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Original Research

Tocilizumab in visual involvement of giant cell arteritis: a multicenter study of 471 patients

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Abstract

Background: Visual involvement is the most feared complication of giant cell arteritis (GCA). Information on the efficacy of tocilizumab (TCZ) for this complication is scarce and controversial.

Objective: We assessed a wide series of GCA treated with TCZ, to evaluate its role in the prevention of new visual complications and its efficacy when this manifestation was already present before the initiation of TCZ.

Design: This is an observational multicenter study of patients with GCA treated with TCZ.

Methods: Patients were divided into two subgroups according to the presence or absence of visual involvement before TCZ onset. Visual manifestations were classified into the following categories: transient visual loss (TVL), permanent visual loss (PVL), diplopia, and blurred vision.

Results: Four hundred seventy-one GCA patients (mean age, 74 ± 9 years) were treated with TCZ. Visual manifestations were observed in 122 cases (26%), of which 81 were present at TCZ onset: PVL ($n = 60$; unilateral/bilateral: 48/12), TVL ($n = 17$; unilateral/bilateral: 11/6), diplopia ($n = 2$), and blurred vision ($n = 2$). None of the patients without previous visual involvement or with TVL had new episodes after initiation of TCZ, while only 11 out of 60 (18%) patients with PVL experienced some improvement. The two patients with diplopia and one of the two patients with blurred vision improved.

Conclusion: TCZ may have a protective effect against the development of visual complications or new episodes of TVL in GCA. However, once PVL was established, only a few patients improved.

Keywords: giant cell arteritis, large-vessel vasculitis, tocilizumab, visual involvement

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Introduction

Giant cell arteritis (GCA) is the most common vasculitis that affects the elderly, especially in subjects of European descent. GCA mainly affects the extracranial branches of the external carotid artery.[1–3] However, visual loss, the most feared complication of the disease, is generally due to the involvement of the ophthalmic branches of the internal carotid artery.[4]

Early diagnosis and treatment of GCA are needed since ocular complications are potentially irreversible.[2–4] Permanent visual loss (PVL) may be preceded by transient visual loss (TVL).[2] Visual

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involvement is usually unilateral,[2,5] but may become bilateral in 20–62% of cases, mainly during the first 2 weeks of the disease.[6,7]

High-dose glucocorticoids (GC), either orally or intravenously, represent the cornerstone of GCA therapy.[2] Nevertheless, once blindness is established, the prognosis is poor and only a few patients recover some degree of visual acuity despite treatment with GC.[2,4,8,9] Before the use of GC, visual manifestations develop in approximately 30–60% of patients,[3] but still occur in 5% of those treated with these agents.[10,11] Therefore, the efficacy of other therapies in the prevention and management of visual complications of GCA needs to be explored.

Interleukin (IL)-6 has been involved in the pathogenesis of GCA.[12] Tocilizumab (TCZ) is a monoclonal antibody against the IL-6 receptor. Two placebo-controlled trials, one open-label trial, and several clinical observation studies have demonstrated the efficacy of TCZ in GCA patients to achieve GC-free remission.[13–19] However, the time course of patients with visual symptoms at the start of TCZ has not been documented in most previous studies.[13,14,16]

Two recent clinical studies have shown that TCZ can prevent the incidence of new visual manifestations in patients with GCA.[17,18] Despite these promising data, three of the patients (5%) reported by Unizony *et al.*[17] and one (0.5%) by Amsler *et al.*,[18] developed visual symptoms after starting TCZ. New episodes of ocular involvement were observed during treatment with TCZ in one patient (0.7%) in the GiACTA trial and another (6%) in the GUSTO trial.[14,15] In contrast, Villiger *et al.* did not report the occurrence of new visual symptoms in patients on TCZ in a phase II clinical trial.[13] Therefore, additional data on the utility of this biological agent for the visual manifestations of GCA are of potential interest.

Keeping in mind these considerations, we assessed a series of patients with GCA treated with TCZ, to evaluate its role in the prevention of visual complications and its efficacy for visual improvement when this manifestation was already present before the initiation of this biologic agent.

Patients and methods

Patients, enrollment criteria, and study protocol

We set up an observational, national open-label, retrospective, multicenter study, including 471 patients diagnosed with GCA and treated with TCZ in real-life clinical practice from January 2014 to May 2020. Before TCZ onset, all of them had received high-dose GC, and 257 (54.6%) conventional synthetic and/or other biologic immunosuppressive agents. To reduce selection bias, we included all the patients who had received at least one dose of TCZ, regardless of the outcome.

The patients were recruited from the Rheumatology or Autoimmune Units of 57 referral centers. They were diagnosed with GCA according to the criteria of the American College of Rheumatology (ACR),[20] and/or a positive biopsy of the temporal artery, and/or the presence of large vessel vasculitis in any of the following imaging techniques: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scan, magnetic resonance imaging angiography (MRI-A), computed tomography angiography (CT-A), or helical CT scan.

Patients were divided into two subgroups according to the presence or absence of visual involvement throughout the course of the disease. Visual manifestations were classified as follows: TVL; PVL, which can be partial or total, unilateral, or bilateral; diplopia; and blurred vision.[2]

Subsequently, we evaluated the patients who had any visual symptoms at the time of TCZ onset and assessed their temporal clinical course. For this purpose, we divided these patients into three groups according to the time elapsed between the onset of visual symptoms and the initiation of TCZ therapy. We considered the following time points: (a) 1–10, (b) 11–30, and (c) more than 30 days.

