)	1 (8)	3 (25)	0 (0)	0.218
	Chest pain	2 (6)	1 (8)	1 (8)	0 (0)	0.701
	Abdominal pain/angina abdominis	2 (6)	2 (17)	0 (0)	0 (0)	0.169
Vascular involvement	Cranial arteries	20 (63)	0 (0)	12 (100)	8 (100)	<0.0001*
	Carotid arteries	14 (44)	7 (58)	7 (58)	0 (0)	0.016*
	Subclavian and upper limb arteries	18 (56)	11 (92)	7 (58)	0 (0)	0.001*
	Thoracic aorta	16 (50)	10 (83)	6 (50)	0 (0)	0.001*
	Abdominal aorta	11 (34)	7 (58)	4 (33)	0 (0)	0.027*
	Iliac and inferior limb arteries	9 (75)	4 (33)	5 (42)	0 (0)	0.112
Acute phase reactants	CRP (mg/l)	100 (15–218)	111 (23–162)	113 (50–263)	31 (12–128)	0.047*
	ESR (mm/h)	70 (31–112)	75 (47–113)	68 (27–118)	49 (17–88)	0.679
B Time between diagnosis and tocilizumab start (months)		6 (1–35)	5 (1–11)	6 (1–41)	7 (2–24)	0.486
Timing of TCZ start	New-onset GCA	18 (56)	6 (50)	7 (58)	5 (63)	0.844
	Longstanding relapsing GCA	14 (44)	6 (50)	5 (42)	3 (37)	0.843
Therapy at TCZ start	GC dose (prednisone mg/day)	25 (13–50)	17 (10–48)	25 (13–49)	50 (30–50)	0.487
	GC dose in new-onset GCA	35 (13–50)	21 (13–50)	31 (20–50)	50 (34–50)	0.072
	GC dose in longstanding relapsing GCA	19 (7–45)	17 (8–28)	18 (8–23)	50 (30–50)	0.190
	Conventional DMARDs	10 (31)	4 (33)	2 (76)	4 (50)	0.284

Data are expressed as the median (10th–90th percentile) or *n* (%). C-GCA: cranial GCA; GC: glucocorticoid; LV-C-GCA: large vessel and cranial giant cell arteritis; LV-GCA: large vessel giant cell arteritis; TCZ: tocilizumab. *: *P* ≤ 0.05.

with constitutional symptoms, such as fever (46 *vs* 0%; $P = 0.029$), fatigue (88 *vs* 76%; $P = 0.557$) and weight loss (50 *vs* 0%; $P = 0.014$) and showed higher levels of CRP [113 (26–222) *vs* 31 (12–128) mg/l; $P = 0.018$] and ESR [71 (40–115) *vs* 49 (17–88) mm/h; $P = 0.467$].

On the contrary, patients with cranial involvement (C-GCA and LV-C-GCA) more often presented with symptoms of polymyalgia rheumatica (45 *vs* 25%; $P = 0.005$), in association with temporal headache ($n = 19$, 95%), jaw claudication ($n = 9$, 45%) and visual manifestations ($n = 9$, 78%; blurred vision or amaurosis fugax $n = 4$; permanent unilateral or bilateral blindness $n = 5$). They also had a shorter time to diagnosis (defined as the time between the onset of symptoms and the diagnosis), if compared with patients having only extracranial vasculitis [1 (0–8) *vs* 5 (2–23) months; $P = 0.002$].

Moreover, patients with only TA were older than patients with LV-C-GCA or LV-GCA at the time of diagnosis [77 (72–82) *vs* 74 (67–77) *vs* 63 (56–81) years, respectively; $P = 0.047$].

