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BOB-ACG study: Pulse methylprednisolone to prevent bilateral ophthalmologic damage in giant cell arteritis. A multicentre retrospective study with propensity score analysis

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ABSTRACT

Introduction: Giant cell arteritis (GCA) is complicated in 10 to 20% of cases by permanent visual ischemia (PVI). International guidelines advocate the use of intravenous pulse of methylprednisolone from 250 to 1000 mg per day, for three days, followed by oral prednisone at 1 mg/kg per day. The aim of this study is to assess whether this strategy significantly reduces the risk of early PVI of the second eye, compared with direct prednisone at 1 mg/kg per day.

Methods: We conducted a multicentre retrospective observational study over the past 15 years in 13 French hospital centres. Inclusion criteria included: new case of GCA; strictly unilateral PVI, prednisone at dose greater than or equal to 0.9 mg/kg per day; for the intravenous methylprednisolone (IV-MP) group, total dose between 900 and 5000 mg, close follow-up and knowledge of visual status at 1 month of treatment, or earlier, in case of contralateral PVI. The groups were compared on demographic, clinical, biological, iconographic, and therapeutic parameters. Statistical analysis was optimised using propensity scores.

Results: One hundred and sixteen patients were included, 86 in the IV-MP group and 30 in the direct prednisone group. One patient in the direct prednisone group and 13 in the IV-MP group bilateralised, without significant difference between the two strategies (3.3% vs 15.1%). Investigation of the association between IV-MP patients and contralateral PVI through classical logistic regression, matching or stratification on propensity score did not show a significant association. Weighting on propensity score shows a significant association between IV-MP patients and contralateral PVI (OR = 12.9 [3.4; 94.3]; $P < 0.001$).

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Improvement in visual acuity of the initially affected eye was not significantly associated with IV-MP (visual acuity difference 0.02 vs –0.28 LogMar), even in the case of early management, i.e., within the first 48 hours after the onset of PVI ($n = 61$; visual acuity difference –0.11 vs 0.25 LogMar). Complications attributable to corticosteroid therapy in the first month were significantly more frequent in the IV-MP group (31.8 vs 10.7%; $P < 0.05$).

Discussion: Our data do not support the routine use of pulse IV-MP for GCA complicated by unilateral PVI to avoid bilateral ophthalmologic damage. It might be safer to not give pulse IV-MP to selected patients with high risks of glucocorticoids pulse side effects. A prospective randomised multicentre study comparing pulse IV-MP and prednisone at 1 mg/kg per day is desirable.

1. Introduction

Giant cell arteritis (GCA) is systemic vasculitis of the large and medium-sized vessels [1]. It is complicated in 10 to 20% of cases by permanent visual ischemia (PVI), most often by acute anterior ischemic optic neuropathy (AAION), and less frequently by central retinal artery occlusion (CRAO) or posterior ischemic optic neuropathy (PION) [2]. These forms require urgent treatment, given the usual severity of the established visual deficit and a high risk of contralateral damage (estimated between 4 and 54%), often asynchronous [3–8]. Although most current guidelines on the treatment of GCA-related PVI recommend the use of high-dose intravenous methylprednisolone (IV-MP), this consensus is not evidence-based. Indeed, no randomised prospective studies have been conducted to confirm the superiority of the high-dose IV-MP regimen over standard direct prednisone therapy for safeguarding, or even improving, residual vision. The value of high-dose IV-MP (versus direct prednisone 1 mg/kg per day) in preventing the involvement of the fellow eye in GCA patients with unilateral eye involvement is controversial and based on small retrospective studies with conflicting results [4,9–11]. For a few authors, early treatment (< 24 h) would also improve the visual function of the initially affected eye [12].

Current international guidelines [13], based on low levels of evidence, advocate the use of intravenous pulse methylprednisolone dosages of 250 to 1000 mg per day, for three days, followed by prednisone therapy at 1 mg/kg/day, aimed essentially at preserving the vision of the contralateral eye. However, some studies show the non-superiority of the use of intravenous pulses.

The aim of the present study is to assess whether this strategy significantly reduces the risk of early PVI of the second eye, compared with direct prednisone therapy at 1 mg/kg per day. Retrospective studies carry a risk of selection bias. To avoid this, propensity scores were used to obtain groups with similar characteristics to those at randomization [14].

