Features and risk factors for new (secondary) permanent visual involvement in giant cell arteritis

M.F. Curumthaullee[1], E. Liozon[2], S. Dumonteil[2], G. Gondran[2], A.-L. Fauchais[2], K.-H. Ly[2], P.-Y. Robert[1], S. Parreau[2]

[1]Department of Ophthalmology, [2]Department of Internal Medicine, Dupuytren University Hospital, Limoges, France.

Abstract

Objective

New permanent visual loss (PVL) in treated patients with giant cell arteritis (GCA) is a rare but worrisome occurrence. In this study, we aimed to describe the frequency and main features of new PVL occurring after the beginning of glucocorticoid therapy in patients with newly diagnosed GCA.

Methods

We included in an inception cohort all consecutive patients newly diagnosed with GCA in the internal medicine department of a tertiary-care hospital between 1976 and May 2020. The study population comprised all the patients without bilateral PVL before treatment who were followed for at least one year. Only well-documented visual events that set after the initiation of glucocorticoid treatment were regarded as new PVL.

Results

Eleven out of 502 patients (2.2%) experienced a new PVL including 6 occurrences during the initial therapeutic phase and 5 during the tapering phase. Patients with new PVL during treatment had higher mean age, more often displayed temporal artery abnormalities on physical examination, and had higher mean platelet counts at GCA onset. There was a strong excess risk of contralateral recurrence during treatment in patients with unilateral loss at GCA onset compared with patients with uncomplicated GCA (10.5% vs 1.1%, OR=10.26, p<0.001).

Conclusion

New PVL in treated GCA is a rare, but significant occurrence. Older patients and patients who already had unilateral PVL at diagnosis have higher risk of new ischaemic visual loss during treatment compared to the other patients. Close clinical, laboratory, and eye monitoring of these high-risk patients is of paramount importance.

Key words

giant cell arteritis, visual, risk factors, cohort studies, glucocorticoids

Muhammad Faiz Curumthaullee, MD
Eric Liozon, MD
Stéphanie Dumonteil, MSc
Guillaume Gondran, MD
Anne-Laure Fauchais, MD, PhD
Kim-Heang Ly, MD, PhD
Pierre-Yves Robert, MD, PhD
Simon Parreau, MD

Please address correspondence to:
Eric Liozon,
Service de Médecine Interne A,
CHRU Dupuytren 2,
16 Rue du Professeur Bernard Descottes,
87042 Limoges, France.
E-mail: eric.liozon@chu-limoges.fr
liozone@yahoo.fr

Received on July 29, 2021; accepted in revised form on November 8, 2021.

Competing interests: none declared.

Introduction

Giant cell arteritis (GCA) is the most common vasculitis in people aged fifty or more and preferentially affects the thoracic aorta and its main branches including temporal arteries (1). Treatment is based on long-term high-dose corticosteroid therapy, which is fraught with frequent side-effects (2). Moreover, relapses occur in half of the patients during tapering and discontinuation of treatment (3). Efforts have been, therefore, made for several decades to better understand the pathophysiology of GCA thereby determining new therapeutic targets aimed at corticosteroid sparing (4).

The primary cause of disability in GCA is permanent visual impairment, which occurs in 14-18% of patients (5-12). Given the high risk of unforeseeable, sudden blindness, sometimes bilateral, GCA remains an absolute medical emergency. Visual loss most often occurs in untreated subjects with new onset GCA, the visual risk decreasing dramatically after initiation of high dose GC treatment. Any delay in initiating treatment may, therefore, be detrimental to the patient's sight.

Conversely, new permanent visual loss in treated patients is regarded as a rare occurrence, although it has been described to occur in the first few days of GC treatment or, exceptionally later, during the GC tapering (5-8, 13, 14). Although the fear of secondary visual events obviously has represented a major constraint on building rapidly decreasing GC protocols, there is still little medical research on this topic. The present study aimed to describe the frequency and main features of, and risk factors for, permanent visual loss occurring after the beginning of therapy in patients with newly diagnosed GCA.

Methods

Patients and data collection

Inception GCA cohort. From 1976 through May 2020, we included all consecutive patients diagnosed in the internal medicine department of a tertiary-care teaching hospital for the diagnosis and treatment of GCA and regularly followed up these patients until they were recovered. GCA was diagnosed based on the criteria of the American College of Rheumatology (15) and was considered present in biopsy-negative cases if at least three of these criteria were fulfilled or if only two criteria were fulfilled but fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans showed strong uptake of the large vessel walls (16). In biopsy-proven cases, GCA was pathologically confirmed on temporal artery biopsy using currently accepted criteria. Clinical, laboratory, and pathological data were prospectively recorded at the time of first admission using a specifically designed 176-item questionnaire of detailed history and log data. All study data were stored in computerised files and regularly updated (17).