Furthermore, by analysing data from FDG-PET/CT scans in patients with large vessel extracranial vasculitis, some differences were found in vascular involvement. Although there was no difference between blood concentrations of inflammatory markers, the FDG uptake in LV-GCA was higher than that in LV-C-GCA patients [vessel-to-liver SUVmax ratio 1.553 (1.353–1.957) *vs* 1.286 (1.202–1.564); $P = 0.019$]. There was also a moderate correlation between the vessel-to-liver SUVmax ratios and CRP levels in GCA patients with large vessel involvement ($R^2 = 0.456$, $P = 0.001$), and this correlation was stronger in LV-C-GCA patients ($R^2 = 0.774$, $P = 0.001$) than in LV-GCA patients ($R^2 = 0.244$, $P = 0.147$; Fig. 1). On the contrary, no correlations between SUVmax ratios and ESR levels or between PET vascular activity score and CRP and/or ESR levels were found.

Two patients had a temporal artery biopsy suggestive of vasa vasorum vasculitis. In the first patient, the diagnosis of GCA was based on a typical clinical presentation, with new-onset temporal headache and blurred vision, and high levels of inflammatory markers. The second patient complained of persistent fever and constitutional symptoms, with large vessel vasculitis on FDG-PET/CT scans and high levels of inflammatory markers. Both patients had no clinical manifestations suggesting a systemic vasculitis other than GCA and were tested for ANA, ANCA, anti-HBV and HCV antibodies, with negative results for all tests [9].

Major co-morbidities at diagnosis were hypertension ($n = 15$, 47%) and type 2 diabetes mellitus ($n = 8$, 25%). Eight patients (25%) were current or former smokers, and four (13%) had a positive QuantiFERON and were treated with antitubercular prophylaxis for latent tuberculosis. The presence of malignancies was ruled out in all the patients.

Outcome of TCZ treatment in GCA

After diagnosis, all 32 patients were treated with glucocorticoids, with an initial median dose of prednisone of 50 (25–63) mg/day. Three patients also received i.v. methylprednisolone pulses for visual impairment at diagnosis.

In 13 cases, TCZ was introduced in long-standing GCA for relapsing disease refractory to previous treatment with glucocorticoids and conventional DMARDs (six with MTX, one with AZA) or glucocorticoids alone ($n = 6$). In these patients, the time between diagnosis and biological therapy was 14 (7–47) months.

In 19 patients, TCZ was started in new-onset GCA, within the first 6 months after the diagnosis. In these cases, the reasons for TCZ introduction included unacceptable glucocorticoid side effects ($n = 3$), contraindications to prolonged high-dose glucocorticoid treatment ($n = 10$) or disease refractory to previous treatment with glucocorticoids ($n = 6$). TCZ was administrated i.v., with an initial dose of 8 mg/kg/4 weeks in 19 patients and s.c. (162 mg/week) in 13.

FIG. 1 Correlation between vessel-to-liver maximum standard uptake value ratio and CRP
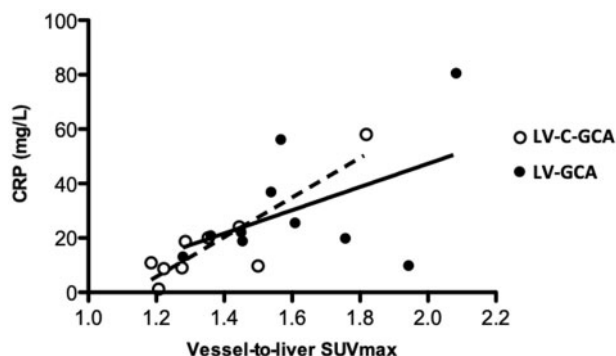
The LV-GCA patients showed a higher vessel-to-liver SUVmax ratio than LV-C-GCA patients, but the correlation with CRP levels was stronger in LV-C-GCA (LV-C-GCA: $R^2 = 0.774$, $P = 0.001$; LV-GCA: $R^2 = 0.244$, $P = 0.147$). LV-C-GCA: large vessel and cranial GCA; LV-GCA: large vessel GCA; SUVmax: maximum standard uptake value.

Twenty-two patients (69%) reported a clinical improvement of GCA symptoms after the first 1 month of treatment and 91% of patients after 3 months. After 6 and 12 months of treatment, 96 and 100% of patients, respectively, were in remission. At the same time, a significant reduction of the acute phase reactants was observed (Table 2).

