Giant cell arteritis in clinical practice: beyond GiACTA

F. Regola[1,2], J. Mora[1,2], M. Riva[3], G. Fontana[1,2], A. Gatti[1,2], I. Cavazzana[1,2], F. Franceschini[1,2], P. Toniati[1]

[1]Rheumatology and Clinical Immunology Unit, ASST Spedali Civili di Brescia; [2]Department of Clinical and Experimental Sciences, University of Brescia; [3]Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Italy.

Abstract

Objective

Giant cell arteritis (GCA) therapy relies on high-dose glucocorticoids (GCs), which are associated with a high incidence of side effects and GCA relapses, highlighting the need for steroid-sparing agents such as tocilizumab (TCZ) and methotrexate (MTX). The aims of this study were to analyse GC side effects and to assess the steroid-sparing efficacy of TCZ and MTX in a real-life cohort of patients with GCA through the application of the Glucocorticoid Toxicity Index (GTI) version 2.0.

Methods

This retrospective cohort study included patients with a new diagnosis of GCA made in our Centre and classified according to therapy, respectively GCs alone, GCs plus MTX, and GCs plus TCZ. GTI was calculated over a 5-year follow-up period.

Results

We enrolled 150 patients, with a median follow-up of 21 (11-39) months. During this period, 88% experienced at least one GC side effect. The cumulative GC dose was an independent predictor of the GTI-cumulative worsening score (CWS), regardless of treatment group or follow-up time. As first-line therapy, TCZ reduced GC dose by 25% compared to GCs alone, leading to fewer side effects (65% vs. 90%), less GC-induced damage, and no GCA relapses (0% vs. 38%). TCZ also independently protected against relapses, regardless of GC dose or follow-up time. In contrast, MTX did not show similar benefits in any aspect.

Conclusion

GCs represent a cornerstone in GCA therapy, but their cumulative dose correlates with induced damage, as quantified by the GTI. TCZ demonstrated steroid-sparing effect and clinical efficacy in a large real-life cohort.

Key words

giant cell arteritis, tocilizumab, methotrexate, glucocorticoids

*Francesca Regola, MD, PhD**
*Jacopo Mora, MD**
Matteo Riva, MD
Giulia Fontana, MD
Alessia Gatti, MD
Ilaria Cavazzana, MD
Franco Franceschini, MD
Paola Toniati, MD

**Contributed equally.*

Please address correspondence to:
Francesca Regola
U.O. di Reumatologia e Immunologia Clinica,
Spedali Civili of Brescia,
Piazzale Spedali Civili 1,
25123 Brescia, Italy.
E-mail: f.regola@unibs.it

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ORCID iD
F. Regola: 0000-0001-6560-1112
J. Mora: 0009-0001-6193-6326
M. Riva: 0009-0000-3444-2489
G. Fontana: 0009-0002-7298-8962
A. Gatti: 0009-0000-9672-780X
I. Cavazzana: 0000-0002-2757-7120
F. Franceschini: 0000-0003-3678-6124
P. Toniati: 0009-0007-1953-7093

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Introduction

Giant cell arteritis (GCA) is a large-vessel vasculitis (LVV), typically involving the extracranial branches of the carotid artery and/or the aorta and its major branches. First-line therapy includes high doses of glucocorticoids (GCs), followed by gradual tapering. However, more than 40% of patients experience relapses or vascular progression during tapering, and over 80% suffer from GC-related adverse events (1). For these reasons, both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) recommend the use of steroid-sparing agents (2, 3). Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX), have shown only limited clinical benefit (4). In contrast, tocilizumab (TCZ), a humanised monoclonal antibody targeting the interleukin (IL)-6 receptor, has demonstrated efficacy and steroid-sparing properties in randomised controlled trials (RCTs) (5, 6).

Despite these findings, there remains a significant gap in the literature regarding the real-life use of TCZ in GCA (7, 8). Specifically, there is a lack of data on its steroid-sparing effect and overall impact on GC toxicity outside of RCT settings. Moreover, the Glucocorticoid Toxicity Index (GTI) version 2.0 has recently been developed as a standardised tool to quantify GC-induced toxicity. However, it has been validated in conditions such as asthma and ANCA-associated vasculitis (9-11), but it has not yet been applied or validated in GCA.

To address these gaps, we conducted a retrospective cohort study involving patients with newly diagnosed GCA followed over a 5-year period at our Centre. Treatment strategies included GC monotherapy, GC combined with MTX, or GC combined with TCZ.

The aims of this study were to analyse the risk of GC side effects and to assess the steroid-sparing efficacy of TCZ and MTX in a well-characterised, real-life cohort of patients with GCA through the application of the GTI 2.0, to quantify GC-related toxicity and the incidence of relapses.

Methods

Study design

A retrospective cohort study of patients with GCA diagnosed at our Centre between January 1st, 2000, and December 31st, 2021 was performed. Patients were enrolled in the study if fulfilling the 2022 ACR/EULAR criteria for GCA (12). Patients with a follow-up of less than 6 months and those who received treatments other than GCs, TCZ, or MTX were excluded. The study was approved by the local institutional ethics committee and conducted according to the Declaration of Helsinki.

Patients

Patients were stratified according to two distinct criteria: the GCA clinical phenotype and the medical therapeutic regimen administered. Concerning the GCA clinical phenotype, patients were classified into three groups in accordance with the 2022 ACR/EULAR criteria for GCA: cranial (C)-GCA, large-vessel (LV)-GCA and LV-C-GCA. Regarding the classification of patients based on the treatment received, the following groups were identified: patients treated with GC alone, patients treated with GC+MTX, and patients treated with GC+TCZ. Patients receiving MTX or TCZ were further subdivided into two subgroups: MTX-1 and MTX-2, and TCZ-1 and TCZ-2, depending on whether the immunosuppressive agent was initiated within three months or after three months from diagnosis. This time interval was selected because it corresponds to the average period required for the comprehensive clinical assessment at diagnosis and the establishment of a complete diagnostic-therapeutic pathway (Table I).