Finally, we tried to compare the characteristics of patients with PVL who experienced visual improvement after starting TCZ with those who did not.

Treatment of GCA was based on the classic pharmacological scheme, starting with high doses of GC (usually, an initial dose of 40–60 mg/day of prednisone or equivalent, gradually tapered in the following months). Conventional synthetic immunosuppressant (csIS) and biologic agents were used as GC sparing agents, mainly in patients with a relapsing disease or in those with GC-adverse side effects.

As indicated by the Spanish National Guidelines for the administration of biologic therapy in patients with rheumatic diseases, the presence of infectious diseases, including tuberculosis and hepatitis B or hepatitis C infection, was ruled out before starting the biologic agent. A tuberculin skin testing (PPD) and/or an interferon assay (quantiFERON), as well as chest radiography, were performed to exclude latent tuberculosis. In positive cases, prophylaxis with isoniazid was initiated at least 4 weeks before biological drug onset and was maintained for 9 months, according to the national guidelines.[21–27] In addition, the presence of malignancies was also excluded, as previously described.[21–27]

TCZ was prescribed at its standard dose, either intravenously (IV) (8 mg/kg/4 weeks) or subcutaneously (SC) (162 mg/week). It was started due to lack of efficacy and/or unacceptable adverse side effects related to standard therapy. In many cases, TCZ was prescribed off-label since it was indicated before its approval by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of GCA. Thus, written informed consent was obtained in these cases.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[28]

Treatment with antiplatelet, anticoagulant, antihypertensive, and/or lipid-lowering drugs was also documented.

Clinical definitions and laboratory data

Fever was present if the temperature was ⩾38°C. Constitutional symptoms included asthenia, anorexia, and weight loss >5% of the normal body weight over the last 6 months before disease diagnosis. Headache had to be of recent onset and with different characteristics from previous ones. Jaw claudication was present when the patient reported pain on chewing, which improved after stopping. Polymyalgia rheumatica (PmR) was defined according to the classification criteria proposed by the EULAR/ACR 2012.[29]

A patient was considered to have visual involvement whether one or more of the following manifestations were present: diplopia, blurred vision, TVL, and/or PVL. TVL ('amaurosis fugax') was defined as a temporary loss of sight referred by the patient, followed by recovery to baseline visual acuity and without abnormalities on ophthalmologic examination. PVL was defined as partial or complete loss of sight in one or both eyes longer than 24 h. Patients with PVL were examined by an experienced ophthalmologist and underwent a thorough ophthalmic examination including best-corrected visual acuity (Snellen charts), refraction, intraocular pressure measurement with Goldmann applanation tonometer, anterior segment biomicroscopy, and dilated fundus examination. The refractive error was recorded using an Autorefractometer Canon RK-F1 (Canon USA Inc., Lake Success, NY, USA). Diplopia was considered if there was palsy of extrinsic ocular muscles on physical examination and when it was a transient symptom recalled by the patient. Stroke and/or transient ischemic attacks were collected as cerebrovascular disease.

Hypertension was considered when the systolic pressure was >130 mm Hg and/or the diastolic pressure was >80 mm Hg. Dyslipidemia was defined if one of the following was present: total cholesterol >200 mg/dl, triglycerides >150 mg/dl, high-density lipoprotein (HDL) cholesterol <40 mg/dl in men or <50 mg/dl in women, or low-density lipoprotein (LDL) cholesterol >130 mg/dl. CHADS2-score (a risk stratification tool to predict the 1-year risk of ischemic stroke in a nonanticoagulated patient with nonvalvular atrial fibrillation) was calculated based on the clinical information available at TCZ onset.[30]

Serum C-reactive protein (CRP) >0.5 mg/dl and erythrocyte sedimentation rate (ESR) in the first hour >20 mm in men or >25 mm in women were considered abnormal. Anemia was defined as a hemoglobin level ⩽11 g/dl.

In patients with PVL, improvement of visual symptoms was defined when the patient experienced an improvement in ocular manifestations, whereas in patients with TVL it was considered as the absence of new episodes of visual loss.

Data collection

Data were extracted from the clinical records according to a specifically designed protocol,

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reviewed for confirmation, and stored in a computerized database. To minimize entry mistakes, all data were double-checked. To maintain the anonymity, all patient data were de-identified. The research project was carried out following the protocol and the standard procedures that ensure compliance with the Declaration of Helsinki and Good Clinical Practice standards.

Statistical analysis

Demographic and clinical characteristics in patients with GCA were described as mean ± standard deviation (SD) or percentages for categorical variables. For non-normally distributed continuous variables, data were expressed as the median and interquartile range (IQR). Univariable differences between GCA patients according to visual involvement were assessed through Student's *t*, Mann–Whitney *U*, chi-square, or Fisher's exact tests according to normal distribution or number of subjects. Hazard ratios (HRs) were calculated through Cox proportional hazards regression analysis. All the analyses were performed using SPSS software, version 26 (IBM, Armonk, NY, USA), and Stata software, version 17/SE (StataCorp, College Station, TX, USA). A p value < 0.05 was considered statistically significant.

Results

Baseline general features at TCZ onset

We included 471 patients (342 women/129 men) diagnosed with GCA and treated with TCZ. The mean age at TCZ onset was 74 ± 9 years. Ninety-one (19.3%) patients had a recent GCA diagnosis (within 6 weeks before TCZ use). One hundred and twenty-two (25.9%) cases had ever had visual manifestations. Baseline characteristics of these subgroups, at TCZ onset, are summarized in Table 1. Figure 1 shows the previous treatments received by the patients.