Similar to the clinical and serological improvement, FDG-PET/CT scans demonstrated a reduction in the uptake. Both the PET vascular activity scores and the vessel-to-liver SUVmax ratios decreased significantly after 6 and 12 months of treatment in comparison to those observed at baseline [PET vascular activity score at 6 months from 19 (9.6–22.6) to 7 (3.2–8), $P = 0.007$; 12 months from 25 (14.5–27) to 8 (3.5–14.5), $P = 0.001$; vessel-to-liver SUVmax ratios at 6 months from 1.612 (1.21–2.02) to 0.86 (0.74–0.94), $P = 0.001$; 12 months from 1.55 (1.4–1.78) to 0.875 (0.78–0.93), $P = 0.007$; Table 3; Fig. 2]. All territories with inflammatory involvement benefited from TCZ therapy, and the higher the SUVmax at baseline FDG-PET/CT, the greater the reduction of the FDG uptake in control ($R^2 = 0.872$; $P < 0.001$). Only one patient continued to present a vessel uptake greater than that in the liver after treatment, albeit reduced from baseline (vessel-to-liver SUVmax ratio from 1.53 to 1.08). In this patient, TCZ tapering was not performed.

TCZ displayed an important steroid-sparing effect: the median prednisone dose at the beginning of treatment was 25 (13–50) mg/day, whereas at the last follow-up it was 5 (3–13) mg/day. Three of seven patients were able to discontinue concomitant therapy with conventional immunosuppressive drugs.

Nineteen patients were treated with TCZ for >1 year, and all of them achieved prolonged remission. In 13 patients, because of good control of the disease, a dose tapering of TCZ was performed. Despite TCZ tapering, 12 patients (92%) maintained a sustained remission. On the contrary, one patient (8%) relapsed during tapering and TCZ was resumed at the standard dose, allowing remission to be achieved again.

Two patients with good control of the disease asked to discontinue TCZ earlier than expected for the tapering regimen, after 18 and 38 months of treatment, respectively. The second patient relapsed after 4 months and was treated with TCZ again.

During the follow-up, another three patients discontinued TCZ permanently: one patient for poor compliance, one for transaminase elevation and one for urinary infection with sepsis. We observed 10 cases of infection, which required temporary discontinuation of TCZ (one pneumonia, one urinary infection, one gastrointestinal infection, one oesophageal candidiasis, one dental abscess, two cutaneous herpes zoster and three cutaneous infections). Most of these infections (8/11, 73%) occurred in the first 6 months of treatment. In patients treated for >1 year there was no increase in the incidence of side effects in comparison to patients treated for <12 months.

Discussion

In our cohort, some interesting clinical differences were found when comparing patients according to vascular involvement. Patients with large vessel extracranial vasculitis were younger, as reported also in previous studies [10, 11], and presented with a longer time to diagnosis, probably as a consequence of their atypical clinical presentation. In fact, LV-GCA patients showed a different pattern of disease manifestations, more often reporting constitutional symptoms, such as fever, fatigue and weight loss, when compared with patients with typical signs and symptoms of TA.

Regarding treatment, in our monocentric cohort, the efficacy of TCZ in GCA was confirmed, and it showed both a rapid short-term effect and a long-term maintained effectiveness. No significant differences were found by comparing different subgroups of patients, based on vascular involvement (LV-GCA vs C-GCA vs C-LV-GCA), disease duration (new diagnosis vs long-standing disease), other concomitant immunosuppressive treatment or TCZ administration route (i.v. vs s.c.).