The response to treatment was assessed by an expert rheumatologist at each visit through evaluation of improvement in clinical symptoms and signs of GCA, as well as reduction of inflammatory markers, when appropriate. Relapses were defined according to the 2018 EULAR recommendations for the management of LVVs as the recurrence of signs or symptoms of GCA and/or worsening findings on radiological imaging. In particular, relapses were further classified as major or minor. A

Table I. Patient classification used in the present study.

C-GCA	Patients classified as GCA according to the 2022 ACR/EULAR criteria with exclusive cranial involvement
LV-GCA	Patients classified as GCA according to the 2022 ACR/EULAR criteria with exclusive large-vessel involvement
LV-C-GCA	Patients classified as GCA according to the 2022 ACR/EULAR criteria with both cranial and large-vessel involvement
GC	Patients treated with GC monotherapy
MTX-1	Patients started on MTX < 3 months after diagnosis due to high risk of GCA relapses or GC side effects
MTX-2	Patients started on MTX ≥3 months after diagnosis due to GCA relapses or GC side effects
TCZ-1	Patients started on TCZ < 3 months after diagnosis due to high risk of GCA relapses or GC side effects
TCZ-2	Patients started on TCZ ≥3 months after diagnosis due to GCA relapses or GC side effects

major relapse was defined as the reappearance of disease activity associated with risk of organ damage or progression of vascular inflammation (*e.g.* severe ischaemic complications such as visual loss and jaw claudication, aortic aneurysm or dissection, or vascular stenosis). A minor relapse was defined as the reappearance of signs or symptoms attributable to GCA that did not meet the severity criteria of a major relapse (*e.g.* new temporal headache and increased inflammatory markers without ischaemic complications) (2).

The GC-induced toxicity was assessed using the GTI 2.0, an algorithm developed by a multispecialty medical team, which allowed to quantify the GC-induced toxicity. GTI 2.0 included two sections: the Composite Index and the Specific List. The Composite Index comprised 9 domains representing the main GC side effects, including variations in body mass index (BMI), glucose tolerance, blood pressure, lipid panel, GC-induced myopathy, bone mineral density (BMD), infections, GC-induced cutaneous toxicity, and GC-induced neuropsychiatric manifestations. The Composite Index was further subdivided into two scores: the Cumulative Worsening Score (CWS), which reflected the cumulative GC-related damage over time, and the Aggregate Improvement Score (AIS), which captured potential improvements between two timepoints, since some side effects may be transient. The Specific List consists of 11 domains that described GC-related toxicities not measurable through the Composite Index and therefore not suitable for statistical analysis due to their descriptive nature. The minimal clinically important difference for GTI score was 10 (11).

Clinical and laboratory data of all patients were collected from clinical charts and GTI 2.0 was calculated 3 months (t3), 6 months (t6), 12 months (t12), 24 months (t24), 36 months (t36), 48 months (t48), and 60 months (t60) after diagnosis, for a total of 5 years of follow-up.

Statistical analysis

Data were presented as median (1^{st}-3^{rd} interquartile) or percentage composition for continuous and categorical variables, respectively. The Fisher's exact test was employed to compare qualitative variables, while the Mann-Whitney U-test was used to compare continuous variables between groups. Variations from baseline to different timepoints were assessed using the Wilcoxon's signed rank test for paired samples. Correlations were assessed with Pearson, Kendall, or Spearman coefficient (according to variable type) to evaluate associations between variables. Statistical analysis was performed either using the R environment with a mixed linear model or with a generalised linear model with the 'lme4' package (R Core Team, 2024) (13), or using the GraphPad statistical software package (GraphPad Software, Inc, CA, USA). Multiple comparisons were assessed with *post-hoc* tests. When performed multiple comparisons, level of significance was corrected according to the Benjamini-Hochberg procedure. A two-tailed *p*-value less than alpha reference of 0.05 was considered statistically significant.

Results

Demographic and clinical features

One hundred and fifty patients were enrolled in the study: 104 patients were females (69%) and 46 were males (31%) with a median age at diagnosis of 73 (67–78) years. Patients were categorised into three groups according to GCA clinical phenotype: 96 with C-GCA (64%), 22 with LV-GCA (15%), and 32 with C-LV-GCA (21%) (Table II). At diagnosis, 130 patients (87%) had at least one comorbidity, with a mean modified rheumatic disease comorbidity index (mRDCI) value of 1 (0–2) and a mean Charlson comorbidity index (CCI) value of 4 (3–5) (Table III). The median follow-up period of the entire cohort was 21 (11–39) months. Fifty-two patients (35%) were treated with GCs alone, 20 (14%) with MTX-1, 26 (17%) with MTX-2, 26 (17%) with TCZ-1, and 26 (17%) with TCZ-2. The median follow-up periods of each category were 12 (6–24) months, 18 (6–36) months, 18 (6–36) months, 12 (6–24 months), and 18 (6-30) months, respectively. Among patients who started DMARDs during follow-up, the median time to initiation was 12 (6–12) months in MTX-2 and 6 (6-6) months in TCZ-2. The median MTX doses were 10 (10–12.5) mg/week in MTX-1 and 15 (10–15) mg/week in MTX-2. In TCZ groups, 20 patients in TCZ-1 and 10 patients in TCZ-2 received subcutaneous TCZ (162 mg/week), while 6 patients in TCZ-1 and 16 in TCZ-2 received intravenous TCZ [median of 560 (540–620) mg/month and 520 (470–560) mg/month, respectively].

GC cumulative dose and side effects

Figure 1 displays the temporal trend of median GC cumulative doses in the different groups, divided according to medical therapy. In comparing TCZ-1

Table II. Signs and symptoms of patients at diagnosis.