2. Methods

2.1. Study design

We conducted a multicentre retrospective observational study on behalf of the French Study Group on GCA.

The different centres participating in the study compiled lists of patients meeting the inclusion criteria between 2005 and 2020. For each inclusion, the practitioners completed the observation form attached to the research protocol.

Patients were recruited using several methods. Centres could either use their own cohort of GCA patients, or search for patients in the hospital's computer software using the ICD-10 coding system through diagnosis codes (M315 or M316) and (H46 or H341 or H470).

2.2. Inclusion criteria

All patients had a diagnosis of GCA with at least three of the five American College of Rheumatology criteria [15] or two criteria associated with evidence of large vessel vasculitis on angiographic CT, angiographic MRI or PET [16,17]. The diagnosis of GCA was made in expert centres. Patients had to have strictly unilateral PVI related to AAION, CRAO, or PION at the time of diagnosis and before treatment. A complete ophthalmologic record, performed by a senior ophthalmologist, had to be available to establish a diagnosis of certainty. Initial prednisone therapy of at least 0.9 mg/kg per day was initiated, preceded or not by IV-MP at a total dose of 900 mg to 5000 mg (administered over one to five days). Patients who started prednisone less than 48 hours before receiving IV-MP were included and analysed in the IV-MP group. The maximal dose received orally by ACG patients at the onset was 1 mg/kg per day. Finally, patients had to be followed up for at least one month by an ophthalmologist or an internist.

2.3. Exclusion criteria

We excluded patients with poorly defined initial visual impairment and cortical blindness following an occipital arterial stroke, as well as those with contralateral impairment (or abnormal contralateral fundus without impaired vision) at diagnosis, and patients with incipient involvement. In our study, incipient involvement was defined by the presence of cottony nodules on the fundus, choroidal delay or papillary diffusion without papilledema on angiography, and no decrease in visual acuity. Patients with incipient involvement were analysed separately. Patients who received oral prednisone more than 48 hours before starting IV-MP were excluded. We excluded patients treated by IV-MP prednisone below a total dose of 900 mg and patients with relapsed GCA.

2.4. Data collection

For each patient, we collected the demographic data, cardiovascular history, clinical findings and imaging results, the time between unilateral vision loss onset and diagnosis/treatment, current use of antiplatelet agent, anticoagulant, and/or statin treatment.

2.4.1. Initial ophthalmologic evaluation

Any history of transient ophthalmologic involvement before PVI was recorded. For the affected eye, laterality, type of involvement (AAION, CRAO, PION, or cilioretinal artery occlusion), and date of onset of visual impairment were noted. The diagnosis of PION was based on normal fundus and retinal angiography along with abnormal visual field analysis, with additional use of papillary optical coherence tomography, and optic nerve MRI in selected cases. Visual function was assessed using visual acuity and completed in some patients by visual field analysis in automated static perime-

try. The VA was evaluated on a LogMAR logarithmic scale (ETDRS scale) or extrapolated from the Monoyer decimal scale.

For the healthy eye, the evaluation also included the VA and visual field. Discrete and/or aspecific abnormalities compatible with early asymptomatic contralateral ophthalmologic involvement, so-called incipient involvement, were recorded.

2.4.2. Treatment

Treatments (corticosteroids, statins, antiplatelet agent, anticoagulant), dosages (in milligrams and milligrams per kilogram), route of administration, and date of start of treatment were recorded.

2.4.3. Ophthalmologic re-evaluation

All patients with new ophthalmologic events were evaluated in an ophthalmologic setting during the first month. Patients who did not develop an ophthalmologic event within a one-month follow-up period were not routinely seen by an ophthalmologist, but were followed up by an internist, clinically assessing the absence of contralateral eye involvement.

2.4.4. Complications

Complications of corticosteroid therapy were defined as the occurrence of rhythm disorders, imbalance of arterial high pressure, angina, myocardial infarction, infectious complications, neuropsychiatric complications and/or glycaemic imbalance justifying a new or extended hospitalisation within the first month.

Bleeding complications possibly related to antiplatelet and/or anticoagulant therapy were recorded.

2.5. Primary endpoint

The primary endpoint was the prevalence of permanent ischemic involvement of the fellow eye (AAION, CRAO or PION). It was assessed at one month of treatment.