In the GiACTA trail, the efficacy of TCZ was demonstrated, but several questions remained unanswered. For example, in the randomized controlled trial, TCZ treatment was continued for 52 weeks, allowing to remission to be achieved, but after discontinuation of treatment half of the patients relapsed, leading to the question of how long treatment should be continued. In our cohort, TCZ was not discontinued after 12 months, and in the subsequent follow-up a dose tapering was performed. Only two patients relapsed: one during TCZ tapering and one after TCZ discontinuation. Therefore, long-term treatment appeared to prevent disease relapses, suggesting that TCZ treatment for >52 weeks should be considered. This suggestion is relevant especially for GCA patients with large vessel involvement. In fact, as shown by Muratore et al. [10], LV-GCA patients usually need longer GC treatment and relapse more frequently and earlier if compared with C-GCA. This could be the consequence of a delayed diagnosis or of a more extended disease or could be attributable to a different phenotype of disease. In our cohort, at commencement of TCZ, half of the LV-GCA patients presented a longstanding relapsing disease, refractory to GC or conventional DMARDs. All these patients improved after TCZ treatment, achieving clinical remission. However, in three cases TCZ tapering was not possible. These patients seemed to present with a chronic disease, in which disease activity was controlled by TCZ but not completely cured. This hypothesis leads to the suggestion that in this subgroup of patients TCZ could not suspended but only reach the minimal effective dose to maintain remission.

In our cohort, the good safety profile of TCZ was confirmed. In fact, most of the observed infections occurred in the first 6 months of treatment, when patients were still being treated with a medium dose of prednisone [11

TABLE 2 Main clinical and laboratory features of patients at baseline and during treatment

Parameter	Baseline n = 32	Month 1 n = 32	Month 3 n = 32	Month 6 n = 25	Month 12 n = 19	Month 24 n = 11	Month 36 n = 6	Month 48 n = 4	Month 60 n = 3
Clinical improvement, n (%)	–	22 (69)	29 (91)	24 (96)	19 (100)	11 (100)	6 (100)	3 (75)	3 (100)
Prolonged remission[a], n (%)	–	–	–	22 (88)	19 (100)	11 (100)	6 (100)	3 (75)	3 (100)
Prednisone dose (mg/day)	25 (13–50)	25 (10–43)	13 (7–22)	10 (5–13)	6 (4–9)	4 (2–7)	2 (1–5)	5 (2–9)	3 (1–5)
Serum CRP (mg/l)	18 (9–56)	0 (0–0)*	0 (0–0)*	0 (0–0)*	0 (0–0)*	0 (0–0)*	0 (0–0)*	0 (0–0)*	0 (0–0)*
Serum ESR (mm/h)	23 (15–48)	3 (1–6)*	2 (1–3)*	2 (1–6)*	3 (2–6)*	6 (5–7)	2 (2–11)	2 (2–15)	2 (2–3)
White blood cell count (cells/mm3)	9360 (6726–12 340)	8625 (4790–11 450)*	7400 (5508–9482)*	7250 (4462–10 220)*	6725 (5351–8687)*	6340 (5000–7950)*	7085 (6355–8918)	5955 (4393–7538)*	5500 (4640–5580)*
Platelet count (×103 cells/mm3)	303 (206–482)	225 (163–304)*	222 (156–292)*	212 (162–274)*	199 (165–271)*	180 (153–268)*	221 (191–253)*	197 (161–223)*	193 (184–195)*
Haemoglobin concentration (g/dl)	12.4 (10.0–14.0)	12.6 (10.9–14.7)*	13.2 (11.0–14.9)*	13.2 (10.9–14.5)*	13.3 (10.5–14.9)*	13.5 (11.3–14.7)	11.7 (11.3–12.9)	12.2 (11.9–12.9)	12.7 (11.9–13.9)

Data are expressed as the median (10th–90th percentile) or n (%). [a]Prolonged remission is defined as the absence of signs and symptoms, with normalization of the acute phase reactants and improvement at radiological imaging for ≥6 months. *$P \leq 0.05$ *vs* baseline.