Signs and symptoms	Cohort (n=150)	C-GCA (n=96)	LV-GCA (n=22)	C-LV-GCA (n=32)	*p*
Temporal headache	117 (78%)	88 (92%)	0 (0%)	29 (91%)	< 0.0001*
Scalp tenderness	64 (43%)	46 (48%)	0 (0%)	18 (56%)	< 0.0001*
Jaw claudication	64 (43%)	51 (53%)	0 (0%)	13 (41%)	< 0.0001*
Visual impairment	55 (37%)	48 (50%)	0 (0%)	7 (22%)	< 0.0001*
Fatigue	110 (73%)	65 (68%)	16 (73%)	29 (91%)	0.0398*
Rheumatic polymyalgia	70 (47%)	47 (49%)	5 (23%)	18 (56%)	0.0398*
Abdominal claudication	5 (3%)	0 (0%)	5 (23%)	0 (0%)	< 0.0001*
Thoracic pain	5 (3%)	0 (0%)	3 (14%)	2 (6%)	0.0033*
Limb claudication	4 (3%)	0 (0%)	1 (4%)	3 (9%)	0.0144*
Weight loss	70 (47%)	37 (38%)	14 (64%)	19 (59%)	0.0278*
Stroke or transient ischaemic attack	4 (3%)	2 (2%)	0 (0%)	2 (6%)	0.3148
Fever	63 (42%)	35 (36%)	11 (50%)	17 (53%)	0.1814
Arthritis	9 (6%)	5 (5%)	2 (9%)	2 (6%)	0.7855

Data are expressed as n (%) values.
*$p \leq 0.05$.

Table III. Comorbidities of patients at diagnosis. Data are expressed as n (%).

Comorbidities	Cohort (n=150)	C-GCA (n=96)	LV-GCA (n=22)	C-LV-GCA (n=32)	*p*
Arterial hypertension	74 (49%)	56 (58%)	5 (23%)	13 (41%)	0.0058*
Dyslipidaemia	37 (25%)	21 (22%)	5 (23%)	11 (34%)	0.3552
Malignant neoplasms	19 (13%)	14 (15%)	2 (9%)	3 (9%)	0.6419
Cardiovascular diseases	17 (11%)	13 (13%)	1 (4%)	3 (9%)	0.4501
Cataract	17 (11%)	10 (10%)	1 (4%)	6 (19%)	0.2416
Diabetes mellitus	16 (11%)	9 (9%)	3 (14%)	4 (12%)	0.7848
Obesity	11 (7%)	8 (8%)	2 (9%)	1 (3%)	0.5841
Chronic lung diseases	11 (7%)	7 (7%)	1 (4%)	3 (9%)	0.7993
Osteoporosis	10 (7%)	6 (6%)	0	4 (12%)	0.1875
Major depression	8 (5%)	4 (4%)	1 (4%)	3 (9%)	0.5165
Peptic ulcer	5 (3%)	3 (3%)	1 (4%)	1 (3%)	0.9429
Chronic renal failure	5 (3%)	4 (4%)	1 (4%)	0	0.4939
Insufficiency fractures	1 (1%)	1 (1%)	0	0	0.7534
mRDCI§ at diagnosis	1 (0-2)	1 (1-2)	1 (0-1)	1 (0-1)	0.0351*
CCI† at diagnosis	4 (3-5)	4 (4-5)	3 (3-5)	4 (3-4)	0.0043*

§Modified Rheumatic Disease Comorbidity index; †Charlson Comorbidity index.
*$p \leq 0.05$.

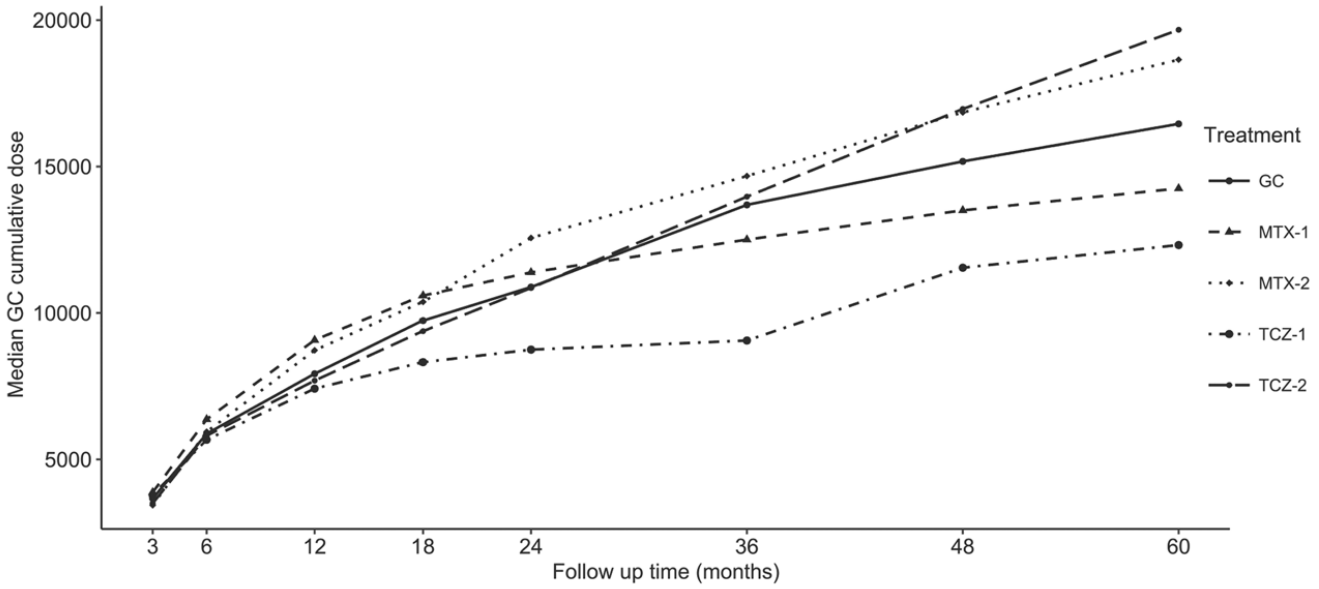
patients with both GC and MTX-1 patients, a notable trend emerged, indicating a lower GC cumulative dose for TCZ-1 patients from the timepoint t24 onwards. Specifically, TCZ-1 patients accumulated a mean GC dose of 8747 (6961–9780) mg at t24 and 9060 (8326–11367) mg at t36, reflecting reductions of 20% (p=0.0327) and 34% (p=0.0222) respectively, compared to GC patients. Similarly, compared to MTX-1 patients, TCZ-1 patients showed reduction of 23% (p=0.0323) and 28% (p=0.0208) at the same timepoints. By t60, TCZ-1 patients accumulated a mean GC dose of 12320 (12193–13259) mg, indicating reductions of 25% compared to GC patients and 14% compared to MTX-1 patients; however, these differences did not reach statistical significance. On the other hand, comparisons between GC *vs*. TCZ-2 and GC *vs*. MTX-2 did not show a statistically significant difference (Table IV).