2.6. Secondary endpoints

In both groups, we compared the change in visual acuity (in LogMAR) and visual field of the initially affected eye as part of ophthalmologic follow-up after the introduction of treatment, and the rate of corticosteroid-induced significant complications during the first month. We sought to determine the predictive factors for new ischemic involvement of the fellow eye.

Visual acuity differences were calculated for each patient, with values before treatment and ophthalmological assessment at 1 month.

2.7. Propensity score analysis

Propensity score analysis was performed using R software version 3.2.2 with the matching package and the Generalized Boosted Models (GBM) package. Given the sample size, propensity scores were inversely weighted and average treatment effects in the entire population were estimated [18]. The best estimate of propensity scores from logistic regression or generalized boosted models were used [19]. In addition, given the very high exposure rate and the rarity of the events, these results were compared with those obtained by matching and stratification.

All covariates affecting selection were included, to obtain a doubly robust estimator, as well as covariates based on clinical expertise: prior transient visual ischemic symptoms, use of statins, jaw claudication, involved eye, temporal artery abnormalities on Doppler studies, platelet and CRP levels, time from visual impairment to initiation of corticosteroid therapy, and time from diagnosis to initiation of corticosteroid therapy.

2.8. Statistical analysis

Continuous variables were expressed as mean with standard deviation or median and interquartile range; categorical variables were expressed as frequencies and percentages. Variables were compared between groups using Pearson's X^2 test, Fisher's exact test, or Wilcoxon test, as appropriate. Missing data were treated using the chained multiple imputation equation (MICE), with four matrices [20].

Two survival curves were constructed using the Kaplan-Meier method to study time to bilateralisation onset between two groups. The validity is verified with a Log-rank test.

Tests were 2-sided, and a P-value < 0.05 was considered significant. All calculations were performed using R software version 3.2.2 with the MICE package.

2.9. Ethics and conflicts of interest

None of the authors declares any funding sources for this work or conflicts of interest. Data for all patients were collected retrospectively, in the absence of an objection to the collection of data. This study was conducted in accordance with good clinical practice and the principles of the Declaration of Helsinki.

3. Results

3.1. Patient characteristics

One hundred and sixteen patients (63.8% women) from 13 university hospitals were included. Eighty-six patients (74.1%) received IV-MP, while 30 (25.9%) received direct prednisone therapy at the outset (Fig. 1). None of the patients in the IV-MP group had received oral corticosteroids before the pulses of methylprednisolone, in the 48 hours before. None of the patients had received treatments by DMARDs or by biologic therapy.

Patient age averaged 77.3 years (Table 1). Cardiovascular risk factors were quite frequent, including hypertension (66.4%), hyperlipidaemia (31.0%) and diabetes (10.3%). Forty-two patients (36.2%) were already treated with antiplatelet agent before GCA onset. The most frequent clinical signs/symptoms were weight loss and asthenia (59.5%), headache (78.4%), clinical abnormality of the temporal artery (59.5%), and scalp hyperesthesia (46.6%).

Temporal artery biopsy showed evidence of GCA in 78.9% of assessed patients ($n = 71$). Forty-five patients did not have histological confirmation (negative biopsy $n = 19$; biopsy not performed $n = 26$). Imaging of temporal arteries was performed in 76 patients. Nineteen of 26 patients without biopsy had iconographic abnormalities of the temporal arteries suggestive of GCA. Eight of 19 patients with a negative biopsy had iconographic abnormalities suggestive of GCA on temporal artery imaging. Imaging of the aorta (angiographic CT, angiographic MRI or 18FDG-PET) was performed in 81 patients and in 28 of the 45 patients without histological confirmation. Thus, 15 patients had neither histological confirmation nor iconographic of the aorta and temporal arteries.

Visual impairment was mainly due to AAION (76.7%), followed by CRAO (19.0%) and PION (5.2%). The mean visual acuity of the affected eye was 1.73 ± 0.92 LogMar. Twenty-one percent of patients described transient visual ischemic manifestations preceding PVI.

The average time between onset of PVI and initiation of corticosteroid therapy was 4.5 ± 6.6 days.

IV-MP patients had more jaw claudication (73.3% vs 50.0%; $P < 0.05$), and a shorter time between the first transient visual

Table 1
Baseline characteristics.