Women outnumbered men in the groups of patients with and without visual complications. However, it was significantly higher among the subgroup of patients without visual manifestations compared with those with visual involvement (Table 1).

At the time of TCZ onset, GCA patients with visual involvement or PVL were older than those without visual manifestations. Overall, traditional cardiovascular risk factors were more commonly present in patients with visual manifestations. It was also the case for the presence of typical manifestations of this vasculitis, such as headache or jaw claudication. In contrast, patients with PVL had a lower frequency of PmR than those without visual manifestations. However, there were no significant differences in serum levels of acute-phase reactants, ESR and CRP, between patients with or without visual manifestations at TCZ onset.

Baseline features of patients with visual involvement at TCZ onset

Visual manifestations were present at TCZ start in 81 of the 122 patients with ocular involvement: unilateral PVL ($n = 48$), bilateral PVL ($n = 12$), unilateral TVL ($n = 11$), bilateral TVL ($n = 6$), diplopia ($n = 2$), and blurred vision ($n = 2$). The remaining 41 patients with previous visual symptoms had fully recovered. Anterior ischemic optic neuropathy (AION) was present in 41 of the 60 patients with PVL. Retrobulbar optic neuropathy occurred in three (one of them also had AION); central retinal artery occlusion (CRAO) in two, while two other cases had papillitis/papillary edema. In 13 patients, this information was not available. Neither of the two patients complaining of diplopia showed palsy of extrinsic ocular muscles. Moreover, AION was observed in one of the two cases with blurred vision, while the ophthalmological examination was normal in the other one. Besides, one of the patients with TVL had an incipient AION.

TCZ therapy and visual manifestations

After a mean of 20 ± 18 months on TCZ and 25 ± 21 months of follow-up, none of the patients without visual symptoms at TCZ onset developed new ocular involvement. Moreover, none of those with TVL suffered new visual episodes after TCZ onset. In addition, 11 of 60 patients with PVL (18.3%) experienced visual improvement (Figure 2). One of the cases with blurred vision and another with diplopia showed partial improvement, while the other patient with diplopia recovered completely.

The 49 patients with PVL who did not experience visual improvement after TCZ onset remained with the same visual symptoms, but did not develop any new visual manifestations during the follow-up period.

Table 1. Main features of 471 patients with giant cell arteritis at TCZ onset.

	Overall (*n* = 471)	GCA without visual involvement (*n* = 349)	GCA with visual involvement (*n* = 122)	GCA with PVL at TCZ onset (*n* = 60)	P visual *versus* nonvisual involvement	P PVL *versus* nonvisual involvement
General features						
Age at diagnosis (mean ± SD)	72 ± 9	71 ± 9	75 ± 8	75 ± 9	**0.001**	**0.001**
Age at TCZ onset (mean ± SD)	74 ± 9	73 ± 9	76 ± 8	76 ± 9	<**0.0001**	**0.005**
Female/male (% of female)	342/129 (73)	265/84 (76)	77/45 (63)	41/19 (68)	**0.006**	0.21
Time from GCA diagnosis to TCZ onset (months), median [IQR]	6 [2–18]	7 [2–22]	5 [1–12]	5 [1–10]	0.088	**0.027**
GCA fulfilling ACR 1990 criteria, *n* (%)	344 (73)	235 (67)	109 (89)	53 (88)	<**0.0001**	**0.001**
Positive TAB, *n* (%)	201 (43)	146 (42)	55 (45)	33 (55)	0.53	0.34
Clinical phenotype of GCA						
Cranial, *n* (%)	217 (46)	138 (40)	79 (65)	40 (67)	–	–
Extra-cranial, *n* (%)	80 (17)	80 (23)	0 (0)	0 (0)	<**0.0001**	<**0.0001**
Mixed, *n* (%)	174 (37)	132 (38)	42 (34)	20 (33)	–	–
Cardiovascular risk factors						
High blood pressure, *n* (%)	272 (58)	189 (54)	83 (68)	40 (67)	**0.013**	0.058
Dyslipidemia, *n* (%)	241 (51)	175 (50)	66 (54)	32 (53)	0.61	0.63
Diabetes, *n* (%)	81 (17)	50 (14)	31 (25)	16 (27)	**0.007**	**0.016**
Previous or current smoking history, *n* (%)	47 (10)	31 (9)	16 (13)	8 (13)	0.21	0.27
CHADS2 score[a], median [IQR]	1 [1–2]	1 [0–2]	2 [1–2]	2 [1–2]	**0.001**	**0.004**
Ischemic manifestations						
Headache, *n* (%)	259 (55)	167 (48)	92 (75)	42 (70)	<**0.0001**	**0.002**
Jaw claudication, *n* (%)	112 (24)	63 (18)	49 (40)	26 (43)	<**0.0001**	<**0.0001**
Cerebrovascular accident, *n* (%)	5 (1)	2 (1)	3 (2)	1 (2)	0.11	0.38
Systemic manifestations						
Fever, *n* (%)	57 (12)	47 (13)	10 (8)	4 (7)	0.12	0.20
Constitutional syndrome, *n* (%)	175 (37)	132 (38)	43 (35)	20 (33)	0.55	0.47
PmR, *n* (%)	284 (60)	218 (62)	66 (54)	29 (48)	0.094	**0.022**
Large-vessel involvement, *n* (%)	254 (54)	211 (60)	43 (35)	20 (33)	<**0.0001**	<**0.0001**
Laboratory findings at the time of TCZ onset						
ESR, mm/first hour, median [IQR]	32 [12–57]	30 [11–54]	34 [15–67]	42 [12–67]	0.22	0.28