Throughout the follow-up period, GC side effects were observed in 132 patients (88%). A total of 451 GC-related side effects were documented with an average occurrence of about 3.4 GC-related side effects per patient. Notably, 369 (82%) side effects occurred within the initial 2 years following diagnosis and the initiation of GC treatment. The most prevalent GC side effects included arterial hypertension (42%) and infections (43%) (Table V). Among infections, urinary tract infections (UTIs) were the most common (20%), followed by pneumonias (11%), acute bronchitis (7%), and herpes zoster (6%).

To identify factors potentially influencing the increased risk of GC-related side effects, an analysis of the overall cohort was conducted using the GTI 2.0. First, to assess the potential role of comorbidities at diagnosis, a correlation analysis was performed between CWS scores in the follow-up period and comorbidity indices at diagnosis. While no statistically significant correlation was found with baseline mRDCI, a high baseline CCI (>3) was associated with significantly higher CWS scores during the follow-up period compared to low baseline CCI (≤3) (Fig. 2). Second, to analyse the potential correlations between the GC cumulative dose and the development of GC-induced side effects, a correlation analysis was performed between the GC cumulative dose and the GTI 2.0 across different timepoints, finding a positive correlation between the GC cumulative dose and the GTI 2.0 CWS when accounted for repeated measures (p<0.0001) (Fig. 3) (14). The analysis was extended using a mixed linear model, which highlighted the GC cumulative dose as a predictor of the GTI-CWS independently of the treatment group and follow-up time (an increase of 1 mg/day of GC causes an increase of 0.0081 points in the GTI-CWS) (b: 0.0081; Std. Error: 0.0003; p<0.0001).

TCZ and MTX effects on GC side effects and GCA relapses

The analysis of GC side effect incidence showed significant variation among treatment groups (Table V). A higher proportion of patients experienced at least one side effect in the GC (90%), MTX-1 (95%), MTX-2 (100%), and TCZ-2 (88%) groups compared to the TCZ-1 group (65%) (p=0.0017). Additionally, patients in these groups reported more GC side effects per patient, with ≥3 side effects in 44% of GC, 70% of MTX-1, 46% of MTX-2, and 50% of TCZ-2 patients compared to 19% in the TCZ-1 group (p=0.0151). In patients who started DMARDs at least 3 months after diagnosis, only 30% of TCZ-2 patients developed GC side effects after



Patients (n)	t3	t6	t12	t18	t24	t36	t48	t60
GC	52	52	49	40	35	25	19	17
MTX-1	20	20	17	17	16	13	13	9
MTX-2	26	26	25	23	21	20	19	17
TCZ-1	26	26	22	16	14	12	3	3
TCZ-2	26	26	25	23	21	16	13	12
Total	150	150	138	119	107	86	67	58

Fig. 1. GC cumulative dose at different timepoints categorised by the type of medical therapy. Data are expressed as median values.

Table IV. GC cumulative dose at different timepoints categorised by the type of medical therapy. Data are expressed as median (1st-3rd interquartile) values.

	GC (n=52)	MTX-1 (n=20)	MTX-2 (n=26)	TCZ-1 (n=26)	TCZ-2 (n=26)	*p* GC *vs.* MTX-1	*p* GC *vs.* MTX-2	*p* GC *vs.* TCZ-1	*p* GC *vs.* TCZ-2	*p* MTX-1 *vs.* TCZ-1	*p* MTX-2 *vs.* TCZ-2
t3	3664 (2526-4222)	3875 (3296-4098)	3436 (2067-4284)	3784 (3089-4145)	3499 (1809-4106)	0.8751	0.3564	0.5457	0.3620	0.7988	0.8049
t6	5876 (4289-7086)	6369 (5063-6990)	5944 (3467-7138)	5671 (4918-6991)	5811 (3811-7419)	0.5546	0.6035	0.9366	0.7829	0.5133	0.8620
t12	7923 (6313-9928)	9075 (7281-9868)	8725 (5736-10173)	7416 (6499-9089)	7689 (6255-11063)	0.4546	0.8981	0.4371	0.9772	0.1696	0.9175
t18	9738 (7639-12316)	10594 (8484-11363)	10379 (7756-12663)	8319 (6724-10343)	9378 (7941-14531)	0.6574	0.3133	0.2135	0.7040	0.1089	0.7576
t24	10885 (8664-13472)	11386 (9150-12529)	12563 (8565-14556)	8747 (6961-9780)	10854 (9531-18910)	0.9272	0.3697	0.0327*	0.5881	0.0323*	0.9900
t36	13691 (10229-16345)	12505 (10689-14103)	14676 (10642-16908)	9060 (8326-11367)	13971 (10696-20353)	0.7818	0.3792	0.0222*	0.6210	0.0208*	0.9113
t48	15176 (11510-19424)	13504 (11859-15763)	16848 (12629-20370)	11545 (11023-12871)	16965 (11363-20590)	0.3866	0.5838	0.1571	0.6451	0.3463	0.9694
t60	16457 (13218-21001)	14253 (13218-20703)	18650 (13065-21761)	12320 (12193-13259)	19670 (12232-23801)	0.6276	0.6543	0.0903	0.6740	0.2091	0.7398

*$p \leq 0.05$.

starting TCZ compared to 70% who had developed them before ($p<0.0001$). In contrast, 45% of MTX-2 patients developed GC side effects after MTX introduction *versus* 55% before ($p=0.2225$). Additionally, specific GC side effects, particularly infections, neuropsychiatric symptoms, and dyslipidaemia, were significantly lower in the TCZ-1 group compared to the GC group.