Patients, *n*	Direct prednisone, (*n* = 30)	IV-MP, (*n* = 86)	Total, (*n* = 116)
	n (%) or mean (standard deviation) or median [IQR]		
Women	22 (73.3)	52 (60.5)	74 (63.7)
Age at diagnosis (y)	79.4 (6.4)	76.6 (7.2)	77.3 (7.1)
Cardiac insufficiency	1 (3.3)	5 (5.8)	6 (5.2)
Hypertension	22 (73.3)	55 (64.0)	77 (66.4)
Diabetes	2 (6.7)	10 (11.6)	12 (10.3)
Dyslipidaemia	10 (33.3)	26 (30.2)	36 (31.0)
Stroke	2 (6.7)	10 (11.6)	12 (10.3)
Atrial fibrillation	3 (10.0)	5 (5.8)	8 (6.9)
Ischemic heart disease	3 (10.0)	11 (12.8)	14 (12.1)
Obliterative arteriopathy	2 (6.7)	4 (4.7)	6 (5.2)
Weight loss/Asthenia	20 (66.7)	49 (57.0)	69 (59.5)
Fever	4 (13.3)	8 (9.3)	12 (10.3)
Headache	23 (76.7)	68 (79.1)	91 (78.4)
Scalp hyperesthesia	14 (46.7)	40 (46.5)	54 (46.6)
Jaw claudication	15 (50.0)	63 (73.3)	78 (67.2)[a]
Arthralgia	9 (30.0)	22 (25.6)	31 (26.7)
Clinical anomaly of TA	20 (66.7)	49 (57.0)	69 (59.5)
Abnormality of the TA biopsy[c]	19 (76.0)	52 (80.0)	71 (78.9)
Abnormal imaging of the TA[d]	15 (78.9)	40 (70.2)	55 (72.4)
Abnormal imaging of the aorta[e]	9 (69.2)	17 (70.8)	26 (70.3)
TVIM (all eyes)	7 (30.4)	10 (17.2)	17 (21.0)
TVIM in unaffected eye	3 (10.0)	6 (7.0)	9 (7.8)
AAION	23 (76.7)	66 (76.7)	89 (76.7)
PION	2 (6.7)	4 (4.7)	6 (5.2)
CRAO	5 (16.7)	17 (19.8)	22 (19.0)
Cilioretinal artery occlusion	0 (0.0)	4 (4.7)	4 (3.4)
Visual acuity in affected eye (Logmar)	1.8 (0.8)	1.7 (0.96)	1.7 (0.9)
Visual acuity in healthy eye (Logmar)	0.2 (0.3)	0.1 (0.2)	0.2 (0.2)
Sedimentation rate (mm/h)	60.0 (29.3)	73.9 (29.6)	70.4 (30.0)[a]
C-reactive protein (mg/L)	56.0 (58.0)	67.9 (45.9)	64.8 (49.3)
Fibrinogen (g/L)	5.7 (1.8)	6.8 (1.7)	6.6 (1.8)
Haemoglobin (g/dL)	12.3 (1.4)	11.9 (1.3)	12.0 (1.3)
Platelets (Giga/L)	349.8 (131.7)	439.1 (123.9)	415.7 (131.4)[b]
Antiplatelet agent	10 (33.3)	32 (37.2)	42 (36.2)
Anticoagulant	3 (10.0)	9 (10.5)	12 (10.3)
Statins	6 (20.0)	26 (30.2)	32 (27.6)
Time between TVIM and CTS (d)	49.6 (63.9)	10.9 (13.2)	20.6 (36.6)[a]
	36.5 [15.3; 44.8]	7 [3; 11.8]	7 [3.8; 21.5]
Time between PVI and CTS (d)	5.5 (7.9)	4.2 (6.1)	4.5 (6.6)
	2.5 [0.3; 7]	2 [1; 5]	2 [1; 5]
Time between CS and CTS (d)	46.5 (52.2)	38.2 (38.2)	40.8 (42.9)
	29 [16.8; 56.0]	24.5 [9.3; 50]	24.5 [10; 55.5]
Time between diagnosis and CTS (d)	0.8 (3.8)	1.1 (3.4)	1.0 (3.5)
	0 [0; 0]	0 [0; 0]	0 [0; 0]

TA: temporal artery; TVIM: transient visual ischemic manifestations; AAION: acute anterior optic ischemic neuropathy; PION: posterior ischemic optic neuropathy; CRAO: central retinal artery occlusion; TVIM: transient visual ischemic manifestations; CTS: corticosteroids; PVI: permanent visual impairment; CS: clinical signs.