(Continued)

Table 1. (Continued)

	Overall (*n* = 471)	GCA without visual involvement (*n* = 349)	GCA with visual involvement (*n* = 122)	GCA with PVL at TCZ onset (*n* = 60)	P visual *versus* nonvisual involvement	P PVL *versus* nonvisual involvement
CRP (mg/dl), median [IQR]	1.5 [0.5–3.4]	1.4 [0.5–3.0]	1.5 [0.4–4.7]	1.5 [0.4–3.6]	0.042	0.30
Hemoglobin (g/dl), mean ± SD	12.6 ± 1.5	12.7 ± 1.5	12.3 ± 1.6	11.9 ± 1.4	**0.016**	**<0.0001**
Treatment at TCZ onset						
Prednisone dose, mg/day, median [IQR]	20 [10–40]	20 [10–30]	30 [15–45]	40 [30–50]	**<0.0001**	**<0.0001**
Methotrexate, *n* (%)	102 (22)	80 (25)	22 (18)	8 (13)	0.26	0.095
Leflunomide, *n* (%)	4 (1)	2 (1)	2 (2)	1 (2)	0.99	0.38
Azathioprine, *n* (%)	10 (2)	8 (2)	2 (2)	2 (3)	0.28	0.65
Hydroxychloroquine, *n* (%)	1 (0)	1 (0)	0 (0)	0 (0)	0.99	0.99
Antiplatelet, *n* (%)	216 (46)	142 (41)	74 (61)	36 (60)	**<0.0001**	**0.004**
Anticoagulant, *n* (%)	56 (12)	40 (11)	16 (13)	8 (13)	0.70	0.68
Lipid-lowering drug, *n* (%)	234 (50)	168 (48)	66 (54)	33 (55)	0.38	0.32
Antihypertensive drugs, *n* (%)	266 (56)	185 (53)	81 (66)	37 (62)	**0.016**	0.16
TCZ schedule						
TCZmono/TCZcombo	353/118	257/92	96/26	49/11	0.27	0.19
TCZ route						
IV/SC, (% IV)	238/233 (50)	176/173 (50)	62/60 (51)	33/27 (55)	0.94	0.51

ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; IQR, interquartile range; IV, intravenously; PmR, polymyalgia rheumatica; PVL, permanent visual loss; SC, subcutaneously; SD, standard deviation; TCZ, tocilizumab; TCZcombo, tocilizumab in combination with conventional synthetic immunosuppressants (besides glucocorticoids); TCZmono, tocilizumab in monotherapy (besides glucocorticoids).
Statistical significance is expressed as bold characters.
[a]CHADS2-score: stratification tool to predict the 1-year risk of ischemic stroke in a non-anticoagulated patient with non-valvular atrial fibrillation. To calculate the CHADS score, patients are assigned different points based on the risk factors for stroke (congestive heart failure: 1 point; hypertension: 1 point; age 75 years or older: 1 point; diabetes mellitus: 1 point; stroke/transient ischemic attack: 2 points).

Comparison between PVL patients who experienced visual improvement after TCZ onset and those who did not

Table 2 summarizes the main features of the patients with PVL who experienced visual improvement after starting TCZ and those who did not. Although the time between the development of visual complications and the initiation of TCZ therapy was shorter in the 11 patients who experienced visual improvement [median 95 (IQR 21–180) days] when compared with the remaining 49 patients with no improvement [median 180 (IQR 40–450) days], the difference was not statistically significant ($p = 0.26$). In this regard, age was the only variable associated with visual improvement following TCZ onset, since the patients who had ocular improvement were younger than those who did not [70 ± 11 *versus* 77 ± 8 years, HR 0.93; 95% confidence interval (CI): 0.87–0.99; $p = 0.034$].

Discussion

The present study provides data on visual involvement in 471 GCA patients treated with TCZ. Our results suggest that TCZ might be useful for the prevention and treatment of the visual manifestations of GCA. It is noteworthy that after the