Figure 4 displays the temporal trend of the GTI 2.0, calculated using the two Composite Index scores, AIS and CWS, in relation to the type of medical therapy. Regarding GTI 2.0 AIS, comparing TCZ-1 patients to GC patients and MTX-1 patients, a trend to statistical significance was showed, with lower scores in TCZ-1 group. In particular, there was a difference of 52%, 90%, 61%, 69%, 78%, 86%, and 86% for TCZ-1 patients *vs*. GC patients, and a difference of 67%, 90%, 68%, 77%, 79%, 86%, and 85% for TCZ-1 patients *vs*. MTX-1 patients, respectively at timepoints t6, t12, t18, t24, t36, t48, and t60. In the same way, GTI 2.0 CWS between TCZ-1 patients and GC patients or MTX-1 patients presented a trend to statistical significance, showing a difference of 43%, 51%, 38%, 49%, 62%, 67%, and 76% for TCZ-1 patients *vs*. GC patients, and a difference of 64%, 65%, 56%, 63%, 61%, 68%, and 67% for TCZ-1 patients *vs*. MTX-1 patients, respectively at time-

Table V. GC side effects categorised by the type of medical therapy. Data are expressed as n (%) or mean values.

GC side effects	Cohort (n: 150)	GC (n: 52)	MTX-1 (n: 20)	MTX-2 (n: 26)	TCZ-1 (n: 26)	TCZ-2 (n: 26)	*p*
Infections, including grade 4 and grade 5 infections	64 (43%)	26 (50%)	9 (45%)	10 (38%)	5 (19%)	14 (54%)	0.0736*
Arterial hypertension	63 (42%)	23 (44%)	12 (60%)	11 (42%)	7 (27%)	10 (38%)	0.2553
Neuropsychiatric manifestations, including GC-induced psychosis	53 (35%)	23 (44%)	12 (60%)	9 (35%)	3 (11%)	6 (23%)	0.0041*
Diabetes mellitus and its complications (diabetic retinopathy, nephropathy, and neuropathy)	42 (28%)	15 (29%)	8 (40%)	6 (23%)	7 (27%)	6 (23%)	0.7197
Cataract	38 (25%)	15 (29%)	3 (15%)	10 (38%)	5 (19%)	5 (19%)	0.3019
Dyslipidaemia	37 (25%)	13 (25%)	8 (40%)	5 (19%)	2 (8%)	9 (35%)	0.0791*
Dermatologic manifestations, including grade 4 dermatologic manifestations	29 (19%)	9 (17%)	7 (35%)	6 (23%)	3 (11%)	4 (15%)	0.3094
Cardiovascular diseases other than arterial hypertension	26 (17%)	12 (23%)	2 (10%)	6 (23%)	2 (8%)	4 (15%)	0.3667
Weight gain	25 (17%)	11 (21%)	5 (25%)	4 (15%)	3 (11%)	2 (8%)	0.4395
Osteoporosis	25 (17%)	6 (11%)	3 (15%)	8 (31%)	3 (11%)	5 (19%)	0.2520
GC-induced myopathy	19 (13%)	6 (11%)	4 (20%)	4 (15%)	1 (4%)	4 (15%)	0.5236
Insufficiency fractures	16 (11%)	5 (10%)	0	4 (15%)	1 (4%)	6 (23%)	0.0741
Cushingoid features	6 (4%)	1 (2%)	1 (5%)	1 (4%)	1 (4%)	2 (8%)	0.8155
Glaucoma	4 (3%)	3 (6%)	0	1 (4%)	0	0	0.4006
Avascular necrosis	2 (1%)	0	0	1 (4%)	0	1 (4%)	0.4309
Tendon rupture	1 (< 1%)	1 (2%)	0	0	0	0	0.7546
Gastrointestinal symptoms	1 (< 1%)	0	0	0	0	1 (4%)	0.3083
Total GC side effects	451	169	74	86	43	79	N/A
Mean of GC side effects per patient	3.4	3.6	3.9	3.3	2.5	3.4	N/A
Number of patients with at least 1 GC side effect	132 (88%)	47 (90%)	19 (95%)	26 (100%)	17 (65%)	23 (88%)	0.0017*
Number of patients with 3 or more GC side effects	67 (45%)	23 (44%)	14 (70%)	12 (46%)	5 (19%)	13 (50%)	0.0151*

*$p \leq 0.05$.

points t6, t12, t18, t24, t36, t48, and t60.

Within the entire cohort, 63 patients (42%) experienced a GCA relapse accounting for a total of 94 relapses. Dividing the cohort based on therapy type, 20 GC patients developed 26 relapses (38%), of which 8 major and 18 minor, 9 MTX-1 patients 15 relapses (45%), of which 5 major and 10 minor, 19 MTX-2 patients 28 relapses (73%), of which 13 major and 15 minor, TCZ-1 patients none, and 15 TCZ-2 patients 25 relapses (58%), of which 14 major and 11 minor. Specifically, significant differences were observed between GC and TCZ-1 ($p<0.0001$ and $p<0.0001$, respectively) and MTX-1 *vs*. TCZ-1 ($p=0.0002$ and $p<0.0001$, respectively). Furthermore, only 4 TCZ-2 patients (16%) developed a minor relapse after initiation of TCZ compared to 12 MTX-2 patients (43%) after initiation of MTX, of which 7 experienced major relapses ($p=0.0410$). In logistic regression for longitudinal data, TCZ was shown to be a protective factor against relapses, independently of GC cumulative dose and follow-up time (b: -21.81; Std. Error: 7.97; $p=0.0062$), a finding not observed for MTX.