Visual impairment

We included in the study all permanent visual impairments that were confirmed by the Ophthalmology staff and resulted from anterior ischaemic optic neuropathy (AION), posterior ischaemic optic neuropathy (PION), central retinal artery occlusion (CRAO), or occipital stroke. Amaurosis fugax, diplopia and oculomotor paralysis were excluded because they do not result in permanent visual impairment. Patients who already had bilateral visual impairment from GCA before initiation of corticosteroid therapy also were excluded from study. Likewise, worsening of an already established visual complication at the beginning of GC treatment was not regarded as a new visual event; only ischaemic visual events that started after the initiation of corticosteroid therapy were eligible to the study.

Clinical variables and definitions

Clinical variables extracted from the computerised files were associated polymyalgia rheumatica, new onset of localised headache, scalp tenderness, jaw claudication, visual ischaemic impairment. Temporal artery was considered abnormal if any among the following features was present: decrease or absent pulse, beaded and/or indurated artery, local redness, or tenderness. Constitutional syndrome was defined

by a temperature of more than 38°C for more than a week associated with severe asthenia and/or a weight loss of more than 5%.

Treatment

Patients were treated using standardised protocols with prednisone at a starting dose of 0.6–1 mg/kg/d, according to clinical severity of the disease. Patients without ischaemic visual symptoms received a dose of 0.6–0.8 mg/kg/d prednisone until they became asymptomatic and the C-reactive protein level has fallen below 0.5mg/dl. Then the dose was gradually decreased to 0.35 mg/kg/d over 4 to 6 weeks. Patients with ischaemic visual impairment or visual threat (amaurosis fugax, abnormal eye fundus or altered ophthalmic artery ultrasound Doppler) initially received a starting dose of 0.9-1mg/kg/d prednisone, often preceded by pulse high dose methylprednisolone, and then the dose was decreased similarly. The initial therapeutic phase comprised the duration of treatment at the initial dose including days on methylprednisolone pulses while the tapering phase represented the duration of GC treatment from the first dosage decrement to planned cessation.

Statistical analysis

Data were extracted and analysed retrospectively from information initially collected prospectively from the patients' charts. We compared the clinical and laboratory variables of patients with new visual impairment with those of the rest of the cohort. We also compared the frequency of occurrence of new PVL, according to the initial eye status of the patient (*e.g.* unilateral PVL versus both spared eyes). Quantitative variables were expressed as medians and standard deviation. Qualitative variables were expressed as frequencies with percentages. Comparisons were made by Pearson's Chi-2 test, Fisher's exact test, or Wilcoxon test as appropriate for each variable. A *p*-value less than 0.05 was considered to be significant. All calculations were performed using R software v. 3.2.2 (R foundation for statistical computing, Vienna, Austria).

Table I. Characteristics of the cohort with comparison between patients with new ischaemic visual loss and patients without that event.