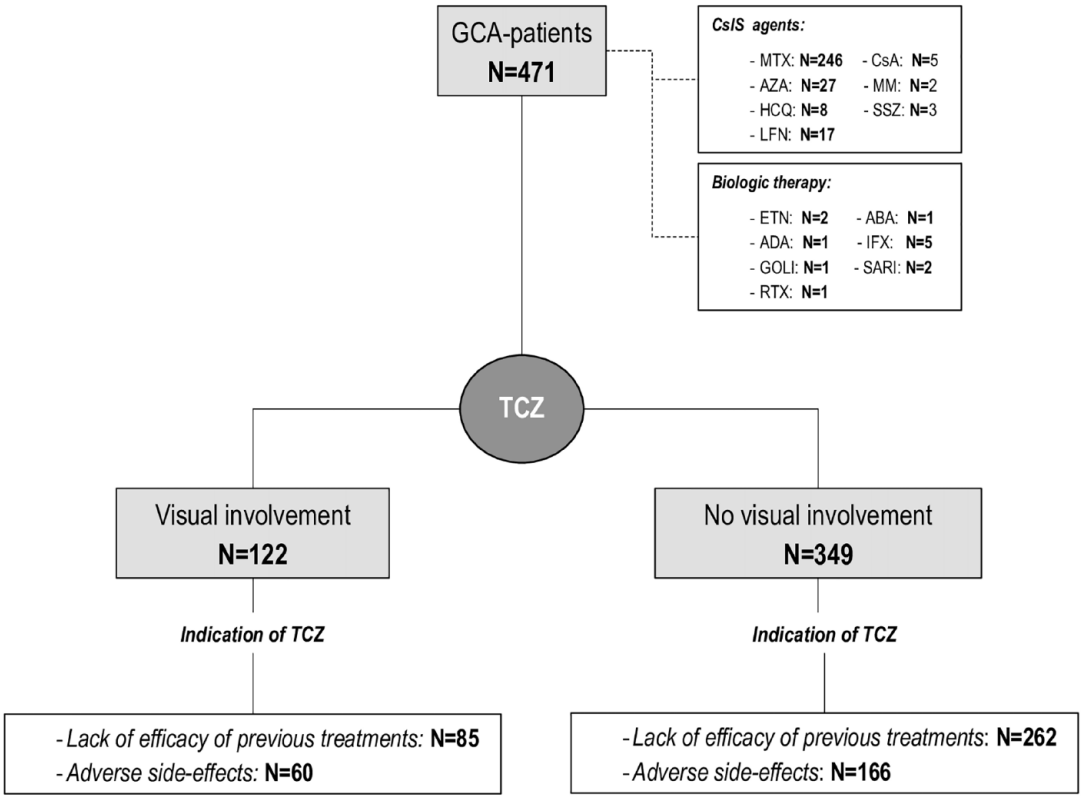

Figure 1. Flowchart summarizing the treatment of 471 patients with GCA treated with TCZ.
ABA, abatacept; ADA, adalimumab; AZA, azathioprine; CsA, cyclosporine A; CsIS, conventional synthetic immunosuppressants; ETN, etanercept; GCA, giant cell arteritis; GOLI, golimumab; HCQ, hydroxychloroquine; IFX, infliximab; LFN, leflunomide; MM, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; SARI, sarilumab; SSZ, sulfasalazine; TCZ, tocilizumab.

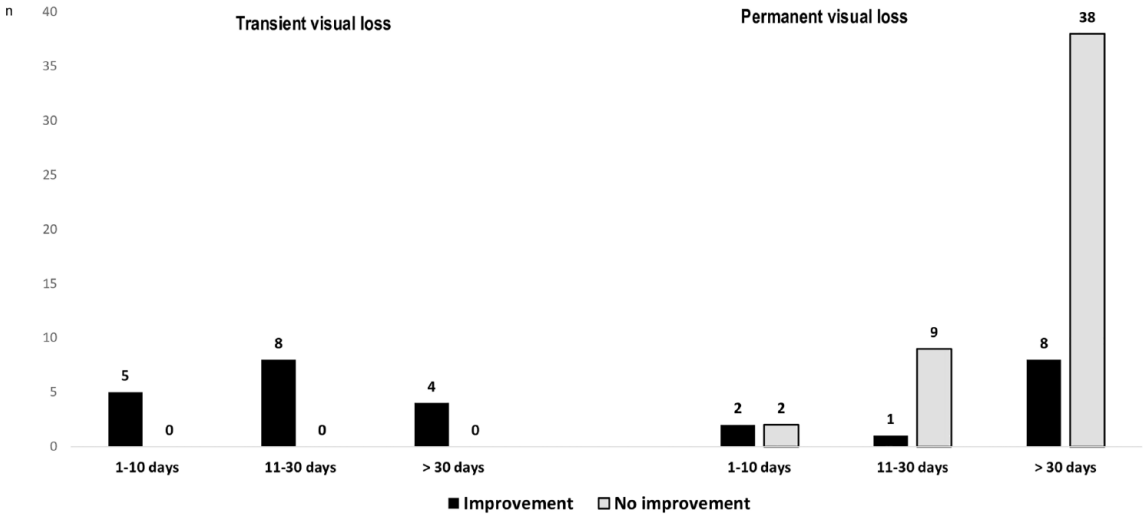

Figure 2. Efficacy of tocilizumab in giant cell arteritis patients with transient visual loss and permanent visual loss, according to the time between ocular involvement and tocilizumab onset.

Table 2. Differences between patients with permanent visual loss who experienced visual improvement after TCZ onset and patients who did not improve: hazards ratios for visual improvement.