TABLE 3 Vessel-to-liver maximum standardized uptake value ratios and PET vascular activity score at baseline and after 6 and 12 months of toclizumab therapy

Parameter	Baseline		Month 6 (*n* = 5)	Month 12 (*n* = 6)
	LV patients (*n* = 10)	LV-C patients (*n* = 9)		
Vessel-to-liver SUVmax ratio				
Right carotid arteries	0.99 (0.42–1–22)	1.06 (0.88–1.52)	0.65 (0.55–0.75)	0.79 (0.65–0.96)
Left carotid arteries	0.88 (0.52–1.33)	0.85 (0.81–1.43)	0.65 (0.56–0.73)	0.76 (0.61–0.93)
Right subclavian arteries	1.10 (0.34–1.51)	1.04 (0.96–1.28)	0.71 (0.55–0.82)	0.72 (0.55–0.95)
Left subclavian arteries	0.86 (0.29–1.46)	0.89 (0.72–1.14)	0.60 (0.47–0.71)	0.56 (0.43–0.71)
Innominate arteries	0.89 (0.32–1.54)	0.93 (0.54–1.20)	0.68 (0.49–0.86)	0.88 (0.77–1.00)
Ascending aorta	1.10 (0.58–1.57)	1.19 (0.92–1.37)	0.85 (0.78–0.93)	0.79 (0.59–0.99)
Aortic arch	1.08 (0.59–1.54)	1.21 (0.92–1.34)	0.85 (0.79–0.91)	0.83 (0.71–0.97)
Thoracic descending aorta	1.21 (0.59–1.38)	1.28 (1.13–1.41)	0.75 (0.63–0.84)	0.65 (0.40–0.84)
Abdominal aorta	1.21 (0.99–1.78)	1.21 (1.01–1.82)	0.82 (0.73–0.87)	0.89 (0.81–0.98)
PET vascular activity score	20 (10.3–26.2)	22 (14.8–27.0)	7 (3.2–8.0)	8 (3.5–1.5)

Fluorodeoxyglucose (FDG)-PET/CT was performed in patients after ≥6 h fasting with glucose concentration <150 mg/dl. An activity of 3.5–4.5 MBq/kg of ^{18}F-FDG was administered i.v.; images were acquired 60 min after radiopharmaceutical injection from the apex to the mid-thigh on a Discovery 690 PET/CT tomograph (General Electric Company, GE, Milwaukee, WI, USA) with standard parameters (CT: 80 mA, 120 kV; PET: 2.5–4 min per bed position, PET step of 15 cm); the reconstruction was performed in a 256 × 256 matrix and 60 cm field of view. To calculate the PET vascular activity score, the degree of FDG uptake in the nine above-mentioned arterial territories was assessed visually relative to liver uptake (0 = no uptake; 1 = less than liver uptake; 2 = same as liver uptake; 3 = greater than liver uptake). The PET vascular activity score was finally calculated by summing the qualitative scores from each arterial territory, with scores from 0 to 27. The maximum standardized uptake value (SUVmax) and vessel-to-liver SUVmax ratio were measured for four segments of aorta (ascending, arch, descending and abdominal) and five branch arteries (innominate, carotids and subclavians). The maximum standardized uptake value (SUV) of vessel walls was measured by drawing a region of interest over the area of maximum activity and the SUVmax was calculated as the highest SUV of the pixels within the region of interest; furthermore, the SUVmax of the liver was calculated at the VIII hepatic segment of transaxial PET images using a circular 10 mm region of interest. For every artery analysed, the vessel-to-liver SUVmax ratio was calculated.

(6–22) mg/day], whereas in patients treated for >1 year there was no increase in the incidence of infections.

Another issue concerning TCZ in GCA is the difficulty of monitoring disease activity. As a consequence of the limited reliability of acute phase reactants, follow-up is largely symptom-based, making disease activity monitoring uneasy.

It is known that, owing to its high sensitivity (87–90%) and specificity (73–98%), FDG-PET/CT is widely used for diagnosis of large vessel involvement in GCA [6, 12, 13], but its use in the follow-up of treated patients is still a matter of debate. Different scores can be used to quantify disease activity by FDG-PET/CT, but the most validated scores are the vessel-to-liver SUVmax ratio [14], a visual continuous score, and the PET vascular activity score, a qualitative summary score [6]. In our cohort, both scores were demonstrated to be able to describe vascular inflammation, although only the vessel-to-liver SUVmax ratio showed a significant correlation with CRP values [15, 16]. Moreover, in patients with large vessel involvement without cranial symptoms, we measured higher values of SUVmax ratio than in patients with cranial and large vessel involvement, suggesting a higher degree of inflammation. One possible explanation of this difference is a longer time to diagnosis in LV-GCA patients, owing to less severe symptoms at disease onset, which can delay the first medical examination and the diagnosis.