Summary of outcomes by treatment group

To provide a concise overview of the main outcomes across treatment groups, a summary table reporting the incidence of relapses, the incidence of GC-related adverse events, the median GC cumulative dose at t60, the median GTI scores (both AIS and CWS), and the corresponding percentage variation for the TCZ- and MTX-groups compared to GC group is reported in Table VI. The table highlights that TCZ-1 patients had the lowest cumulative GC exposure (percentage reduction vs GC group of 25%) and the most pronounced reductions in both GTI-AIS (86%) and GTI-CWS (76%) scores, with no patients experiencing disease relapses. In contrast, MTX-2 patients showed the highest relapse rate (73%) and only moderate reductions in GTI

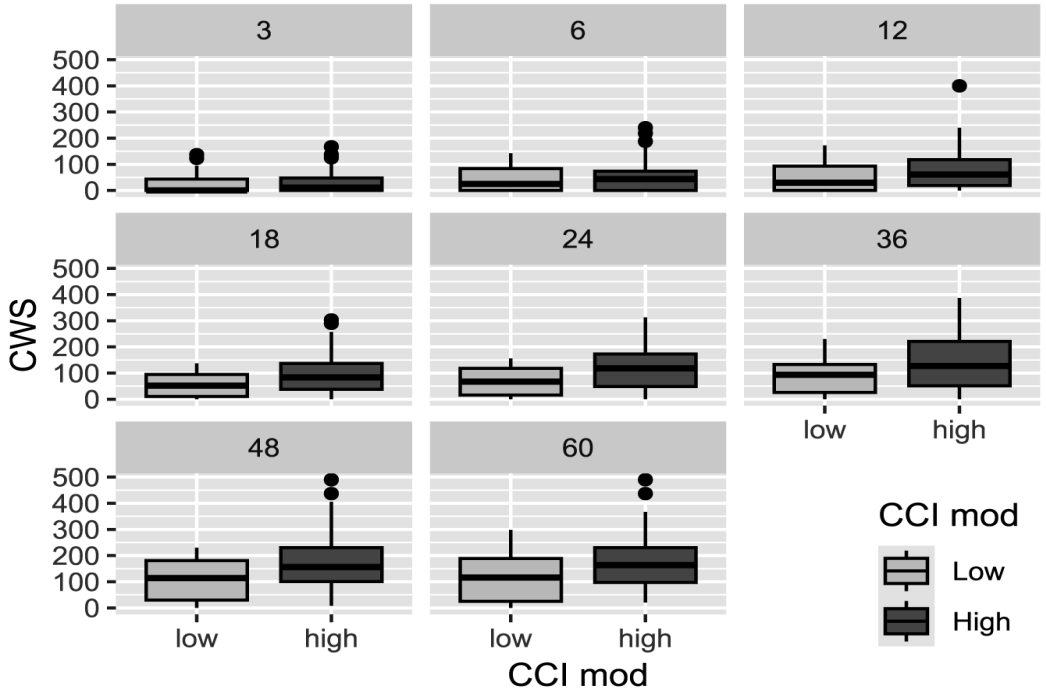


Fig. 2. Correlation analysis between the Glucocorticoid Toxicity Index (GTI) 2.0 Cumulative Worsening Score (CWS) and the Charlson Comorbidity index (CCI) at diagnosis. A baseline CCI value ≤3 was categorised as low (low CCI), while a baseline CCI value >3 was categorised as high (high CCI).

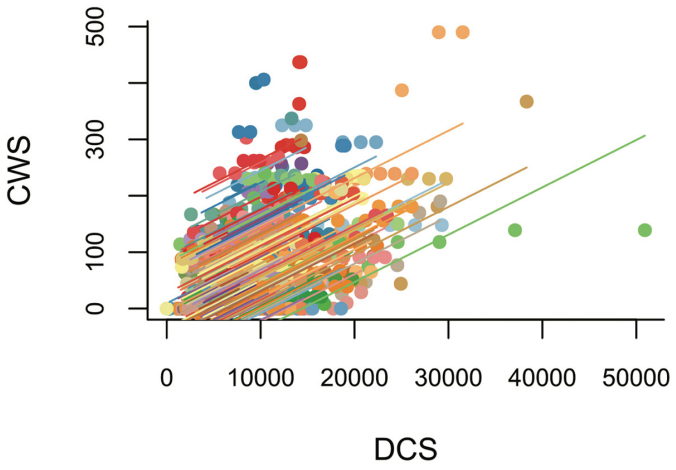


Fig. 3. Correlation analysis between the GC cumulative dose (DCS) and the Glucocorticoid Toxicity Index (GTI) 2.0 Cumulative Worsening Score (CWS) when accounted for repeated measures.

scores. The incidence of GC-related side effects was lowest in the TCZ-1 group (65%), while the other groups experienced higher rates, particularly MTX-2 (100%). These findings underscore the superior steroid-sparing effect and relapse prevention associated with early TCZ therapy compared to MTX therapy and GC monotherapy.

