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Safety and Efficacy of Long-Term Tocilizumab in a Cohort of Patients with Giant Cell Arteritis: An Italian Monocentric Retrospective Study

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Objective: Tocilizumab (TCZ) is the only biologic drug approved for the treatment of giant cell arteritis (GCA), having clinical trials and real-life studies proved its efficacy and safety. However, the optimal duration of the treatment has yet to be determined, being its early interruption associated with an increased risk of relapse. Conversely, prolonged schemes of therapy may rise safety concerns. The aim of the study was to evaluate the incidence of adverse events (AEs) and remission/relapse rate in a cohort of GCA patients treated with TCZ and an accelerated steroid tapering scheme, followed for 24 months.

Methods: We retrospectively included patients referring to our clinic from January 2019 to November 2021 who were diagnosed with GCA and started subcutaneous TCZ treatment (162 mg/week). They also received up to 62,5 mg of prednisone (PDN), tapered following an accelerated six-month scheme.

Results: We collected 38 patients, with a mean age of 76,4 years, treated with TCZ for an average of 22,3 months. AEs occurred in 11 (29%) subjects, and only one serious AE was reported; 7 (18%) patients permanently discontinued TCZ. At the end of the follow-up, all the patients continuing treatment showed clinical remission, with a PDN dosage <5mg. We registered 3 (8%) minor relapses under TCZ, after an average of 15 months.

Conclusion: Our data support the evidence of a safe and effective long-term use of TCZ in GCA patients, especially when combined with moderate GCs doses for the shortest possible duration.

Keywords: giant cell arteritis, vasculitis, tocilizumab, biological therapy, safety

Introduction

Giant cell arteritis (GCA) is the most common type of large vessel vasculitis (LVV) and overall, the most prevalent vasculitis in Western countries, with a peak incidence in individuals aged between 70 and 80 years old.[1] It is typically characterized by the inflammatory involvement of temporal artery and its branches and/or extra-cranial large vessels (common carotid, axillary arteries, subclavian arteries, ascending aorta etc.…) with frequently associated constitutional symptoms (fever, anorexia, malaise, myalgia) and a high risk of disabling and fatal complications (loss of vision, stroke, aneurysm formation and rupture, aortic dissection) which requires a timely and adequate therapeutic intervention.[2]

Traditionally, systemic glucocorticoids (GCs) (orally administered or as intravenous boluses) have been referred to as the gold-standard treatment for this disease, being able to induce a rapid and complete remission of symptoms in most patients.[3] However, a high rate of relapse has been associated with their tapering or discontinuation,[4,5] as well as a burden of adverse events related to their cumulative dosage over time.[5,6]

Therefore, several conventional synthetic disease-modifying anti-rheumatic drugs (cDMARDs) and biological DMARDs have been investigated as GCs sparing agents and background therapy in GCA, though until now only Tocilizumab (TCZ), an interleukin-6 receptor antagonist, has been approved by FDA and EMA for the treatment of this disease and has been

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recommended to be started in association with GCs (rather than initiating GCs alone) in patients with newly diagnosed GCA by the 2021 American College of Rheumatology (ACR) guidelines on the management of GCA.[7] Indeed, TCZ proved its efficacy and safety in two randomized, double-blind, placebo-controlled trials in which its administration reduced the total number of relapses and the cumulative dose of GCs compared to GCs alone without increasing serious adverse events (SAEs) in both newly diagnosed and refractory/relapsing GCA.[8,9] In addition, subsequent recent real-life observational studies confirmed those promising results.[10–12]

Nevertheless, the optimal duration of TCZ treatment has yet to be determined, and GCs discontinuation might not be easy to achieve in patients on TCZ; not least, an extension of the treatment with TCZ could rise the concern of increased AEs over time. The data available so far show that discontinuation of TCZ after up to one year of treatment in patients in sustained remission is frequently followed by relapse.[13–15] However, Goercke et al demonstrated that TCZ optimization (by progressively reducing the TCZ dose and/or by increasing the TCZ dosing interval) can represent a successful strategy in the management of long-term TCZ treatment.[16] Eventually, the currently ongoing METEORITICS trial is investigating the efficacy and safety of methotrexate (MTX) in maintaining remission in patients with GCA who have previously been treated with GC and TCZ.[17] Overall, the extension of TCZ treatment did not seem to significantly increase the risk of AEs.[18]

To broaden the current evidence, which remains substantially scarce and sometimes conflicting, we aimed to assess the efficacy and safety of a treatment scheme characterized by the prolonged administration of TCZ and an accelerated steroid withdrawal schedule.