	Improvement (*n* = 11)	No improvement (*n* = 49)	*p*	HR (95% CI)
General features				
Age (years), mean ± SD	70 ± 11	77 ± 8	**0.034**	**0.93 (0.87–0.99)**
Gender, female/male (% female)	9/2 (82)	32/17 (65)	0.15	0.92 (0.29–3.00)
Time from visual symptoms to TCZ onset				
Median [IQR]	95 [21–180]	180 [40–450]	0.26	1.00 (0.99–1.00)
⩽10 days, *n* (%)	2 (18)	2 (4)	0.28	2.48 (0.48–12.76)
11–30 days, *n* (%)	1 (9)	9 (18)	0.67	1.68 (0.77–3.66)
>30 days, *n* (%)	8 (73)	38 (78)	0.71	1.40 (0.37–5.32)
Cardiovascular risk factors				
High blood pressure	6 (55)	34 (69)	0.45	0.56 (0.16–1.99)
Dyslipidemia	8 (73)	24 (49)	0.16	3.03 (0.64–14.31)
Diabetes	4 (36)	12 (24)	0.45	1.80 (0.51–6.43)
Previous or current smoking history, *n* (%)	0 (0)	2 (4)	0.99	–
CHADS2 score,[a] median [IQR]	2 [0–2]	2 [1–2]	0.28	0.79 (0.40–1.56)
Ischemic manifestations				
Headache	7 (64)	35 (71)	0.71	0.72 (0.21–2.48)
Jaw claudication	6 (55)	20 (41)	0.51	1.69 (0.51–5.57)
Cerebrovascular accident	0 (0)	1 (2)	0.99	–
Systemic manifestations				
Fever	0 (0)	4 (8)	0.99	–
Constitutional syndrome	4 (36)	16 (33)	0.99	0.95 (0.28–3.24)
PmR	4 (36)	25 (51)	0.51	0.52 (0.15–1.81)
Large-vessel involvement	5 (45)	15 (31)	0.48	2.13 (0.65–7.01)
Laboratory findings				
ESR, mm/first hours, median [IQR]	44 [31–69]	36 [12–66]	0.54	1.01 (0.99–1.03)
CRP (mg/dl), median [IQR]	1.6 [0.4–4.1]	1.3 [1.0–2.3]	0.62	1.16 (0.87–1.21)
Hemoglobin (g/dl), mean ± SD	11.7 ± 1.1	12.0 ± 1.5	0.61	0.83 (0.52–1.34)
Pulses of IV MP at visual symptoms onset	7 (64)	35 (71)	0.72	0.73 (0.21–2.52)
Concomitant therapy at TCZ onset				
Prednisone dose (mg/day), median [IQR]	40 [30–45]	40 [29–50]	0.86	1.00 (0.97–1.04)

(Continued)

Table 2. (Continued)

	Improvement (*n* = 11)	No improvement (*n* = 49)	*p*	HR (95% CI)
Methotrexate	2 (18)	6 (12)	0.63	1.84 (0.40–8.54)
Other DMARDs	0 (0)	3 (6)	–	–
Antiplatelet	5 (45)	31 (63)	0.30	0.49 (0.14–1.71)
Anticoagulant	1 (9)	7 (14)	0.99	0.77 (0.90–6.80)
Lipid-lowering drug	8 (73)	25 (51)	0.17	2.93 (0.62–13.81)
Antihypertensive drug	6 (55)	31 (63)	0.71	0.65 (0.18–2.33)

CI, confidence interval; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HR, hazard ratio; IQR, interquartile range; IV, intravenously; MP, methylprednisolone; PmR, polymyalgia rheumatica; SD, standard deviation; TCZ, tocilizumab. Statistical significance is expressed as bold characters. *p* values refer to the difference between 'improvement' and 'nonimprovement' groups. [a]CHADS2-score: stratification tool to predict the 1-year risk of ischemic stroke in a non-anticoagulated patient with nonvalvular atrial fibrillation. To calculate the CHADS score, patients are assigned different points based on the risk factors for stroke (congestive heart failure: 1 point; hypertension: 1 point; age 75 years or older: 1 point; diabetes mellitus: 1 point; stroke/transient ischemic attack: 2 points).

initiation of TCZ, no patient developed a new visual impairment. Furthermore, none of the patients with TVL had more episodes and 18% of the cases with PVL experienced a total or partial improvement.

We observed that GCA patients who had jaw claudication and headache had more commonly visual manifestations. On the contrary, patients with PmR or those in whom extracranial large-vessel vasculitis involvement was confirmed had less visual manifestations. The frequency of ocular involvement in GCA varies widely, from 10% to 70%.[2,3,8,31–33] GC represent the cornerstone of the therapy for GCA, and adequate doses quickly improve clinical manifestations and prevent most additional cranial ischemic events.[2,34] Therefore, GC therapy must be started as soon as GCA is suspected to reduce the risk of blindness.[9] In this regard, ocular complications have been reduced since the introduction of GC therapy in GCA. In a population-based study from Olmsted County, the frequency of blindness decreased from 19% observed between 1950 and 1969 to 6% in the period of 1980–1985.[35] Regrettably, relapse of visual symptoms during the disease was described in about 5% of patients treated with GC in monotherapy.[10,11] The presence of new clinical manifestations and especially the high relapse rate in GCA despite GC, as well as the high morbidity associated with prolonged use of GC, has led to the search for new GC sparing agents. In our series, before TCZ onset, visual manifestations were observed in 122 (25.9%) cases throughout the disease. This proportion was similar to that reported in other series.[2] Once blindness is established, the visual prognosis is poor and only 15% of patients recover an acceptable vision despite the treatment with GC.[2,4,8] Therefore, the prevention and therapeutic approach of visual impairment in GCA patients receiving GC remain unmet needs, and new therapeutic targets are required. Noteworthy, serum IL-6 levels and IL-6 RNA expression within inflamed arteries are increased in patients with GCA.[10,36] TCZ is a monoclonal antibody against both the soluble and membrane-bound forms of the IL-6 receptor, which has been recently approved for the treatment of GCA. The GiACTA trial confirmed the efficacy of TCZ to induce remission, prevent relapses, and reduce the GC adverse effects deleterious burden in GCA patients.[14]