Patients, n	Absence of new permanent visual impairment (n = 491)	New permanent visual impairment (n = 11)	Total (n = 502)	*p*-value*
	numbers (%) or median [interquartile]			
Clinical characteristics				
Male gender	174 (35.4)	3 (27.3)	177 (35.3)	0.7541
Body weight (kg)	62.9 (12.4)	61.5 (12.7)	62.8 (12.4)	0.7099
Age (y)	74.0 (7.8)	79.4 (9.0)	74.1 (7.9)	0.0138
Abnormal temporal artery	277 (57.2)	10 (90.9)	287 (58.0)	0.0293
Polymyalgia rheumatica	161 (32.8)	2 (18.2)	163 (32.5)	0.5161
Headache	405 (82.5)	10 (90.9)	415 (82.7)	0.6987
Scalp tenderness	230 (48.4)	8 (72.7)	238 (49.0)	0.1344
Jaw claudication	154 (31.4)	6 (54.5)	160 (31.9)	0.1938
Fever	207 (42.6)	3 (27.3)	210 (42.3)	0.3699
Constitutional syndrome	364 (74.7)	6 (54.5)	370 (74.3)	0.2432
Amaurosis fugax	43 (8.8)	0 (0.0)	43 (8.7)	0.6105
Unilateral permanent visual loss	51 (10.4)	6 (54.5)	57 (11.4)	<0.0001
Positive TAB	346 (72.5)	9 (81.8)	355 (72.7)	0.7350
Number of ACR criteria met	4.0 (0.9)	4.6 (0.7)	4.04 (0.9)	0.0656
Laboratory characteristics				
ESR, mm/h	86.4 (29.5)	85.1 (30.0)	86.4 (29.5)	0.9373
CRP, mg/dl	95.8 (67.6)	102.9 (40.0)	96.0 (67.1)	0.3415
Fibrinogen, g/l	6.8 (1.7)	7.7 (1.4)	6.8 (1.7)	0.1293
Albumin, g/l)	33.8 (5.7)	31.4 (4.5)	33.8 (5.7)	0.2238
Haemoglobin, g/l	115.6 (17.2)	119.0 (16.9)	115.7 (17.2)	0.5175
White blood cells, g/l	9289.8 (3123.2)	9901.8 (2880.7)	9304.0 (3116.3)	0.4239
Platelets, G/l	436.0 (156.9)	537.3 (159.5)	438.1 (157.5)	0.0116
Treatment				
Pulse methylprednisolone	109 (22.2)	7 (63.6)	116 (23.1)	0.0043
Prednisone initial dose (mg/kg/d)	0.8 (0.2)	0.9 (0.1)	0.8 (0.2)	0.0030
Duration of initial treatment (d)	19.1 (10.0)	21.9 (7.5)	19.1 (10.0)	0.1550
Dose at 3 months (mg/d)	18.3 (6.3)	18.0 (5.5)	18.3 (6.2)	0.9505
Dose at 6 months (mg/d)	12.3 (4.8)	10.3 (5.2)	12.2 (4.8)	0.4562
Dose at 12 months (mg/d)	7.0 (4.4)	12.0 (7.9)	7.1 (4.5)	0.0531
Duration of treatment (mo.)	34.2 (26.3)	30.2 (25.6)	34.1 (26.3)	0.8631
Outcome issues				
Duration of follow-up (mo.)	95.0 (66.5)	68.6 (66.5)	94.4 (66.5)	0.1332
Relapses	301 (61.3)	8 (72.7)	309 (61.6)	0.5430
Death during treatment	32 (6.5)	4 (36.4)	36 (7.2)	0.0051

* Comparisons were made using Pearson's Chi-2 test, Fisher's exact test, or Wilcoxon test as appropriate for each variable.

TA: temporal artery; PMR: polymyalgia rheumatica; TAB: temporal artery biopsy; ACR: American college of rheumatology; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Ethics board approval and informed consent

All data concerning these elderly patients with GCA were retrospectively collected. This study was conducted in compliance with the Good Clinical Practice and Declaration of Helsinki principles. In accordance with the French law, formal approval from an ethics committee and written informed consent were not required for this type of retrospective study, provided the patient has not exercised the right to reject his participation to study.

Results

Characteristics of the cohort

From 1976 through May 2020, 584 patients were included in the inception cohort. Seventeen patients with initial bilateral PVL from GCA before the initiation of glucocorticoid therapy were excluded, as were 65 other patients, for various reasons, mainly early death or inadequate follow-up. A total of 502 GCA patients (355 biopsy-proven) met the entry criteria and were included in the study (Fig. 1). Fifty-seven (11.4%) patients had unilateral permanent vis-

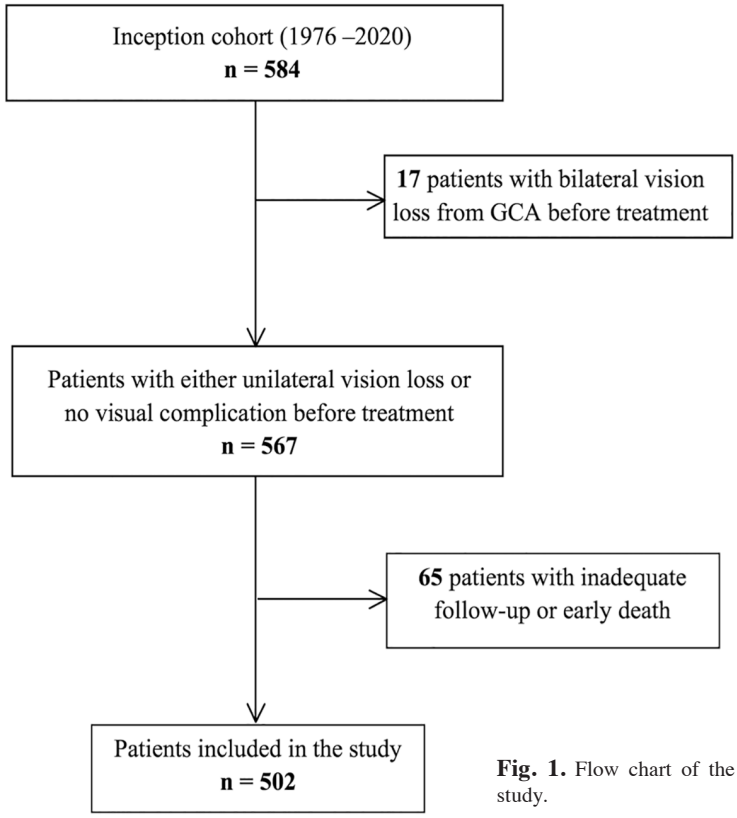

Fig. 1. Flow chart of the study.

ual loss occurrence at GCA onset. The 502 patients were followed for 7.9 (5.5 SD) years.

