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Tocilizumab in Giant Cell Arteritis: A Real-Life Retrospective Study

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Abstract

This study aims to evaluate (1) the efficacy and safety of tocilizumab (TCZ) as a steroid-sparing agent in patients with giant cell arteritis (GCA) and (2) the usefulness of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the follow-up and to detect disease activity. We retrospectively evaluated 12 patients with GCA treated with TCZ (8 mg/kg/mo). Pre- and posttherapy data about clinical signs and symptoms, laboratory results, FDG-PET imaging study, and the mean glucocorticoid (GC) dose were used to assess disease activity. Tocilizumab achieved complete disease remission in all patients. Mean FDG-PET-detected standard uptake value decreased from 2.05 $\pm$ 0.64 to 1.78 $\pm$ 0.45 ($P = .005$). In 2 patients in whom temporal arteries color Doppler sonography examination was consistent with temporal arteritis, the hypoechoic halo disappeared after TCZ treatment. Mean GC dose was tapered from 26.6 $\pm$ 13.4 mg/d to 3.3 $\pm$ 3.1 mg/d ($P < .0001$). One-half of the patients discontinued GC therapy. Three patients experienced severe adverse reactions and had to stop TCZ therapy. In accordance with previous reports, TCZ is an effective steroid-sparing agent for GCA, although careful monitoring of adverse drug reactions is needed. ^{18}F-fluorodeoxyglucose positron emission tomography could be used to monitor disease activity in TCZ-treated patients, but prospective studies are needed to confirm these data.

Keywords

giant cell arteritis, temporal arteritis, systemic vasculitis, biologics, positron emission tomography, tocilizumab

Introduction

Giant cell arteritis (GCA) involves the aorta and its major branches with predilection for the extracranial branches of the carotid arteries.[1] Large-vessel involvement (LVI) has been demonstrated in one-half to two-thirds of patients with GCA by ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG-PET).[2] Glucocorticoids (GCs) are the treatment of choice, albeit GC-related adverse events, such as diabetes mellitus, osteoporosis with bone fractures, and infections, are common.[3] Methotrexate (MTX) might be a useful steroid-sparing agent in patients at high risk of side effects[3] and seems to lower the risk of relapse.[4] Anti-TNF-α monoclonal antibodies have shown no clear benefits.[5] Tocilizumab (TCZ) is a humanized immunoglobulin G1 κ monoclonal antibody that binds to the α chain of the interleukin 6 (IL-6) receptor.[6] Tocilizumab has been approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Interleukin 6 has a central role in the pathogenesis of GCA, and several case studies, a phase II trial, and a phase III trial with TCZ have recently shown induction and maintenance of remission in patients with GCA.[7-16]

We conducted a retrospective real-life study in patients with GCA to evaluate (1) the efficacy and safety of TCZ as a steroid-sparing agent in patients with relapsing FDG-PET-detected large-vessel vasculitis (LVV) as well as in patients in which comorbidities prevented the use of corticosteroids and (2) the usefulness of FDG-PET to confirm clinical and laboratory evident disease remission.

Materials and Methods

Study Design

This is an observational, retrospective real-life case series of patients with GCA with FDG-PET-detected LVI who failed to

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achieve control of the disease either with GCs or GCs plus MTX and/or with contraindications to the use of steroids. Because of the observational, retrospective design of the study and the anonymization of information, approval from the local ethics committee was not required.

Study Definitions

The patients included in our study (1) had to be older than 50 years and had received a diagnosis of GCA according to the 1990 American College of Rheumatology criteria,[17] confirmed by a positive temporal artery biopsy (2 patients) and/or a temporal arteries color Doppler sonography (TA-CDS) that demonstrated the presence of a hypoechoic halo $\geq$1 mm thick in at least one of the main branches (all patients); (2) presented an LVI secondary to GCA detected by FDG-PET at the time of diagnosis or before TCZ therapy was started; (3) had to be clinically and humorally active before TCZ therapy was started,;(4) were evaluated free from hepatitis B, hepatitis C, and human immunodeficiency virus infection, latent tuberculosis, and malignancy before the use of any biologic therapy; and (5) signed a written informed consent to start an off-label TCZ therapy. The reasons for TCZ introduction were (1) unacceptable GC side effects, (2) relapse after GC tapering, and/or (3) comorbidities that interfere with GC treatment (patient 11). In patients who relapsed during GC tapering, GC dose was not augmented prior to starting biologic therapy.