Nonetheless, data on the usefulness of TCZ for the visual manifestations of GCA remain scarce.[17,18,37,38] Three clinical trials, two placebo-controlled, phase II and III (GiACTA), and one open-label (GUSTO) trial have shown the efficacy of TCZ in GCA.[13–15] In the phase II trial, 25% of the patients who were randomized to TCZ plus prednisone had visual impairment at baseline.[13] However, no data about their visual outcomes during the follow-up were reported. At the baseline visit of the phase III GiACTA trial, 4 patients had unilateral blindness, 1 bilateral blindness, 2 ischemic optic neuropathy, 2 *amaurosis fugax*, and 14 reported blurred vision.[39] However, their clinical outcome throughout the study was not reported. One patient assigned to

TCZ (162 mg s.c. every other week) developed AION at week 24, while the patient was on concomitant prednisone (2 mg/day). On the other hand, 6 of the 18 patients in the GUSTO trial had visual involvement at baseline. The results of this trial have not yet been published, so data regarding this issue are unknown. We know that one of the patients developed AION 15 days after GC pulse therapy, while the patient was treated with TCZ in monotherapy. This patient had coronary heart disease and arterial hypertension as associated cardiovascular comorbidity.[15,18]

Recently, Unizony *et al.*,[17] have attempted to evaluate the potential usefulness of TCZ to control the visual manifestations in 60 patients diagnosed with GCA from clinical practice. In that series, 27 (45%) cases had GCA-related visual manifestations before starting TCZ. After TCZ onset, three patients had at least one flare with visual manifestations (*amaurosis fugax*, $n = 1$; blurred vision, $n = 3$). One of them was a patient without previous visual involvement before TCZ onset who had an episode of blurred vision after starting the biologic agent. No cases of AION occurred after starting TCZ.

Twenty-one (11%) of 186 GCA patients treated with GC and TCZ reported by Amsler *et al.*[18] had suffered from vision loss before inclusion. Fifty-four percent of eyes with visual loss showed stabilization of visual acuity, while 29% of eyes experienced improvement while taking TCZ plus GC. Two patients developed AION, one of them in the setting of the GUSTO clinical trial described above. The other was a 69-year-old male who developed AION in the left eye 2 weeks after the first cranial symptoms appeared and 2 days after an episode of *amaurosis fugax*. He received immediate treatment with pulses of 1 g of methylprednisolone for 3 days plus an IV infusion of TCZ at a dose of 8 mg/kg of body weight. Because the AION did not improve, he received three additional pulses of 500 mg of methylprednisolone followed by oral prednisolone. Two weeks later, while still taking prednisone (75 mg/day), he also lost vision in his right eye.

Our patients had a longer duration of disease and, consequently, had received GC, and in some cases, csIS for a longer period. All the included patients in the GUSTO trial, as well as 80% in the series by Unizony *et al.*, had a new-onset GCA.[15,17]

Some features of the disease such as *amaurosis fugax* or jaw claudication have been associated with PVL, whereas others such as PmR appeared to be associated with a reduced risk of visual complications.[1,2,5,8,31,40]

Most of these observations were also confirmed in our cohort. Furthermore, we also observed that large-vessel involvement may be a protective factor for the development of visual symptoms. Certainly, patients with a predominant extracranial-large vessel vasculitis pattern of the disease had a reduced risk of blindness.[41,42] These findings contribute to reinforcing the fact that GCA is a T-cell-driven disease with two main pathogenic pathways and phenotypes. Type 1 helper T cells (Th1) response is associated with the production of interferon-gamma (IFN-γ), being responsible for the ischemic manifestations, while Th17 response and its related cytokines such as IL-6 have been linked to the systemic inflammatory features.[43] In this regard, some studies have shown an association between lower levels of acute-phase reactants and the development of visual symptoms in GCA.[3,18,40,44] In our series, we did not observe such an association, probably because most of our patients had already been followed up for a long period, and had received previous treatment with high doses of GC and, many of them, also with csIS.

Moreover, classic atherosclerosis risk factors increase the risk of GCA ischemic ocular complications in several reports.[33,45,46] The presence of atherosclerosis risk factors at the time of diagnosis of GCA may influence the development of severe ischemic manifestations of the disease.[47] The presence of a high CHADS2-score has also been reported as a predictor of PVL.[45,48] In our series, we observed that hypertension and diabetes were more frequent in patients with visual involvement, as was the CHADS2-score.

Currently, the role of antiplatelet/anticoagulation therapy in reducing the risk of ischemic complications in GCA is controversial, and some authors disagree with the value of low-dose aspirin in GCA.[49–51] In fact, in our series, the percentage of patients who received antiplatelet therapy was lower in the group of patients with PVL and visual improvement than in the group of patients with PVL who did not improve, although statistical significance was not reached.