New visual impairment

In all, 11 patients (2.2%) developed new ischaemic visual impairment after the initiation of corticosteroid therapy. Nine (82%) had biopsy-proven GCA. Table II depicts the main characteristics of these patients. Six (55%) had a visual event during the initial therapeutic phase (median=6 days) while the remaining 5 (45%) patients including 4 with biopsy-proven GCA experienced visual loss during the tapering phase (median=11 months). Of the 11 patients, 6 had contralateral AION prior to corticosteroid treatment, four of whom developed contralateral loss during the early phase of GC treatment. New visual impairments during treatment were mainly AION (73%). Other impairments included CRAO (n=1), PION (n=1) and, occipital stroke (n=1). One patient had two consecutive episodes AION occurring after the start of treatment (2 and 9 days respectively). During the period of tapering, all the patients with secondary visual impairment also showed an increase in their biological inflammatory parameters. No patients had a visual relapse after planned treatment discontinuation.

Among-groups comparisons

Table I shows the comparison between both groups of patients. Patients with a new visual event were older and more often displayed abnormality on temporal artery palpation compared with patients without a new event. Other symptoms characterising GCA were not different between the two groups. Among the inflammatory parameters, only platelet levels were higher in the group with new visual event. Regarding treatment issues, patients with a

Table II. Characteristics of the 11 patients with new visual impairment (*e.g.*, event occurring after initiation of treatment).

Case	Sex/Age	Initial visual impairment*	Associated symptoms	CRP (mg/dl)	TAB	Initial corticosteroid treatment (mg/kg/day)	Pulse MP	Duration of initial treatment (days)¶	New visual impairment§	Time of onset	Prednisone dose during new visual impairment (mg/d)
1	F/79	AION	Headache	9.7	+	1	+	11	AION	4 days	50
2	F/85	-	JC, CS	9.1	+	1	+	16	Bilateral AION	2 + 9 days	60
3	M/90	AION	-	-	+	0.85	-	23	AION	6 days	50
4	F/91	AION	-	6.6	+	1	+	30	AION	7 days	60
5	F/78	AION	-	14.1	+	1	+	32	AION	8 days	80
6	F/78	-	Headache, JC	12.0	+	0.7	-	21	CRAO	11 days	85
7	M57	AION	Headache	1.9	-	1	+	23	PION	6 months	17
8	F/78	-	Headache, PMR	12.0	+	1	-	30	AION	8 months	9
9	M/77	-	Headache, CS	8.9	+	0.7	-	14	AION	11 months	11
10	F/78	-	Headache, PMR	15.7	+	0.7	-	13	Occipital stroke	13 months	7
11	F/82	AION	-	1.29	-	1	+	28	AION	15 months	3

AION: anterior ischaemic optic neuropathy; JC: jaw claudication; CS: constitutional syndrome; PMR: polymyalgia rheumatica; CRP: C-reactive protein; TAB: temporal artery biopsy; CRAO: central retinal artery occlusion; PION: posterior ischaemic optic neuropathy; MP: methylprednisolone.
*Before initial corticosteroid therapy.
¶Since the diagnosis of GCA.
§After initial corticosteroid therapy.

Table III. Review of published studies both focusing on early and late ischaemic visual events in patients with giant cell arteritis.

Study (year)	Numbers of patients	Visual events occurring during initial GC treatment, n (%)	Visual events occurring during GC tapering or after discontinuation, n (%)	Total, n (%)
Beevers (1973)	36	0	2 (5.5)	2 (5.5)
Jonasson (1979)	136	4 (2.9)	4 (2.9)	8 (5.9)
Myles (1992)	96	0	1 (1)	1 (1)
Kyle (1993)	35	0	1 (2.8)	1 (2.8)
Aiello (1993)	327	3 (0.9)	2 (0.6)	5 (1.5)
Liu (1994)	185	3 (1.6)	6 (3.2)	9 (4.9)
Font (1997)	146	1 (0.7)	1 (0.7)	2 (1.4)
Gonzalez gay (1998)	239	4 (1.6)	0	4 (1.6)
Hoffman (2002)	98	0	8 (8)	8 (8)
Hayreh (2003)	144	1 (0.7)	0	1 (0.7)
Nesher (2004)	166	0	8 (4.8)	8 (4.8)
Salvarani (2005)	136	0	1 (0.7)	1 (0.7)
Hoffman (2007)	44	0	7 (16)	7 (16)
Nesher (2008)	116	0	5 (4.3)	5 (4.3)
Alba (2014)	106	0	1 (0.9)	1 (0.9)
Hoçevar (2016)	68	0	1 (1.5)	1 (1.5)
Restucia (2017)	157	0	1 (0.6)	1 (0.6)
Leon (2018)	168	0	1 (0.6)	1 (0.6)
Unizony (2021)	60	0	2 (3.3)	2 (3.3)
Total	2[a]463	16 (0.7)	52 (2.1)	68 (2.8)