Materials and Methods

Patients

We retrospectively included all the patients followed by our "Vasculitis Clinic" (pertaining to the Rheumatology Department of Siena University Hospital) who were diagnosed with GCA from January 2019 to November 2021 and treated with subcutaneous TCZ, 162 mg/weekly, in association with a definite steroid tapering scheme.

Inclusion criteria were a diagnosis of GCA according to 1990 ACR classification and/or GiACTA trial criteria,[9] a treatment with TCZ 162 mg/weekly (started at diagnosis or at time of relapse), a follow-up of at least 24 months and the availability of a definite core set of clinical, serological, and imaging features.[19]

Exclusion criteria were a diagnosis of any other large-vessel vasculitis, a previous diagnosis of any other autoimmune rheumatic disease, a previous and/or concomitant treatment with any other bDMARD, a GCs tapering scheme different from the below-mentioned and the lack of any of the previously stated clinical and serological data. Patients lost at follow-up were excluded too.

Inclusion and exclusion criteria are summarized in Figure 1.

Treatment

At the time of diagnosis (or relapse presentation) all patients received GCs orally (up to a maximum of 62.5 mg of prednisone (PDN)) or through intravenous boluses if ischemic visual impairment was present, followed by oral administration according to a planned discontinuation scheme over 6 months (Table 1). Antiresorptive therapy was then administered for the entire duration of the steroid treatment. TCZ (162 mg subcutaneously once a week) was initiated together with GCs (at diagnosis or at relapse presentation) after adequate infective screening (QuantiFERON, hepatitis B and hepatitis C virus serology) and was not discontinued unless any adverse event (AE) directly attributable to the treatment arose. All patients underwent influenza, pneumococcal and recombinant zoster vaccination (according to availability in Italy).

Baseline and Follow-Up Visits

Patient monitoring was structured as follows: after a baseline assessment (T0), follow-up visits were performed at 3 (T1), 6 (T2), 12 (T4), 18 (T5) and 24 (T6) months, then annually if sustained remission was achieved. Further assessments could be arranged in case of relapse. Patients who permanently interrupted TCZ continued to be monitored according to