In the present study, none of the patients with TVL developed PVL while on TCZ, whereas once PVL was established, only a few recovered

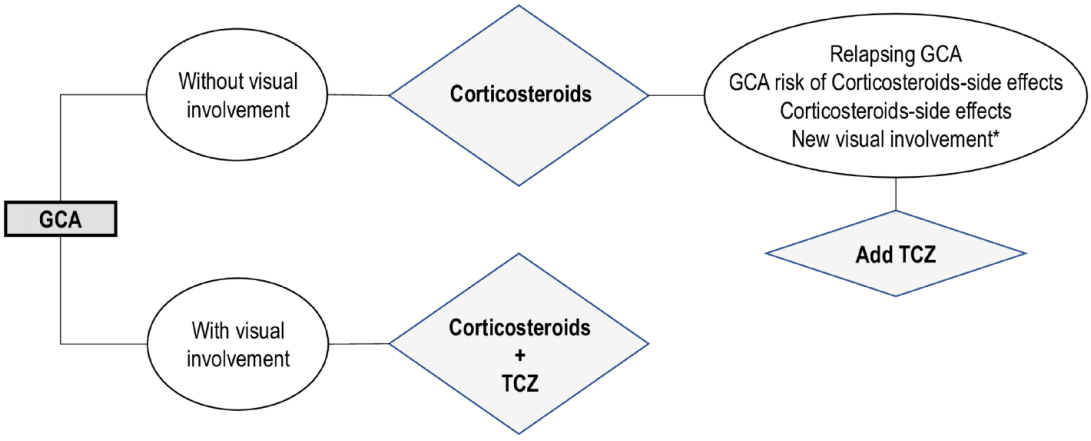

Figure 3. Proposed algorithm for the use of tocilizumab in giant cell arteritis with and without visual involvement.
GCA, giant cell arteritis; TCZ, tocilizumab.
*If new visual involvement, in addition to additional tocilizumab we recommend increased glucocorticoids dose.

the visual acuity. This was in accordance with studies from patients who only received GC.[2] In this regard, improvement of PVL is rare, especially if treatment is not started early. In a previous report,[2] seven of eight patients who experienced partial improvement started treatment with high-dose GC within 24 h of the onset of visual symptoms. In our series, the number of patients with PVL who started TCZ within 10 days of the onset of visual symptoms is small and none of them started TCZ within first 24 h. Considering the absence of recurrences in patients with TVL and the trend of a visual improvement in patients with PVL who started TCZ within the first 10 days after the onset of ocular manifestations, as occurs with GC therapy, a prompt initiation of TCZ seems to be essential for visual recovery. Therefore, the key message of our study can be that TCZ seems to be particularly effective to prevent the development of new ocular involvement or PVL in those patients with previous TVL. In addition, TCZ may also be useful in patients with PVL as long as it is started immediately after the onset of visual symptoms. According to these data, we propose the management algorithm shown in Figure 3. Thus, we suggest that in patients with GCA and visual manifestations the combination of GC plus TCZ can be used as the first-line therapeutic scheme.

Our study has some limitations, mainly due to its retrospective design. Furthermore, the multicenter design may be associated with some bias in data collection. Although no quantification of changes in visual acuity of the subjects was assessed in this study, an experienced ophthalmologist analyzed these modifications in the medical record. We acknowledge the limitation that, since our study was retrospective and performed in a real clinical practice setting, no sample size was calculated. In previous reports, TCZ prevention of new visual involvement has been described to range from 0.3% to 5%.[17,18] Since in our study, 11 of 60 (18%) patients improved after TCZ treatment, the statistical power calculated to detect such therapy effect was 99%. On the other hand, we recognize that the influence that steroids may have on the effect of TCZ was not clearly established in our study. However, according to our results, no significant differences were found in prednisone dose at TCZ onset between patients with visual improvement and those without it. Furthermore, to our knowledge, the present study represents the largest real-world study of the use of TCZ for GCA-related visual symptoms.

In conclusion, our results suggest that TCZ might be an effective therapy to control visual complications and to prevent the development of new visual manifestations in patients with GCA.

Author's note

This study was presented in part as an oral communication at the virtual EULAR meeting held in Frankfurt, Germany, in June 2021.

Declarations

Ethics approval and consent to participate

This research project was approved by the Clinical Research Ethics Committee of Cantabria with the internal code 2018.080 (signed on 19 September 2018).

Consent for publication

This is a retrospective study and signed consent for publication was not requested. To maintain anonymity, all patient data were de-identified. The research project was conducted following standard protocol and procedures that ensure compliance with the Declaration of Helsinki and standards of good clinical practice.

All co-authors have given their consent for publication of the article.

Author contribution(s)

Javier Loricera: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Writing – original draft.

Santos Castañeda: Formal analysis; Investigation; Supervision; Validation; Writing – review & editing.

Clara Moriano: Investigation; Supervision; Validation; Visualization; Writing – review & editing.

Javier Narváez: Formal analysis; Supervision; Validation; Visualization; Writing – review & editing.

Vicente Aldasoro: Conceptualization; Supervision; Validation; Writing – review & editing.

Olga Maiz: Methodology; Supervision; Validation; Visualization; Writing – review & editing.

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José L. Callejas: Investigation; Supervision; Validation; Visualization; Writing – review & editing.

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Lara Sánchez-Bilbao: Formal analysis; Supervision; Validation; Visualization; Writing – review & editing.

Mónica Calderón-Goercke: Investigation; Supervision; Validation; Visualization; Writing – review & editing.

Alfonso Casado: Conceptualization; Formal analysis; Funding acquisition; Methodology; Supervision; Validation; Visualization; Writing – review & editing.

José L. Hernández: Formal analysis; Investigation; Supervision; Validation; Visualization; Writing – review & editing.

Miguel A. González-Gay: Formal analysis; Investigation; Supervision; Validation; Visualization; Writing – review & editing.

Ricardo Blanco: Conceptualization; Formal analysis; Investigation; Supervision; Validation; Writing – review & editing.

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Competing interests

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Availability of data and materials

Not applicable.

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