new visual event more often had received pulse methylprednisolone and an initial dose of prednisone of 1 mg/kg/d. In contrast, the duration of treatment of the initial and tapering phases did not differ, nor did the doses at 3, 6 and 12 months. In addition, there was an excess risk of contralateral recurrence during treatment in patient with unilateral loss at GCA onset compared with the rest of the cohort (10.5% *vs*. 1.1%, Fisher's exact test, OR=10.26, CI: 2.51-44.08, $p<0.001$).

Discussion

In patients with newly diagnosed GCA, the risk of permanent visual event after initiation of treatment is a key element of the disease management. In this large comparative study, we found 2.2% of permanent visual loss after the beginning of corticosteroid therapy, making it a rare event. Pooling the results of 18 clinical studies including a total of 2463 patients (5-8, 11-13, 18-29), we found that secondary permanent visual loss occurred in 2.8% of the cases in average (Table III). Noteworthy, the proportion of patients experiencing a visual event during the initial phase of GC treatment is higher in the present study (55%) than in the literature review (25%). In a recent meta-analysis by Bugdayli *et al*. (30), the incidence of secondary permanent visual damage was lower (1.5%), but the authors excluded events occurring less than 4 weeks after starting GC treatment. The highest rate of secondary visual events was found in the clinical trial of methotrexate by Hoffmann *et al*. in which 16% of the patients suffered a secondary permanent visual loss (21). Use of an aggressive GC tapering best explains late visual events being observed at such a high frequency. In fact, patients included in this study were planned to receive a prednisone dose less than 10mg/d at 3 months, which may prove risky. On the contrary, of 174 patients with biopsy-proven GCA uniformly treated and followed with prudent corticosteroid tapering, 74 experienced relapses or recurrences, none of whom suffered visual loss (31). Thus, blindness following disease relapses in GCA patients adequately treated is very uncommon.

The predictive factors of new visual event after the beginning of corticosteroid therapy still are not well established. In an epidemiologic study, the best predictive model of biopsy-proven GCA included an abnormal temporal artery on physical examination (OR =3.2), and the presence of visual complications (OR = 4.9) (32). Although patients included in the present study displayed either of these features in 100% of the cases, the too small sample precludes any statistical confirmation of a relationship between biopsy-proven GCA and late visual loss. In the present study, most patients (4 in the early group and 2 in the tapering group) who experienced visual loss during GC treatment already had unilateral PVL from AION and there was strong excess risk of contralateral recurrence during treatment in such patients. Accordingly, Nesher *et al*. found a strong association between ischaemic visual impairment at GCA onset and subsequent cranial ischaemic events including permanent visual loss and stroke (OR=8.3, $p=0.001$) (11). In the study by Aiello *et al*. in case of an initial ischaemic visual damage, the probability of developing a new PVL was 13% at 5 years, whereas it was only 1% in its absence (5). In a study of 67 GCA-related AION, Chan *et al*. found 7 ischaemic eye recurrences (10%), occurring between 3 and 36 months (33). In this study, no predictive factors for recurrence were identified. In a meta-analysis of 39 studies including 1296 patients, Loddenkemper *et al*. found a highly significant correlation (Pearson's correlation coefficient 0.604, $p<0.0001$) between the percentage of patients with visual loss on presentation and visual loss under corticosteroid therapy (34). Thus, patients with permanent loss of vision of one eye at GCA onset should be closely monitored during corticosteroid therapy until recovery to detect any disease flare early. This should lead to readjust the treatment in a timely manner, thereby avoiding a devastating ischaemic recurrence on the fellow eye.