[a] $P < 0.05$.

[b] $P < 0.001$.

[c] TA biopsy was performed in 90 patients.

[d] Imaging of the TA was performed in 76 patients.

[e] Imaging of the aorta was performed in 81 patients.

event and treatment (10.9 vs 49.6 days; $P < 0.05$). They also had stronger inflammation responses including platelet count (439 Giga/L vs 349 Giga/L; $P < 0.001$) and sedimentation rate (73.9 mm vs 60.0 mm; $P < 0.05$).

3.2. Primary endpoint achievement

Fourteen patients developed PVI of the fellow eye during the first month of treatment. There was no significant difference between the participating centres.

Among the 14 patients, one patient bilateralised in the direct prednisone group, and 13 in the IV-MP group (3.3% vs 15.1%; NS) (Table 2). Of the fourteen patients who bilateralised, we were able to collect data for ten of them on the time to bilateralisation from the start of treatment (Fig. 2). The missing patients were from the IV-MP group.

Patients with bilateral PVI did not differ from the patients with no bilateral PVI according to their clinical characteristics, their laboratory parameters, the use of antiplatelet agent or anticoagulant, and the time between first PVI or GCA diagnosis and treatment onset (Table 3). Among the nine patients who previously presented contralateral visual manifestations before the treatment onset, zero developed contralateral PVI.

The contralateral eye involvement mainly occurred in the week following the treatment onset (8/10 patients), with a median time of 3.5 [1–7] days. We do not have data for 4 patients.

Of the patients who had fellow eye impairment, 12 patients with unilateral AAION progressed to bilateral AAION, 1 patient with

Table 2
Primary and secondary endpoints results.

Patients, *n*	Direct prednisone, (*n* = 30)	IV-MP, (*n* = 86)	Total, (*n* = 116)
	n (%) or mean (standard deviation) or median [IQR]		
Bilateralisation under treatment	1 (3.3)	13 (15.1)	14 (12.1)
Fleeting visual signs	0 (0.0)	1 (1.2)	1 (0.9)
Diplopia	0 (0.0)	0 (0.0)	0 (0.0)
AAION	1 (3.3)	11 (12.8)	12 (10.3)
CRAO	0 (0.0)	0 (0.0)	0 (0.0)
PION	0 (0.0)	1 (1.2)	1 (0.9)
Cilioretinal artery occlusion	0 (0.0)	0 (0.0)	0 (0.0)
Complications	3 (10.7)	21 (31.8)	24 (25.5)[a]
Cardiovascular complications	1 (3.6)	5 (7.6)	6 (6.4)
Confirmed rhythm disorders	1 (3.6)	0 (0.0)	1 (1.1)
Angina/myocardial infarction	0 (0.0)	1 (1.5)	1 (1.1)
Infectious complications	1 (3.6)	2 (3.0)	3 (3.2)
Extended or new hospitalisation	3 (10.7)	10 (15.2)	13 (13.8)
Neuropsychological complications	0 (0.0)	9 (13.6)	9 (9.6)
Glycaemic imbalance	3 (10.7)	10 (15.2)	13 (13.8)
Bleeding complications	0 (0.0)	1 (1.2)	1 (0.9)
Visual acuity of the affected eye			
Visual acuity before treatment (LogMar)	1.76 (0.82)	1.73 (0.96)	1.73 (0.92)
Visual acuity after treatment (LogMar)	1.35 (0.94)	1.83 (0.95)	1.70 (0.97)[a]
Visual acuity difference (LogMar)	−0.28 (0.78)	0.02 (0.68)	−0.06 (0.72)

AAION: acute anterior optic ischemic neuropathy; CRAO: central retinal artery occlusion; PION: posterior ischemic optic neuropathy.
[a] $P < 0.05$ but > 0.01.

PION to bilateral PION, and 1 patient with CRAO to contralateral AAION.