Large-vessel involvement secondary to GCA was defined by the presence of large-vessel ^{18}F-FDG uptake consistent with vasculitis on FDG-PET and not attributed to atherosclerotic changes or fibromuscular dysplasia. ^{18}F-fluorodeoxyglucose positron-emission tomography assessment was repeated in all patients after a mean of 11.6 (8.8) months (range: 3-24 months) since the initiation of TCZ therapy. One hour before imaging, a weight-related dose of ^{18}F-FDG was injected intravenously (3.7 MBq/kg). Whole-body images were obtained using an FDG-PET Gemini time of flight (Philips, Milano, Italy). Whole-body emission imaging was performed in 3-D mode with an acquisition time of 2 minutes per bed position starting at 60 (5) minutes after injection of ^{18}F-FDG. Prior to emission imaging, a low-dose computed tomography (CT) scan (29 mA·s, 120 kV, 5 mm slice thickness) for attenuation correction of the PET results was done. Positron emission tomography scans were reviewed by a nuclear specialist, and the standardized uptake value (SUVmax, SUVmean) was extracted in several vascular regions (thoracic aorta, abdominal aorta, subclavian left and right, carotid left and right, iliac left and right, and femoral left and right arteries) on coronal 2-D tomographic images by mean standard software package of PET-CT Gemini (Philips). For each vessel, a rectangular region-of-interest well-fitting vessel shape involving the wall and lumen of the artery was drawn: Therefore, SUVmax represented pathologic hypermetabolism of inflammation-involved walls and SUVmean represented mean blood component for each vessel.[18] The SUVmax was chosen as semiquantitative measure of LVI. Therefore, a mean value (standard deviation [SD]) could be calculated.

Clinical activity was assessed by the presence of headache, jaw claudication, scalp tenderness, fever (defined as axillary temperature $\geq$37.5°C), constitutional symptoms (asthenia, anorexia, weight loss >5% of the normal body weight during the last 6 months), polymyalgia rheumatica (PMR), and/or any visual symptoms.

Humoral activity was based on erythrocyte sedimentation rate (ESR) of $\geq$40 mm in the first hour, C-reactive protein (CRP) level of $\geq$0.5 mg/dL, and fibrinogen level of $\geq$440 mg/dL. White blood cell, red blood cell, and platelet count; liver and renal function; and any adverse drug reaction were carefully monitored every month in all patients. All patients were treated with intravenous TCZ 8 mg/kg/mo.

Data Collection

A database was created to include all patients assessed from January 2014 to October 2016. Demographic data, features of the disease at onset, reasons for TCZ introduction, duration of patient follow-up, pre-TCZ and post-TCZ clinical and laboratory findings, pre-TCZ and post-TCZ FDG-PET evaluation, pre-TCZ and post-TCZ GC dose, and pre-TCZ and post-TCZ use of MTX as a steroid-sparing agent were registered. Response to therapy was evaluated by clinical assessment, laboratory findings (ESR, CRP, and fibrinogen), and FDG-PET, as previously defined. In 2 patients, response to therapy was also evaluated by TA-CDS.

Statistical Analysis

Data were compared by Student t test for continuous variables. Statistical analysis was carried out using IBM SPSS Statistics version 24.0. Results were expressed as mean (standard deviation [SD]).

Results

A total of 12 patients (8 women, mean age at diagnosis 68.6 [8.5]) were included. Demographic, clinical, laboratory, and treatment data before TCZ treatment are shown in Tables 1 and 2. The average patient follow-up after TCZ therapy onset was 16.2 (12.1) months (range: 4-35 months).