Secondary visual impairment in GCA appears biphasic. The first peak of frequency is during the first week of the treatment and the second peak during the tapering phase. In most patients, visual loss is due to AION. The optic nerve head is vascularised primarily by the short posterior ciliary arteries (35). Angiographic (36) and histological (37) studies showed that these arter-

ies are completely occluded in AION. According to Hayreh, there is also a decrease in choroidal perfusion in the unaffected controlateral eye, despite normal visual acuity, in patients with AION (38). The progression of visual loss in these patients may be due to the delay in initiating corticosteroid therapy and its progressive onset of action. In complicated GCA, the short posterior ciliary arteries present granulomatous inflammation with giant cells, intimal thickening, and thrombotic occlusion of the arterial lumen (39). Even aggressive corticosteroid therapy will take time or might be ineffective to stop the threatening vasculitic process, especially the vascular remodelling that has already occurred. Nevertheless, the earlier the treatment is started, the better the chances of preventing blindness (7, 26).

Hypoperfusion of the optic nerve head may be another factor precipitating early recurrence. Ocular perfusion depends on mean arterial blood pressure, intraocular pressure and blood flow resistance (40). Any decrease in mean arterial blood pressure or increase in intraocular pressure or a combination of both can compromise the blood supply to the papilla and accelerate visual loss (41). Visual decline often occurs in the morning upon awakening, as in non-arteritic AION (42), suggesting that nocturnal arterial hypotension could either contribute to completing a thrombotic stasis occlusion or decrease the perfusion pressure below the critical threshold of partially occluded ciliary arteries, compromising circulation for a period long enough to cause AION (43). It is therefore legitimate to prevent hypotensive overmedication during this critical period. Overall, other traditional cardiovascular risk factors (44, 45) and the $CHADS_2$-VASc score (46) may increase the risk of PVL in GCA patients. Whether these factors also apply to the risk of developing new visual loss during treatment is unknown, however, owing to the rarity of this event.

Although most reversible manifestations of GCA improve within hours or days of initiation of corticosteroid therapy, vascular parietal inflammation persists for a long time. Histological analysis of temporal artery biopsies months after treatment demonstrated the persistence of inflammatory lesions in situ several months after the diagnosis of GCA even under corticosteroid therapy (47). This may explain late PVL recurrences, especially if corticosteroid therapy is reduced too quickly, as the methotrexate and the infliximab prospective trials highlighted (21, 23), or stopped prematurely. Whether the addition of antiplatelet agents to GCs therapy in GCA would improve the visual prognosis is disputed (48-50).

The role of tocilizumab in complicated GCA deserves discussion. Interleukin-6 blockade has been shown to decrease significantly the risk of GCA relapses during corticosteroid tapering, along with a favourable safety profile, both in randomised controlled trials and a retrospective study (51). In a real-life observational study, Unizony *et al*. recently demonstrated that Tocilizumab significantly decreases the rate of ischaemic visual recurrences including amaurosis fugax, transient diplopia, blurred vision and PVL in patients with inaugural ischaemic visual manifestations in GCA (29). Offering to patients with complicated GCA a targeted therapy such as tocilizumab early could have a beneficial effect on the ultimate visual prognosis. Further studies are needed to confirm this hypothesis. Moreover, the early addition of tocilizumab in complicated forms of GCA could have a positive impact on survival. Indeed, we recorded more fatalities occurring during GC treatment in patients with secondary visual impairment compared to other patients. A higher mean patient's age and heavier burden of GC treatment may best explain this finding, since these patients more often received initially pulse methylprednisolone and/or prednisone at 0.9 mg/kg/day or more and might thus have been overexposed to serious therapeutic complications.

New permanent visual loss in treated GCA patients is a rare, but serious occurrence. There is an increased risk of developing permanent visual loss during treatment after a first loss at disease onset and such patients could also have decreased survival. Besides the compelling need for closer monitoring and thorough management of disease flares in patients with initial unilateral visual loss, both pathophysiological backgrounds of ischaemic visual deterioration and recent data supporting the use of IL-6 blockade in uncomplicated (52) or complicated (29) GCA call for prospective studies aimed at determining to which extent tocilizumab prevents further visual deterioration and has steroid-sparing effect in patients with unilateral visual loss at GCA onset.