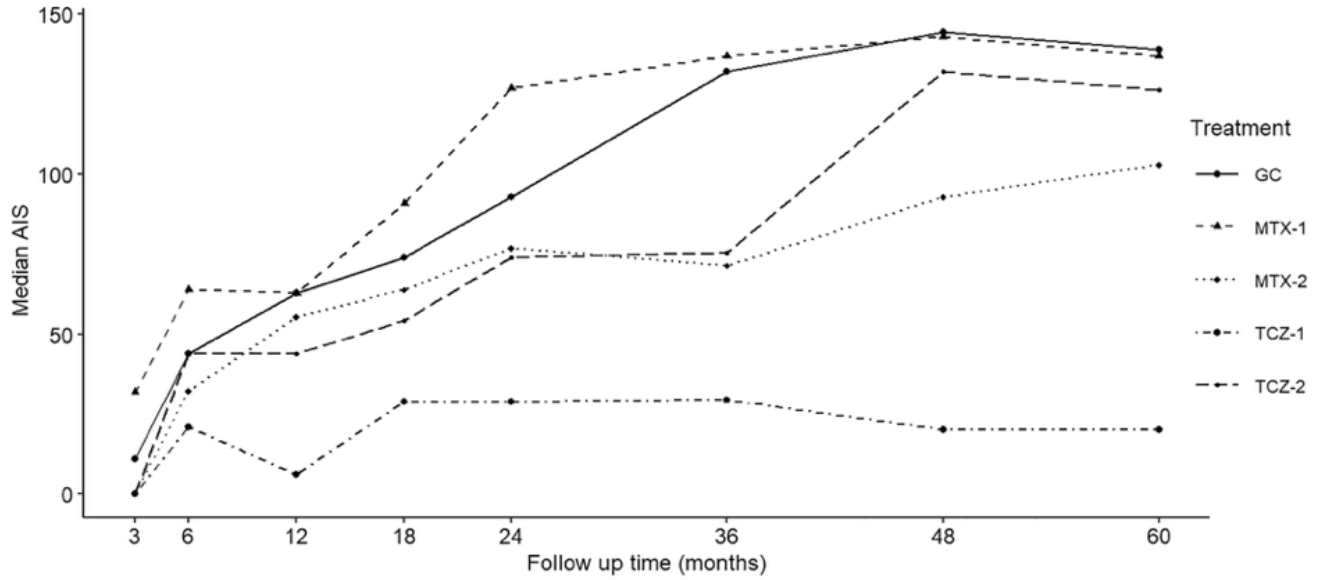
Discussion

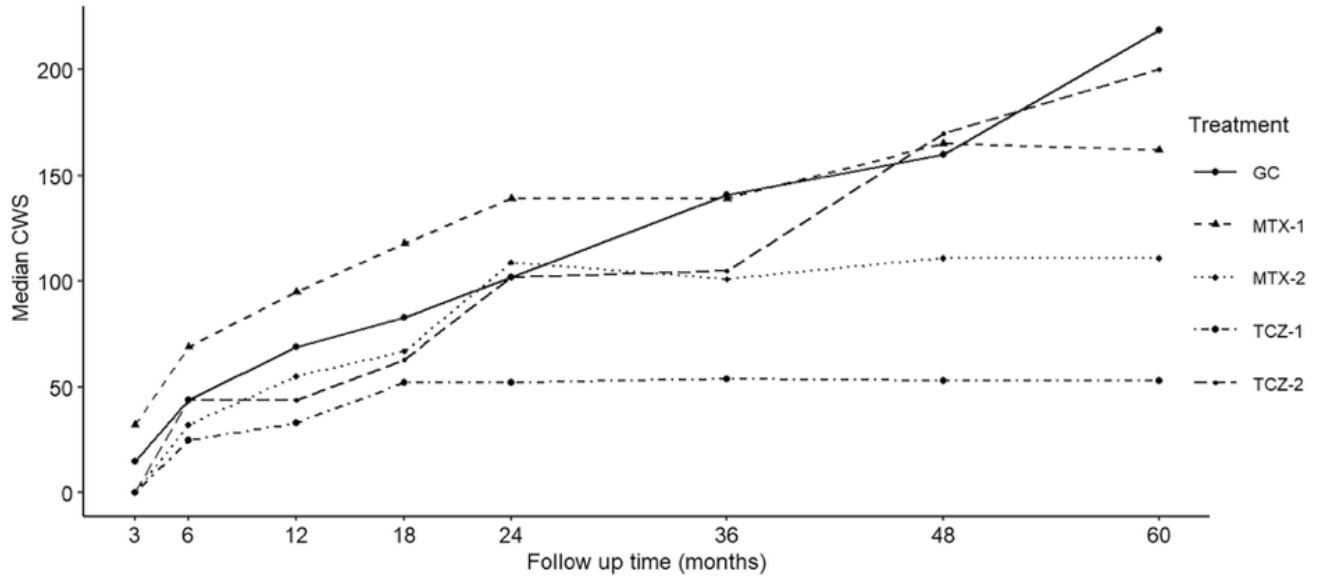
The treatment of GCA relies on the use of high-dose GCs, but around 40% of patients still experience relapses, and chronic GC use leads to side effects, impacting prognosis. Consequently, recent focus has shifted toward combining GCs with immunosuppressive agents, especially MTX and TCZ. The aims of this study were to analyse the risk of GC side effects and to assess the steroid-sparing efficacy of TCZ and MTX in a well-characterised, real-life cohort of patients with GCA through the application of the GTI 2.0 (15) to quantify GC-related toxicity and the incidence of relapses.

In this study, the cumulative GC dose at 1 and 5 years (7,923 mg and 16,457 mg, respectively) was higher compared to RCTs, yet aligned with the limited available data in the literature (6) (16). This difference is likely due to the personalised GC tapering protocol in the outpatient setting, as opposed to the standardised approaches in RCTs.

Chronic GC therapy is recognised as a risk factor for numerous diseases and for most of these side effects, a dose-dependent effect of the cumulative GC dose has been demonstrated (17). During follow-up, approximately 90% of patients developed at least one GC-related side effect (average of 3.4 events per patient), with arterial hypertension and infections being the most frequent. The increased risk of severe infections (grade ≥3 according to GTI 2.0) observed in this study was an expected finding due to the immunosuppressive effect of steroid therapy, and it aligned with previously published data (18). Neuropsychiatric side effects, including anxiety, insomnia, and depression, were also commonly reported, although they may partly stem from the emotional burden of a GCA diagnosis, especially when visual complications are present at onset, rather than being solely attributable to GC use.