Tocilizumab treatment was associated with a dramatic clinical improvement in all patients, with a complete remission of the symptoms within 1 to 3 months after the onset of therapy, along with the complete normalization of ESR, CRP, and fibrinogen level in all cases. As shown in Figure 1, FDG-PET demonstrated a statistically significant reduction in the SUV (pre-TCZ: 2.05 [0.64], post-TCZ: 1.78 [0.45]; $P = .005$). In particular, all territories involved by the vasculitic process benefited from TCZ therapy.

All patients were able to taper the GC dose (pre-TCZ: 26.6 [13.4] mg/d, post-TCZ: 3.3 [3.1] mg/d; $P < .0001$). In addition, 4 patients were able to discontinue corticosteroids. Three patients discontinued MTX therapy without stopping

Table 1. Demographic and Pre- and Post-TCZ Data Regarding Glucocorticoids and Methotrexate Usage, TA-CDS Examination, and FDG-PET Mean SUV.

Variable	Pre-TCZ	Post-TCZ	*P* Value
Age at diagnosis, mean (SD), years	68.6 (8.5)		
Female, n (%)	8 (67)		
Symptoms, n (%)			
Headache	10 (83)	0 (0)	
Jaw claudication	5 (42)	0 (0)	
Scalp tenderness	5 (42)	0 (0)	
Any visual manifestation	2 (17)	0 (0)	
PMR	3 (25)	0 (0)	
Systemic symptoms	7 (58)	0 (0)	
Comorbidities, n (%)			
Hypertension	4 (33)		
Diabetes mellitus	4 (33)		
Dyslipidemia	2 (17)		
Stroke	2 (17)		
Laboratory, n (%)			
Increased ESR	12 (100)	0 (0)	
Increased CRP	12 (100)	0 (0)	
Increased fibrinogen	12 (100)	0 (0)	
Prednisone use after LVV diagnosis, n (%)	12/12 (100%)	6/10 (60%)	
Prednisone dose, mean (SD), mg	26.6 (13.4)	3.3 (3.1)	.0001
MTX use, n (%)	7/12 (58.3%)	4/10 (40%)	
FDG-PET-detected LVV, n (%)	12 (100)	0 (0)	
Mean SUV (SD)	2.05 (0.64)	1.78 (0.45)	.005
TA-CDS-detected temporal arteritis, n/n (%)	2/2 (100)	0/2 (0)	

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; LVV, large-vessel vasculitis; MTX, methotrexate; PMR, polymyalgia rheumatica; SD, standard deviation; SUV, standardized uptake value; TA-CDS, temporal arteries color Doppler sonography; TCZ, tocilizumab.

GC therapy. Data are summarized in Table 1. In the 2 cases in whom TA-CDS examination had results consistent with temporal arteritis, the hypoechoic halo disappeared after TCZ treatment.

Nine of 12 patients were still receiving TCZ treatment at the end of the study. Three patients had to discontinue TCZ due to side effects possibly related to the treatment. One patient had infectious pneumonia after the fourth infusion which resolved after empirical oral antibiotic therapy, 1 patient experienced a cutaneous fistula after 19 infusions treated with surgical excision, and 1 patient presented thrombocytopenia (80×10^9/L platelets) and hypofibrinogenemia (93 mg/dL) which resolved promptly after TCZ discontinuation.