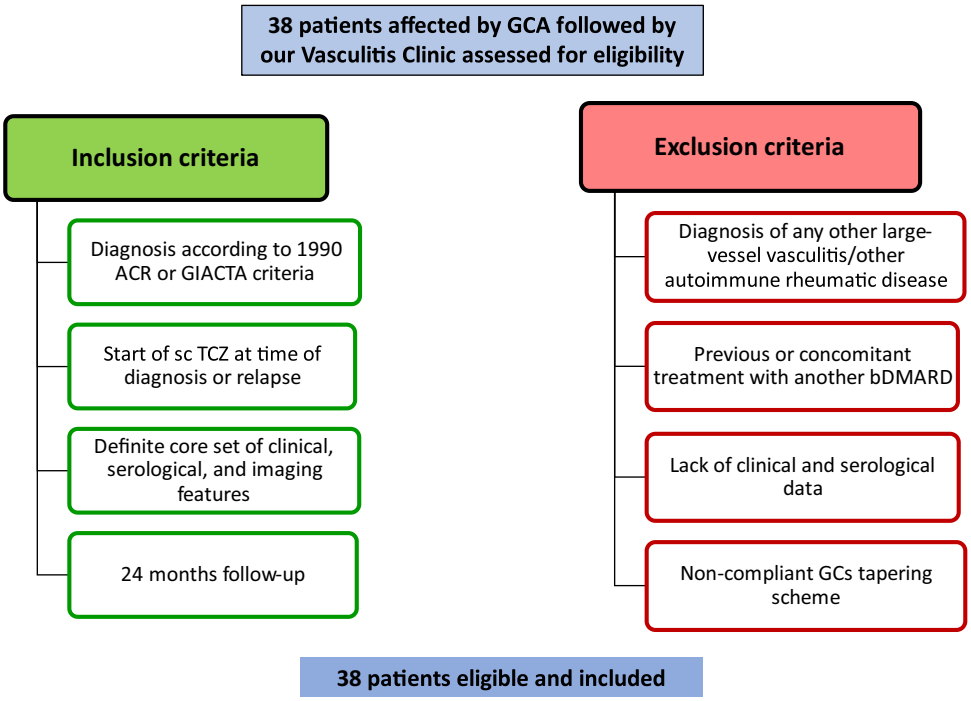

Figure 1 Inclusion and exclusion criteria.

the abovementioned scheme. During each visit, disease activity, routine blood tests, color Doppler ultrasonography (CDUS) findings (if available) and therapeutic modifications were recorded. Other imaging findings, such as PET, MRI/MRA and CT, were recorded, too, when available.

Table 1 Glucocorticoids Tapering Scheme for Patients with a Novel Diagnosis of GCA

Week	GC Dosing (mg/Day, Prednisone Equivalent)
1–4	50
4–6	43,75
6–8	37,5
8–10	31,25
10–12	25
12–14	18,75
14–16	12,5
16–18	6,25
18–20	5
20–22	3,75
22–24	2,5
24–26	1,25
>26	–

Abbreviations: GCs, glucocorticoids; TCZ, Tocilizumab.

Safety was evaluated based on the incidence of AEs during the follow-up, while effectiveness outcomes included the assessment of relapses (as outlined by EULAR consensus definitions for disease activity states in GCA and other types of LVV[20]), diagnostic imaging analysis and GCs dose at the last observation point and/or GCs discontinuation over time. Relapses were treated according to EULAR 2018 recommendations.

Statistical Analysis

Parametric data are presented as mean ± standard deviation (SD) and non-parametric data as medians with interquartile ranges (IQR). Categorical variables are presented as either a percentage of the total or numerically, as appropriate.

Ethics

The study was conducted in accordance with the declaration of Helsinki and further amendments and was approved by our local ethical committee (RHELABUS 22271). All patients signed a "Patient Consent Form" in full knowledge of how their data would be used.

Results

A total of 38 patients were included, with a mean age of 76.4 ± 8.6 years and an M:F ratio of 0.46. Nineteen (50%) were diagnosed with cranial GCA, 6 (16%) with large vessel GCA (LV GCA) and 13 (34%) with LV and cranial GCA. Clinical and laboratory findings collected at baseline are summarized in Table 2. Temporal artery biopsy was performed and available only in 1 (3%) patient, while PET scan in 7 (18%) and CDUS in 26 (68%). Fourteen (37%) patients reported ocular symptoms and nearly half of them required the administration of GC intravenous boluses as rescue therapy.

Table 2 Demographic, Clinical and Laboratory Data of Patients at Baseline

Variable	N (%)	Mean Value ± sd
Age		76,4 ± 8.6 years
Sex		
Male	12 (32)	
Female	26 (68)	
Type of GCA		
Cranial	19 (50)	
LV	6 (16)	
Cranial and LV	13 (34)	
Disease course		
New onset	30 (79)	
Relapsing	8 (21)	
Duration		12,6 months
GCA-related signs and symptoms (at onset)		
Ocular involvement	14 (37)	
Transient/permanent vision loss	8 (21)	

(*Continued*)

Table 2 (Continued).