Furthermore, in our case series, both SUVmax ratios and PET vascular activity scores decreased significantly in all control FDG-PET/CT scans, according to clinical and humoral disease remission, indicating a reduction in vessel inflammation, similar to what was seen by Salvarani *et al.* [17]. The reduction of FDG uptake was observed at both 6 and 12 months after starting TCZ treatment, suggesting that the effectiveness of TCZ could be evaluated early with FDG-PET/CT and remained stable during the following period.

The main limits of the present study are the small number of patients enrolled and the retrospective design. On the contrary, the monocentric design of the study accounts for limited variability in the management of patients, because all patients were followed in our Vasculitis Clinic with the same tight-control strategy. Moreover, in the majority of our LV-GCA and LV-C-GCA patients, clinical remission was confirmed by FDG-PET/CT, whereas in previous case series of GCA patients treated with TCZ radiological data were not commonly provided.

The results of our study should be confirmed by new randomized controlled trials or by prospective studies in order to support the use of prolonged TCZ treatment in

Fɪɢ. 2 Reduction of vessel-to-liver SUVmax ratio (**A**) and PET vascular activity score (**B**) after 6 (T6) and 12 months (T12) of TCZ therapy
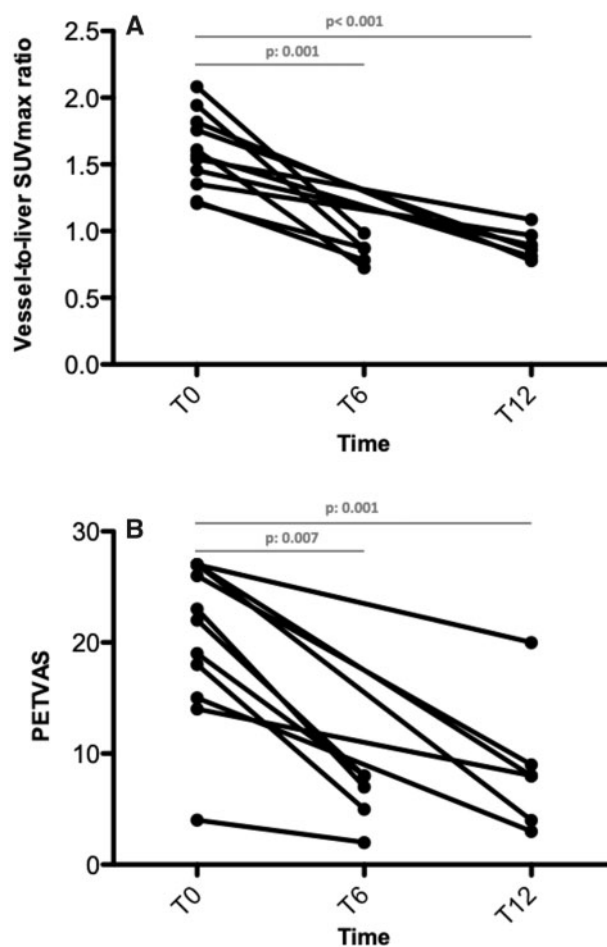
GCA patients, along with the capability of FDG-PET/CT for monitoring disease activity and predicting relapse.

In our monocentric cohort of patients, the efficacy of TCZ in the induction and maintenance of remission of GCA was confirmed, regardless of the type of vascular involvement, disease duration or route of administration. TCZ also demonstrated an important steroid-sparing effect and a good safety profile. Moreover, long-term treatment with this drug appeared to prevent relapse of GCA, suggesting that TCZ treatment for >52 weeks should be considered.

Finally, in our case series FDG-PET/CT scanning was demonstrated to be useful to study GCA patients at diagnosis and in the follow-up of patients treated with immunosuppressive drugs.

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