Discussion

Giant cell arteritis often requires long-term GC therapy, and only a subgroup of patients with limited and less frequently relapsing disease requires a treatment of shorter duration.[19] Prolonged GC therapy is associated with serious adverse events, and therefore, a steroid-sparing agent is needed in patients with several relapses or with comorbidities that prevent the use of GC.[3,7] In our case series, all patients had a positive clinical response to TCZ and disease remission was achieved in 1 to 3 months after therapy onset. Indeed, TCZ helped to significantly reduce GC therapy in all patients and allowed half of them to suspend GCs. In our experience, TCZ was an effective steroid-sparing agent. These results are in keeping with those of the literature.[7-16] In particular, the first phase 2, randomized, double-blind, placebo-controlled trial demonstrated TCZ effectiveness in inducing and maintaining remission in patients with GCA, with a cumulative reduction in GC dose.[7] Phase 3 Giant Cell Arteritis Actemra (GiACTA) trial study broadly confirmed these data.[16]

In the GiACTA trial,[16] 1 patient who had been assigned to receive subcutaneous TCZ every other week at the dosage of 162 mg developed anterior ischemic optic neuropathy (AION) in the context of a disease flare. The visual impairment resolved with GC treatment. The authors concluded that it is important to maintain vigilance for vision complications even in patients receiving active therapy. In our cohort, 2 patients presented visual manifestations before TCZ therapy was started. Patient 5 was an 85-year-old lady affected by PMR since 2012, who developed fatigue, weight loss, temporal headache with jaw claudication, and unilateral visual loss in December 2013. A TA-CDS results consistent with temporal arteritis and the FDG-PET demonstrated moderate hyperfixation in the large vessels (aorta and subclavian arteries). Intravenous methylprednisolone 1000 mg was administered for 3 days and then shifted to oral prednisone 1 mg/kg every day. The disease was considered not fully controlled after 3 months of GC therapy at a dosage of 37.5 mg, and therefore, TCZ treatment was considered.

Patient 10 was an 86-year-old lady with a long-lasting history of PMR and a diagnosis of biopsy-proven GCA since 2009 treated with oral GC prednisone 10 mg every day, who developed progressive bilateral visual loss despite GC therapy. Adjunctive MTX (15 mg/wk) was suspended after 3 months due to liver toxicity. Because of incessant headache, PMR, and constitutional symptoms along with persistent FDG-PET positivity, TCZ was introduced.

The efficacy of TCZ in a patient with corticosteroid-resistant visual symptoms has been recently described and the authors claimed the possibility of adjunctive TCZ treatment in corticosteroid-resistant AION to prevent bilateral blindness.[20] In the 2 cases of our cohort with visual symptoms, TCZ had no documented influence likely because of the too late introduction to therapy.

Our study confirms that clinical remission is accompanied by the normalization of ESR, CRP, and fibrinogen. However, it is known that this reduction is related to a direct effect of IL-6 receptor blockade. Therefore, the humoral inflammation parameters are not reliable,[7] and even though the disease activity should be determined on clinical grounds only, there is no clinical score to define the disease as "active." In addition to this, Unizony et al[9] described persistent LVV at autopsy of a TCZ-treated patient who had shown clinical remission and

Table 2. Main Features in 12 Patients With GCA at the Time of Tocilizumab Onset and Outcome at Last Follow-Up.