Variable	N (%)	Mean Value ± sd
Headache	15 (39)	
Scalp tenderness	11 (29)	
Jaw claudication	12 (32)	
Temporal artery abnormality	6 (16)	
B symptoms	14 (37)	
PMR	8 (21)	
Stenosis	0 (0)	
Dilatation/aneurysm	1 (3)	
Imaging findings		
Sonographic evidence of arteritis	26 (68)	
Histological arteritis	1 (3)	
Inflammatory wall thickening (PET-TC/US)	15 (39)	
Laboratory		
ESR		75,9 ± 38.9 mm/h
CRP		8,4 ± 8.6 mg/dL
Hemoglobin		12,2 ± 1.5 mg/dL
Comorbidities	19 (50)	
Treatment		
GCs dosage (PDN eq.)		40,8 ± 19.3 mg
GC IV boluses	8 (21)	
cDMARD	13 (34)	
TCZ start	17 (45)	

Abbreviations: Cdmard, conventional disease modifying antirheumatic drug; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; F, females; GCs, glucocorticoids; GCA, giant cell arteritis; Hb, hemoglobin; IV, intravenous; LV, large vessels; M, males; MTX, Methotrexate; PDN, prednisone; PET, positron emission tomography; PMR, polymyalgia rheumatica; SD, standard deviation; TCZ, Tocilizumab; US ultrasound.

The average follow-up time was 25.9 ± 10.9 months, while the average duration of treatment with TCZ was 22 months.

For what concerns safety, AEs occurred in 11 (29%) patients, and we registered only 1 (3%) Serious Adverse Event (SAE) (perforated diverticulitis) (Table 3) with an average interval of occurrence of 12.9 months after the start of TCZ. Consequently, 7 patients permanently suspended TCZ treatment (with a mean duration of treatment of 17.8 months), while 3 patients temporary stopped it. All AEs subsequently resolved. Lastly, 6 (16%) patients reported intolerance towards long-term GCs use (2 cases of GC-induced diabetes and 4 cases of adrenocortical insufficiency) with no serious side effects (eg, psychosis, fragility fractures, Cushing syndrome, etc.…) being recorded.

Regarding TCZ efficacy and GCs sparing effect, at the end of the follow-up period, 27 (71%) patients were still under TCZ treatment (7 discontinued the treatment because of AEs while 4 for unspecified reasons), and all of them showed clinical remission or sustained remission (>6 months); 23 (85%) discontinued GCs and among those who continued steroid treatment,

Table 3 Adverse Events Recorded During TCZ Treatment

Adverse Event	N (%)
Neutropenia (0.5–1 x 10^9 cell/L)	3 (8)
Infections (non-serious: herpes zoster, erysipelas)	2 (5)
Liver enzymes elevation (1–3 times the upper reference limit)	2 (5)
Thrombocytopenia (50–100 x 10^3 cell/mL)	2 (5)
Hypersensitivity reaction (at injection site)	2 (5)
Perforated diverticulitis	1 (3)

Table 4 Relapses

	During TCZ Treatment	After TCZ Discontinuation
Type		
Major	0	0
Minor	3	3
Clinical/laboratory/imaging findings		
Symptoms		
Eye pain	0	1
Headache	3	1
B-symptoms	1	1
PMR	1	0
ESR and/or CPR elevation	0	3
US/PET evidence of arteritis	3	2
GCs dosage at relapse (PDN equivalent)	7,5 mg	2,1 mg

Abbreviations: CPR, c-reactive protein; ESR, erythrocyte sedimentation rate; US, ultrasound; PET, positron emission tomography; GCs, glucocorticoids; PDN, prednisone; PMR, polymyalgia rheumatica; TCZ, tocilizumab.

mean dosage was <5 mg PDN equivalent. In more detail, 2 patients were receiving 5 mg PDN equivalent, and the remaining 2, 2.5 mg PDN equivalent. Overall, 6 cases of minor relapse were observed (Table 4), of which 3 (8%) under TCZ treatment and 3 after TCZ discontinuation (27%). No major relapses were reported. Average relapse-free interval during and after TCZ was of 15 months and 19 months, respectively.

Discussion

Overall, our data support the evidence of a good safety and efficacy profile for TCZ use even for prolonged periods of treatment. They also provide slightly more encouraging results with reference to the likelihood of discontinuation of GCs and avoidance of relapse in GCA patients treated with TCZ, compared to other recent studies.