3.3. Propensity score

Investigation of the association between IV-MP patients and contralateral PVI through classical logistic regression, matching or stratification on propensity score did not show a significant association (Table 4).

Weighting on propensity score shows a significant association between IV-MP patients and contralateral PVI (OR = 12.9 [3.4; 94.3]; $P < 0.001$).

The differences in the proportion of each variable, used for propensity score calculation, before and after PS matching was provided as Table S1.

3.4. Secondary endpoint achievement

More adverse events due to corticosteroids occurred among the IV-MP patients than among the patients with direct prednisone (31.8% vs 10.7%; $P < 0.05$); these were mostly neuropsychological, notably including anxiety, agitation, and insomnia (13.6% vs 0.0%; NS) (Table 2).

Among the cardiovascular complications, arterial hypertension ($n = 3$) occurred only in patients receiving IV-MP. An episode of palpitations during IV-MP ($n = 1$), an episode of angina after pulse dosage ($n = 1$), and paroxysmal atrial fibrillation in a patient in the direct prednisone group ($n = 1$) were observed. Infectious complications included urinary tract infection and *Staphylococcus aureus* bacteraemia for two patients in the IV-MP group and peritonitis in one patient in the direct prednisone group.

Improvement in visual acuity of the initially affected eye was not significantly associated with IV-MP (visual acuity difference 0.02 vs −0.28 LogMar), even in the case of early management, i.e., within the first 48 hours after the onset of PVI ($n = 61$; visual acuity difference −0.11 vs 0.25 LogMar).

As regards visual field outcomes, the large proportion of missing data on the initially or subsequently affected eye before or after the introduction of treatment precluded any statistically relevant comparison.

No strokes occurred during the first month of follow-up.

3.5. Patients with incipient involvement

Three patients had incipient disease prior to diagnosis, before the initiation of treatment. All three patients were treated with pulses of methylprednisolone and only one bilateralised on the sixth day of treatment. When these patients were included in the cohort, there was still no significant difference between the two groups (3.3% vs 15.7%). There was also no change with the Propensity score (weighted propensity score: OR 10.4 [3.0; 62.4]; $P < 0.001$).

4. Discussion

To our knowledge, we have presented the first study to evaluate the interest of pulse IV-MP in preventing contralateral impairment using a propensity score, a method minimising selection bias, and thereby enhancing the accuracy of the results of the comparative study.

In our study, 14 of 116 (12.1%) patients developed contralateral PVI during the first month of corticosteroid treatment, including 1 of 30 (3.3%) in the direct prednisone group, and 13 of 86 (15.1%) in the IV-MP group. Based on these results, the use of high-dose methylprednisolone does not seem to significantly improve the ischemic prognosis of the contralateral eye in patients with newly diagnosed GCA complicated by unilateral PVI. However, owing to the retrospective study design, the groups were not well-balanced, suggesting a selection bias towards the use of pulse IV-MP in more severe cases and/or younger patients with fewer comorbid conditions. Significantly, patients in the IV-MP group exhibited more frequent jaw claudication and a greater increase in biological inflammatory parameters. It is worth noting that jaw claudication and thrombocytosis have been associated with an increased visual ischemic risk at disease onset [12,21–24], although other studies have not observed such associations [25–27].

In contrast, the two groups were statistically comparable in terms of the time of treatment onset after PVI, initial daily corticosteroid doses, major cardiovascular risk factors, and associated treatments (antiplatelet agents, anticoagulants, statins). To minimise selection bias, we weighed the weight of variables with a potential link with visual ischemic risk using a propensity score.

Table 3
Characteristics of patients with bilateral events.