Patient	Sex/Age at GCA Diagnosis	Time From Diagnosis to TCZ Onset (years)	Clinical Features at TCZ Onset	Biopsy-proven/ TA-CDS-proven GCA	Previous MTX	Prednisone Dose at TCZ Onset (mg/d)	Prednisone Dose at Last Visit (md/d)	Abnormal ESR/CRP/ Fibrinogen at TCZ Onset	Abnormal ESR/CRP/ Fibrinogen at Last Visit	Follow-Up With TCZ (months)	Clinical Outcome at Last Visit	Adverse Drug Reactions
1	F/65	5	Headache	No/Yes	Yes	20	0	Yes/Yes/Yes	No/No/No	26	Clinical Remission	
2	M/68	2	Headache, constitutional symptoms	No/Yes	No	37.5	6.25	Yes/Yes/Yes	No/No/No	19	Clinical remission	Cutaneous fistula
3	F/80	1	Headache, PMR	No/Yes	Yes	20	ND	Yes/Yes/Yes	No/No/No	4	Clinical remission	Infectious pneumonia
4	M/62	4	Headache, PMR	No/Yes	Yes	10	5	Yes/Yes/Yes	No/No/No	7	Clinical remission	
5	F/82	1	Headache, jaw claudication, scalp tenderness, fever, constitutional symptoms	No/Yes	No	37.5	0	Yes/Yes/Yes	No/No/No	27	Clinical remission	
6	F/62	3	Headache	No/Yes	Yes	12	0	Yes/Yes/Yes	No/No/No	24	Clinical remission	
7	F/65	4	Headache, jaw claudication, scalp tenderness, fever, constitutional symptoms	Yes/Yes	No	37.5	6.25	Yes/Yes/Yes	No/No/No	8	Clinical remission	
8	F/53	9	Headache, constitutional symptoms, PMR	No/Yes	No	50	5	Yes/Yes/Yes	No/No/No	3	Clinical remission	
9	M/74	1	Fever, constitutional symptoms	No/Yes	Yes	20	ND	Yes/Yes/Yes	No/No/No	32	Clinical remission	Low platelet count plus hypofibrinogenemia
10	F/78	5	Headache, jaw claudication, scalp tenderness, constitutional symptoms	Yes/Yes	Yes	10	2.5	Yes/Yes/Yes	No/No/No	35	Clinical Remission	
11	M/67	0	Headache, jaw claudication, scalp tenderness, fever, constitutional symptoms	No/Yes	No	25	0	Yes/Yes/Yes	No/No/No	6	Clinical remission	
12	F/67	1	Headache, jaw claudication, scalp tenderness	No/Yes	Yes	40	8	Yes/Yes/Yes	No/No/No	4	Clinical remission	

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; GCA, giant cell arteritis; M, male; MTX, methotrexate; PMR, polymyalgia rheumatica; TCZ, tocilizumab; TA-CDS, temporal arteries color Doppler sonography.

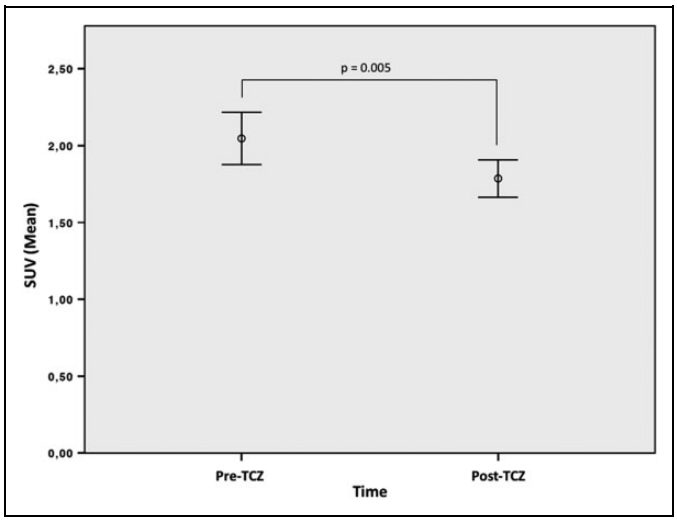

Figure 1. The reduction in the overall SUV after therapy with tocilizumab, which indicates a significant reduction in the FDG-PET-detected vessel wall inflammation. FDG-PET indicates ^{18}F-fluorodeoxyglucose positron emission tomography; SUV, standard uptake value.