References

1. WEYAND CM, GORONZY JJ: Giant-cell arteritis and polymyalgia rheumatica. *N Engl J Med* 2014; 371: 50-7.
2. PROVEN A, GABRIEL SE, ORCES C, O'FALLON WM, HUNDER GG: Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003; 49: 703-8.
3. MAINBOURG S, ADDARIO A, SAMSON M *et al*.: Prevalence of giant cell arteritis relapse in patients treated with glucocorticoids: a meta-analysis. *Arthritis Care Res* 2020; 72: 838-49.
4. AKIYAMA M, OHTSUKI S, BERRY GJ, LIANG DH, GORONZY JJ, WEYAND CM: Innate and Adaptive Immunity in Giant Cell Arteritis. *Front Immunol* 2021; 11: 621098.
5. AIELLO PD, TRAUTMANN JC, MCPHEE TJ, KUNSELMAN AR, HUNDER GG: Visual prognosis in giant cell arteritis. *Ophthalmology* 1993; 100: 550-5.
6. LIU GT, GLASER JS, SCHATZ NJ, SMITH JL: Visual morbidity in giant cell arteritis. Clinical characteristics and prognosis for vision. *Ophthalmology* 1994; 101: 1779-85.
7. GONZALEZ-GAY MA, BLANCO R, RODRIGUEZ-VALVERDE V *et al*.: Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. *Arthritis Rheum* 1998; 41: 1497-504.
8. GONZALEZ-GAY MA, GARCIA-PORRUA C, LLORCA J *et al*.: Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. *Medicine* 2000; 79: 283-92.
9. LIOZON E, HERRMANN F, LY K *et al*.: Risk factors for visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. *Am J Med* 2001; 111: 211-7.
10. FONT C, CID MC, COLL-VINENT B, LOPEZ-SOTO A, GRAU JM: Clinical features in patients with permanent visual loss due to biopsy-proven giant cell arteritis. *Br J Rheumatol* 1997; 36: 251-4.
11. NESHER G, BERKUN Y, MATES M *et al*.: Risk factors for cranial ischemic complications in giant cell arteritis. *Medicine* 2004; 83: 114-22.
12. SALVARANI C, CIMINO L, MACCHIONI P *et al*.: Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. *Arthritis Rheum* 2005; 53: 293-7.
13. JONASSON F, CULLEN JF, ELTON RA: Tempo-