Patients, *n*	No bilateralisation, (*n* = 102)	Bilateralisation, (*n* = 14)	Total, (*n* = 116)
	n (%) or mean (standard deviation) or median [IQR]		
Age at diagnosis (y)	77.3 (6.9)	77.9 (8.9)	77.3 (7.1)
Women	65 (63.7)	9 (64.3)	74 (36.8)
Antiplatelet agent before diagnosis	37 (36.3)	5 (35.7)	42 (36.2)
Anticoagulant before diagnosis	11 (10.8)	1 (7.1)	12 (10.3)
Statins	27 (26.5)	5 (35.7)	32 (27.6)
Weight loss/Asthenia	61 (59.8)	8 (57.1)	69 (59.5)
Fever	10 (9.8)	2 (14.3)	12 (10.3)
Headache	79 (77.5)	12 (85.7)	91 (78.4)
Scalp hyperesthesia	48 (47.1)	6 (42.9)	54 (46.6)
Jaw claudication	68 (66.7)	10 (71.4)	78 (67.2)
Arthralgia	30 (29.4)	1 (7.1)	31 (26.7)
Clinical anomaly of TA	62 (60.8)	7 (50.0)	69 (59.5)
Abnormality of the TA biopsy[a]	60 (75.9)	11 (100.0)	71 (78.9)
Abnormal imaging of TA[b]	50 (73.5)	5 (62.5)	55 (72.4)
TVIM	31 (30.4)	5 (35.7)	36 (31.0)
TVIM in unaffected eye	9 (8.8)	0 (0.0)	9 (7.8)
Time between prior events and treatment	22.3 (39.2)	11.4 (16.7)	20.6 (36.6)
AAION	77 (75.5)	12 (85.7)	89 (76.7)
PION	5 (4.9)	1 (7.1)	6 (5.2)
CRAO	19 (18.6)	3 (21.4)	22 (19.0)
Cilioretinal artery occlusion	3 (2.9)	1 (7.1)	4 (3.4)
IV-MP	73 (71.6)	13 (92.9)	86 (74.1)
Pulse dosage per day	433.0 (332.2)	485.7 (323.1)	439.4 (330.2)
Pulse duration (d)	2.9 (0.3)	3.0 (0.0)	2.9 (0.3)
Direct prednisone therapy	29 (28.4)	1 (7.1)	30 (25.9)
Dosage (mg/kg/d)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
Dosage (mg/d)	61.4 (11.6)	63.2 (9.5)	61.6 (11.3)
Time CS – treatment (d)	41.9 (44.4)	31.0 (26.5)	40.8 (42.9)
	24 [10; 56]	29 [17; 34]	24.5 [10; 55.5]
Time diagnosis – treatment (d)	0.9 (3.1)	1.7 (5.5)	1.0 (3.5)
	0 [0; 0]	0 [0; 0]	0 [0; 0]
Time between PVI and treatment (d)	3.7 (4.4)	10.6 (13.6)	4.5 (6.6)
	2 [1; 5]	2.5 [0.5; 20]	2 [1; 5]
Antiplatelet agent after diagnosis	84 (82.4)	11 (78.6)	95 (81.9)
Anticoagulant after diagnosis	14 (13.7)	3 (21.4)	17 (14.7)
Sedimentation rate (mm/h)	69.9 (30.0)	74.2 (30.9)	70.4 (30.0)
C-reactive protein (mg/L)	62.7 (48.8)	80.6 (51.8)	64.8 (49.3)
Fibrinogen (g/L)	6.6 (1.8)	6.8 (1.7)	6.6 (1.8)
Haemoglobin (g/dL)	12.0 (1.4)	12.2 (0.9)	12.0 (1.3)
Platelets (Giga/L)	412.5 (132.3)	438.2 (127.6)	415.7 (131.4)

TA: temporal artery; TVIM: transient visual ischemic manifestations; AAION: acute anterior optic ischemic neuropathy; PION: posterior ischemic optic neuropathy; CRAO: central retinal artery occlusion; IV-MP: intravenous methylprednisolone; CS: clinical signs; PVI: permanent visual impairment. Analyse was performed in 116 patients. All the results are not significant.

[a] TA biopsy was performed in 90 patients.

[b] Imaging of the TA was performed in 76 patients.

Table 4
Association between IV-MP patients and contralateral PVI in original and matching cohort.

	OR	95%CI
Logistic regression	5.2	1.0; 95.9
Exact matching method	3.2	0.4; 67.3
Stratification	7.7	0.8; 74.7
Weighting	12.9	3.4; 94.3[a]

The differences in the proportion of each variable used for propensity score calculation before and after propensity score matching are described in the table as supplementary material.

[a] $P < 0.001$.

The use of the weighed Propensity score is the most appropriate statistical method for our study. We did not retain the exact matching method, because only 25 patients could have been matched, and they would not necessarily have been representative of our sample. We also did not retain stratification analysis, because the population was too small to obtain good categories to stratify.