decrease in acute phase indices. For all these reasons, not only could humoral remission not be considered reliable in these patients, but even a complete clinical remission could hide a low-grade but persistent vessel wall inflammation.[21] In this regard, imaging techniques, such as FDG-PET and TA-CDS, can be employed in the evaluation and management of patients with LVV.[22] Indeed, it has been recently demonstrated that ^{18}F-FDG uptake by large vessels has a high sensitivity and specificity for the diagnosis of GCA.[23] Taken together, these data suggest that FDG-PET assessment could be a reliable tool to assess vessel inflammation in patients with GCA treated with TCZ. In our case series, a statistically significant reduction in the SUV score was observed, suggesting a reduction in vessel inflammation. In a smaller case series (n = 4) published by Salvarani et al,[15] FDG-PET findings significantly improved in all patients, in agreement with clinical and humoral disease remission. Despite the aforementioned evidence, the role of FDG-PET for the follow-up of patients with LVV is still not clear. A prospective 6-month study[24] showed that ^{18}F-FDG uptake drops after the first 3 months of therapy but remained stable during the following period. It is unknown whether this could be related to smoldering vasculitis or to tissue repair and remodeling phenomena. In addition, FDG-PET is not considered a reliable instrument in predicting which patients will relapse or not.[24] However, all these studies were conducted under medium to high-dose steroid treatment, with the consequence that vascular uptake could be hardly altered.[25] In contrast, our patients were under low-dose GC, and reduction in the ^{18}F-FDG uptake was statistically significant, thus suggesting that although our case series is limited, FDG-PET could be useful to monitor therapy efficacy in TCZ-treated patients.

Patients with GCA with LVI have an increased mortality rate in comparison with those without.[2] This is due to an increased risk of developing thoracic and abdominal aneurysms or aortic dissection independently of the presence of aneurysms.[26] Two retrospective studies assessed the rate of aneurysms in patients with GCA with FDG-PET-detected LVI. Positive FDG-PET was significantly associated with a larger diameter of the ascending and descending aorta[27] and a higher risk of aortic complications,[28] indicating a possible role for FDG-PET in predicting vascular complications in this group of patients.[25] Of note, despite that almost the totality of our patients exhibited ascending aortic and, to a lesser extent, descending aortic dilatation, none of them developed any vascular complication during the follow-up.

Although performed only in 2 patients, the disappearance of the hypoechoic halo in TCZ-treated patients seems to suggest that TA-CDS evaluation might represent an easier tool to monitor amelioration of the inflammation of the vascular wall. Therefore, ultrasound examination will be evaluated as an outcome parameter in the sirukumab in Giant Cell Arteritis trial (NCT02531633).

The type and frequency of TCZ side effects have been well characterized by large clinical studies of rheumatoid arthritis and by multinational patient registries. In our study, TCZ was well tolerated in 9 of 12 patients, while 3 patients experienced serious adverse drug reactions. In particular, reversible hypofibrinogenemia associated with low platelet count was observed in 1 patient after the third TCZ infusion. Decline in platelet count classified as Common Toxicity Criteria grade 1 is a predictable side effect when using TCZ.[2] Indeed, IL-6 stimulates thrombopoiesis, and consequently, the binding of TCZ to IL-6 receptor decreases platelet production.[3] Although hypofibrinogenemia does not seem to be related to an increased hemorrhagic risk, the drug was in any case suspended due to low platelet count.[29] Concerning the risk of infections, whether this can be attributed to the biological agent or to the combination of TCZ and GCs remains unknown.[7]

The main strength of our study is that all patients underwent FDG-PET after TCZ therapy to confirm the clinical and humoral remission of the disease, suggesting that this imaging technique could be used to achieve a more comprehensive follow-up of these patients. Another strength is the long observation time of these patients.

On the other hand, limitations of our study are the retrospective design and the small sample size. Moreover, the post-TCZ FDG-PET was repeated in all patients but in a wide range interval of time after therapy onset. For this reason, a prospective study should be designed to assess the actual trend of ^{18}F-FDG uptake in patients treated with TCZ.

In conclusion, this study reports that FDG-PET may be a useful tool in defining large-vessel inflammation in TCZ-treated patients, but additional data from prospective studies are needed to better evaluate the correct timing for FDG-PET throughout the follow-up. Moreover, this case series confirms, as seen in previous reports, that TCZ is a valuable steroid-sparing agent for the treatment of GCA. Placebo-controlled studies with longer follow-up and larger numbers of patients could confirm the long-term efficacy and safety profile of TCZ in patients with GCA.

Authors' Note

All authors had substantial contributions to (1) conception and design, acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published. Gianfranco Vitiello and Carolina Orsi Battaglini equally contributed to this work.

Declaration of Conflicting Interests

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