Furthermore, our data confirm that patients with multiple baseline comorbidities and higher cumulative GC doses were at an increased risk of developing new comorbidities or worsening pre-existing ones. Indeed, using a mixed linear model, we identified the GC cumulative dose as an independent predictor of the GTI-CWS, regardless of the treatment group or the follow-up





Patients (n)	t3	t6	t12	t18	t24	t36	t48	t60
GC	52	52	49	40	35	25	19	17
MTX-1	20	20	17	17	16	13	13	9
MTX-2	26	26	25	23	21	20	19	17
TCZ-1	26	26	22	16	14	12	3	3
TCZ-2	26	26	25	23	21	16	13	12
Total	150	150	138	119	107	86	67	58

Fig. 4. Glucocorticoid Toxicity Index (GTI) 2.0 Aggregate Improvement Score (AIS) and GTI 2.0 Cumulative Worsening Score (CWS) at different time-points categorised by the type of medical therapy. Data are expressed as median values.

time (an increase of 1 mg/day of GC caused an increase of 0.0081 points in the GTI-CWS) (b: 0.0081; Std. Error: 0.0003; $p<0.0001$).

TCZ demonstrated its efficacy in two RCTs (5, 6), ensuring disease remission after 52 weeks of treatment and resulting in a reduced cumulative GC dose. These results were anticipated by a first open-label multicentre study, which suggested the potential of TCZ to reduce GC requirements and toxicity in GCA (19). However, there are no published studies on its steroid-sparing effect in cohorts other than those from the two RCTs. Our analysis revealed that TCZ, when used as first-line therapy and started within 3 months after diagnosis (TCZ-1), significantly reduced the cumulative GC dose by 25% compared to GC therapy alone at t60. TCZ treatment also resulted in improved GTI 2.0 scores, with a reduction in both AIS, the index of the active damage at each time-point, and CWS, the index of the cumulative patient damage, when compared to GC therapy alone, with a difference of 86% and 76% at t60, respectively.

These results were further supported by the lower incidence of GC-related side effects in the TCZ groups. In the entire cohort, approximately 40% of patients experienced at least one dis-

Table VI. Main outcomes across treatment groups. Δ: percentage variation.

Outcomes\groups	GC (n=52)	MTX-1 (n=20)	MTX-2 (n=26)	TCZ-1 (n=26)	TCZ-2 (n=26)
Patients with ≥1 GCA relapse	38%	45%	73%	0	16%
Patients with ≥1 GC side effect	90%	95%	100%	65%	88%
Median GC cumulative dose at t60 (Δ *vs*. GC group)	16457 mg (N/A)	14253 mg (–13%)	18650 mg (+13%)	12320 mg (–25%)	19670 mg (+19%)
Median GTI-AIS score at t60 (Δ *vs*. GC group)	139 (N/A)	137 (–1%)	103 (–26%)	20 (–86%)	127 (–9%)
Median GTI-CWS score at t60 (Δ *vs*. GC group)	219 (N/A)	162 (–26%)	111 (–49%)	53 (–76%)	200 (–9%)

ease relapse, but none occurred in the TCZ-1 group. Similarly, in the TCZ-2 group, which included patients who started TCZ following a disease relapse or GC-induced side effects, only 16% of patients experienced a relapse after starting TCZ. Moreover, in logistic regression for longitudinal data, TCZ was shown to be a protective factor against relapses, independently of GC cumulative dose and follow-up time (p=0.0062). These findings confirmed the efficacy of TCZ in both inducing and maintaining disease remission, regardless of whether it is used as first-line or second-line treatment.

In contrast, the steroid-sparing effect of MTX was modest, with limited reductions in GC cumulative dose and side effects, consistent with previous retrospective studies and meta-analyses (4). Moreover, MTX did not appear to be a protective factor against relapses. These findings are in line with two RCTs, which similarly failed to demonstrate a significant benefit of adding MTX to GC therapy, either in terms of steroid-sparing effect, GC side effects, or GCA relapses (20, 21).

One major limitation of this study is its retrospective design. The GTI 2.0 score, originally designed for prospective RCTs, was applied to a retrospective cohort, which makes the study susceptible to missing or incomplete data, potentially affecting the uniformity and statistical power of the results. To mitigate this, we included only patients with complete clinical follow-up data for at least 6 months. Additionally, the absence of standardised treatment protocols in the real-world setting introduced variability in treatment regimens, which might have acted as confounding factors.

On the contrary, one of the key strengths of this study is its large sample size, along with the uniformity of data collection due to the single-centre design and the extended follow-up period. Notably, while the GTI 2.0 score has been validated for conditions such as bronchial asthma and ANCA-associated vasculitis (9) (10) (11), analysing the variation of this parameter over a 1-year period, its application in GCA has been limited. To our knowledge, this study is the first to utilise the GTI 2.0 in a cohort followed longitudinally for over 12 months. Additionally, this study contributes valuable insights into the steroid-sparing effects of TCZ and MTX in a real-world setting, thereby enhanced our understanding of long-term treatment strategies for GCA.

In conclusion, this study provides further evidence that chronic GC use in GCA patients is associated with a high incidence of side effects, observed in approximately 90% of patients, which correlate with the GC cumulative dose and the presence of comorbidities at diagnosis. TCZ, when used as first-line therapy, significantly reduced the GC cumulative dose by 25% and decreased GC-related side effects, as quantified by the GTI 2.0. Logistic regression further revealed that GC cumulative dose is an independent predictor of the GTI-CWS. Moreover, TCZ, whether used as first-line or second-line therapy, prevented disease relapses in a real-world cohort, proving to be a protective factor against relapses independent of GC cumulative dose and follow-up time. These findings highlight the efficacy of TCZ as a steroid-sparing agent in achieving remission and maintaining long-term disease control, emphasising its value as a key component in treatment strategies for GCA to improve outcomes and limit GC-related toxicity. In contrast, MTX did not show similar results in reducing GC use or preventing relapses.

Take home messages

- Glucocorticoids are associated with a high incidence of side effects in giant cell arteritis patients.
- Glucocorticoid cumulative dose correlates with induced damage, as quantified by the Glucocorticoid Toxicity Index version 2.0.
- Tocilizumab demonstrated steroid-sparing effect and clinical efficacy in a large real-life cohort.

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