Indeed, incidence of AEs and SAEs was modest, and led to treatment discontinuation in a reasonable percentage of patients (30%). The most frequently observed AEs were neutropenia, thrombocytopenia, elevation of liver enzymes (all mild intensity) and non-serious infections, while the only case of SEA was a perforated diverticulitis in a patient with pre-existing diverticular disease. This is consistent with both the information reported in the RoActemra safety data sheet and the findings from previous clinical trials and observational studies.[8–12,18,21] Interestingly, we observed that in our cohort

AEs tended to occur after >1 year of treatment, instead of within the first six months of therapy:[18] that possibly suggests a smaller effect of TCZ in their determination, compared to other contributing factors (eg, age, comorbidities, etc.…). The overall low rate of infections and, mostly, the lack of serious infections observed points in the direction of the importance of a reduction of GCs cumulative dose over time and of a timely and target vaccination in patients undergoing immunosuppressant therapy, especially the elderly.

All the patients who were still taking TCZ at the end of the follow-up period (71%) showed clinical remission and only 15% continued to require the administration of GCs (<5 mg PDN equivalent on average) due to the occurrence of mild withdrawal symptoms (malaise, fatigue, myalgias). Nevertheless, steroid treatment was well tolerated by almost all patients (no serious side effects linked to GCs usage were reported). Moreover, relapse rate during TCZ treatment or after its discontinuation (after a mean period of treatment of 16 months) proved to be relatively low overall (respectively 8% and 27%, respectively). In this regard, it is worth highlighting that in patients under TCZ therapy, symptoms attributable to relapse were not accompanied by signs of inflammation on laboratory tests. This is consistent with the observation that TCZ treatment leads to a significant reduction in CRP, making it difficult to detect a reactivation of the underlying disease.[22] Our group has previously showed that CDUS can represent an effective and sensitive tool to predict relapse in GCA patients treated with TCZ.[23] Indeed, we found evidence of vasculitis in the temporal artery during ultrasound examination of all the aforementioned patients in our cohort who had no elevation of CRP.

Up to date, clinical trials and real-life studies generally outlined a higher occurrence of relapses and a smaller success in discontinuing GCs therapy, with few exceptions.[10,14,16,18,21,24] In a 2023 multicentric cohort study that included 114 GCA patients with median TCZ treatment of 2.3 years, Samec et al observed disease relapse in >50% patients following TCZ initiation and only slightly more than half the patients in the cohort were able to stop GCs while receiving TCZ.[12] Another multicenter service evaluation in England which analyzed 336 GCA patients from 40 centers described rates of relapse of 21.4%, 35.4% and 48.6% at 6, 12 and 24 months after stopping TCZ.[13] Differently, a recent Japanese observational study which recruited 117 GCA patients treated with TCZ found an 85% relapse-free proportion and a 6% rate of relapse after remission, with mean ± SD glucocorticoid doses of 2,4 ± 2,7 mg/day at the last evaluation; however, the observation period was limited to 52 weeks, and 9% of patients did not reach remission.[11]

Our positive results can be interpreted in the light of the successful employment of a therapeutic scheme based on the early introduction of an immunosuppressive agent alongside with a quick GCs decalage, to reach persistent remission of the underlying pathology and to mitigate AEs due to pharmacological treatment. Indeed, this therapeutic strategy is recommended, as already mentioned, by the GCA international guidelines,[7,20] and its suitability is supported by the available scientific evidence.[25–27] Also, despite the rather small sample of patients, we uniformly administered the same formulation and dosage of TCZ which is rarely observed in similar trials and cohort studies and could give strength and reliability to our findings. Lastly, this is one of the few studies to cover an extended period of treatment of almost 2 years with TCZ in GCA patients.

Conclusions

This monocentric cohort study including a total of 38 patients affected by GCA treated for an average of 2 years with subcutaneous TCZ provides encouraging data about its long-term efficacy and safety, demonstrating that this can represent a successful tool to minimize disease relapse and reduce the cumulative dose of GCs over time. Although the appropriate timing and methods to discontinue TCZ remain unclear and will require further investigation, careful tapering once sustained GCs free remission is achieved could represent the strategy of choice so far.

Ethics

The study was conducted in accordance with the declaration of Helsinki and further amendments and was approved on 22 May 2022 by the Institutional Ethics Committee of University of Siena (RHELABUS 22271). All patients signed a "Patient Consent Form" in full knowledge of how their data would be used.

Disclosure

Authors declare no conflicts of interest.

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