ral arteritis. A 14-year epidemiological, clinical and prognostic study. *Scott Med J* 1979; 24: 111-17.
14. HAYREH SS, ZIMMERMAN B: Visual deterioration in giant cell arteritis while on high doses of corticosteroid therapy. *Ophthalmology* 2003; 110: 1204-15.
15. HUNDER GG, BLOCH DA, MICHEL BA *et al*.: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990; 33: 1122-28.
16. DE BOYSSON H, DUMONT A, LIOZON E *et al*.: Giant-cell arteritis: Concordance study between aortic CT angiography and FDG-PET/CT in detection of large-vessel involvement. *Eur J Nucl Med Mol Imaging* 2017; 44: 2274-9.
17. LIOZON E, DALMAY F, LALLOUE F *et al*.: Risk factors for permanent visual loss in biopsy-proven giant cell arteritis: A study of 339 patients. *J Rheumatol* 2016; 43: 1393-9.
18. BEEVERS DG, HARPUR JE, TURK KA: Giant cell arteritis--the need for prolonged treatment. *J Chronic Dis* 1973; 26: 571-84.
19. MYLES AB, PERERA T, RIDLEY MG: Prevention of blindness in giant cell arteritis by corticosteroid treatment. *Rheumatology* 1992; 31: 103-5.
20. KYLE V, HAZLEMAN BL: The clinical and laboratory course of polymyalgia rheumatica/giant cell arteritis after the first two months of treatment. *Ann Rheum Dis* 1993; 52: 847-50.
21. HOFFMAN GS, CID MC, HELLMANN DB *et al*.: A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002; 46: 1309-18.
22. HAYREH SS, ZIMMERMAN B: Visual deterioration in giant cell arteritis patients while on high doses of corticosteroid therapy. *Ophthalmology* 2003; 110: 1204-15.
23. HOFFMAN GS, CID MC, RENDT-ZAGAR KE *et al*.: Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med* 2007; 146: 621-30.
24. NESHER G, NESHER R, MATES M, SONNENBLICK M, BREUER GS: Giant cell arteritis: intensity of the initial systemic inflammatory response and the course of the disease. *Clin Exp Rheumatol* 2008; 26: (Suppl. 49): S30-4.
25. ALBA MA, GARCÍA-MARTÍNEZ A, PRIETO-GONZÁLEZ S *et al*.: Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. *Medicine* (Baltimore) 2014; 93: 194-201.
26. HOCEVAR A, ROTAR Z, JESE R *et al*.: Do early diagnosis and glucocorticoid treatment decrease the risk of permanent visual loss and early relapses in giant cell arteritis. *Medicine* (Baltimore) 2016; 95: e3210.
27. RESTUCCIA G, BOIARDI L, CAVAZZA A *et al*.: Long-term remission in biopsy proven giant cell arteritis: A retrospective cohort study. *J Autoimmun* 2017; 77: 39-44.
28. LEON L, RODRIGUEZ-RODRIGUEZ L, MORADO I *et al*.: Treatment with methotrexate and risk of relapses in patients with giant cell arteritis in clinical practice. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S121-8.
29. UNIZONY S, MCCULLEY TJ, SPIERA R *et al*.: Clinical outcomes of patients with giant cell arteritis treated with tocilizumab in real-world clinical practice: decreased incidence of new visual manifestations. *Arthritis Res Ther* 2021; 23: 8.
30. BUGDAYLI K, UNGPRASERT P, WARRINGTON K, KOSTER M: Visual ischemia during relapse and follow-up of giant cell arteritis: a systematic review [abstract]. *Arthritis Rheumatol* 2020; 72 (Suppl. 10).
31. MARTINEZ-LADO L, CALVINO-DIAZ C, PINEIRO A *et al*.: Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. *Medicine* (Baltimore) 2011; 90: 186-93.
32. GONZALEZ-GAY MA, GARCIA-PORRUA C, LLORCA J *et al*.: Biopsy-negative giant cell arteritis: clinical spectrum and predictive factors for positive temporal artery biopsy. *Semin Arthritis Rheum* 2011; 30: 249-56.
33. CHAN CC, PAINE M, O'DAY J: Predictors of recurrent ischemic optic neuropathy in giant cell arteritis. *J Neuroophthalmol* 2005; 25: 14-7.
34. LODDENKEMPER T, SHARMA P, KATZAN I, PLANT GT: Risk factors for early visual deterioration in temporal arteritis. *J Neurol Neurosurg Psychiatry* 2007; 78: 1255-9.
35. HAYREH SS: The 1994 von Sallman lecture the optic nerve head circulation in health and disease. *Exp Eye Res* 1995; 61: 259-72.
36. HAYREH S: Anterior ischaemic optic neuropathy: II. Fundus on ophthalmoscopy and fluorescein angiography. *Br J Ophthalmol* 1974; 58: 964-80.
37. HENKIND P, CHARLES NC, PEARSON J: Histopathology of ischemic optic neuropathy. *Am J Ophthalmol* 1970; 69: 78-90.
38. HAYREH SS: Ischemic optic neuropathies. Springer 2011.
39. MACFAUL PA: Ciliary artery involvement in giant cell arteritis. *Br J Ophthalmol* 1967; 51: 505-12.
40. HAYREH SS: Factors influencing blood flow in the optic nerve head. *J Glaucoma* 1997; 6: 412-25.
41. HAYREH SS, PODHAJSKY PA, ZIMMERMAN B: Ocular manifestations of giant cell arteritis. *Am J Ophthalmol* 1998; 125: 509-20.
42. HAYREH SS, PODHAJSKY PA, ZIMMERMAN B: Nonarteritic anterior ischemic optic neuropathy: time of onset of visual loss. *Am J Ophthalmol* 1997; 124: 641-7.
43. HAYREH SS, ZIMMERMAN MB, PODHAJSKY P, ALWARD WL: Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. *Am J Ophthalmol* 1994; 117: 603-24.
44. GONZALEZ-GAY MA, PINEIRO A, GOMEZ-GIGIREY A *et al*.: Influence of traditional risk factors of atherosclerosis in the development of severe ischemic complications in giant cell arteritis. *Medicine* (Baltimore) 2004; 83: 342-7.
45. YATES M, MACGREGOR AJ, ROBSON J *et al*.: The association of vascular risk factors with visual loss in giant cell arteritis. *Rheumatology* (Oxford) 2017; 56: 524-8.
46. CZIHAL M, TSCHAIDSE J, BERNAU C *et al*.: Ocular ischaemic complications in giant cell arteritis: CHADS-score predicts risk of permanent visual impairment. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S61-4.
47. MALESZEWSKI JJ, YOUNGE BR, FRITZLEN JT *et al*.: Clinical and pathological evolution of giant cell arteritis: a prospective study of follow-up temporal artery biopsies in 40 treated patients. *Mod Pathol* 2017; 30: 788-96.
48. NESHER G, BERKUN Y, MATES M, BARAS M, RUBINOW A, SONNENBLICK M: Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. *Arthritis Rheum* 2004; 50: 1332-7.
49. LEE MS, SMITH SD, GALOR A, HOFFMAN GS: Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. *Arthritis Rheum* 2006; 54: 3306-9.
50. MOLLAN SP, SHARRACK N, BURDON MA, DENNISTON AK: Aspirin as adjunctive treatment for giant cell arteritis. *Cochrane Database Syst Rev* 2014; CD010453.
51. STONE JH, TUCKWELL K, DIMONACO S *et al*.: Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med* 2017; 377: 317-28.
52. FERRO F, QUARTUCCIO L, MONTI S *et al*.: One year in review 2021: systemic vasculitis. *Clin Exp Rheumatol* 2021; 39 (Suppl. 129): S3-12.