With the weighted propensity score, the risk of contralateral PVI appeared to be significantly associated with pulse IV-MP treatment. Despite these statistical results, we do not conclude a disadvantage of pulse because in our study, ophthalmologic events are rare, and the confidence interval is wide. Thus, the results of the present study do not support the routine use of pulse IV-MP in patients with GCA complicated by unilateral PVI.

The rate of contralateral involvement (12%) in our study is within the range of the findings of other studies (4–54% of cases) [3–8]. In a retrospective study by Dumont et al. [8], 4 out of 102 patients with initial ophthalmologic involvement (4%) showed early contralateral impairment after the introduction of treatment. Of these four patients, three had initially received pulse methylprednisolone therapy.

Our study also did not show a benefit of initial use of pulse IV-MP in improving visual acuity in the initially affected eye, even in the subgroup of patients treated within the first two days after PVI. The retrospective setting with missing data on visual fields limit the value of the results. Indeed, sequential visual fields are important to be able to differentiate true improvement in vision from functional improvement of visual acuity by progressive effective eccentric fixation training in cases of AAION [3]. A previous study by Gonzalez-Gay et al. [12] suggested, after adjustment for the treatment regimen (IV-MP versus direct prednisone), treatment within the first 24 hours was the only predictor of improvement. Indeed, in our work, intravenous treatment rather than oral treatment does

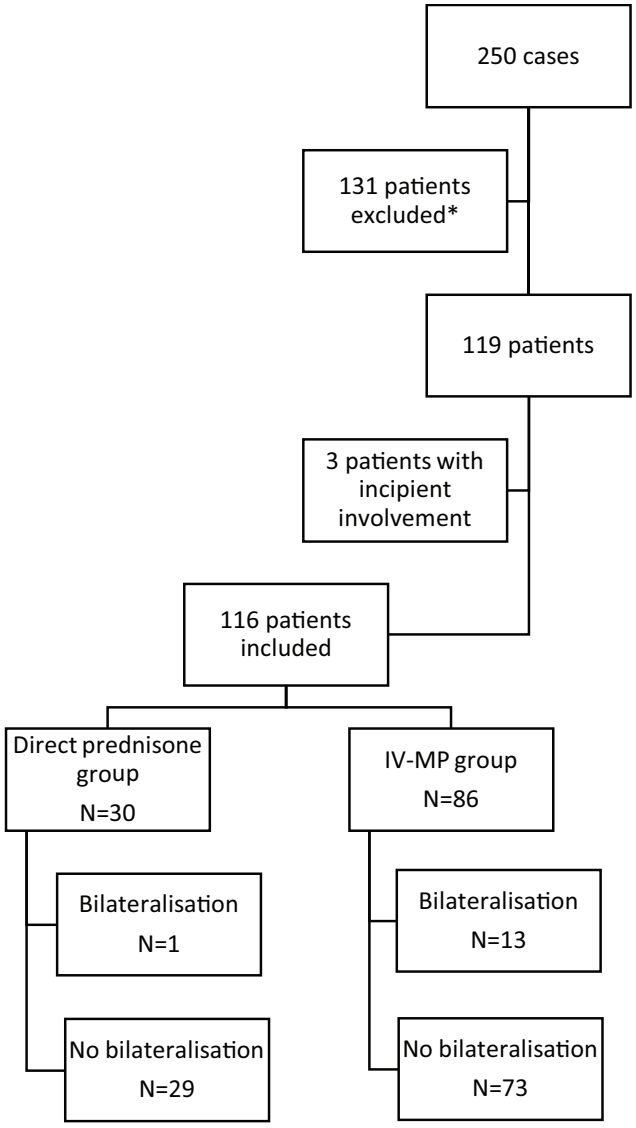

Fig. 1. Flowchart. IV-MP: intravenous methylprednisolone. *Patients excluded: 13 patients with direct prednisone therapy under 0.9 mg/kg per day, 24 patients with IV-MP under 300 mg/day or under 900 mg in total, 25 patients with initial bilateral involvement, 2 early deaths, 8 patients with another ocular condition in the contralateral eye, 25 patients with too much missing data or unproven giant cell arteritis, 1 patient without initial visual impairment, 33 cases before 2005.

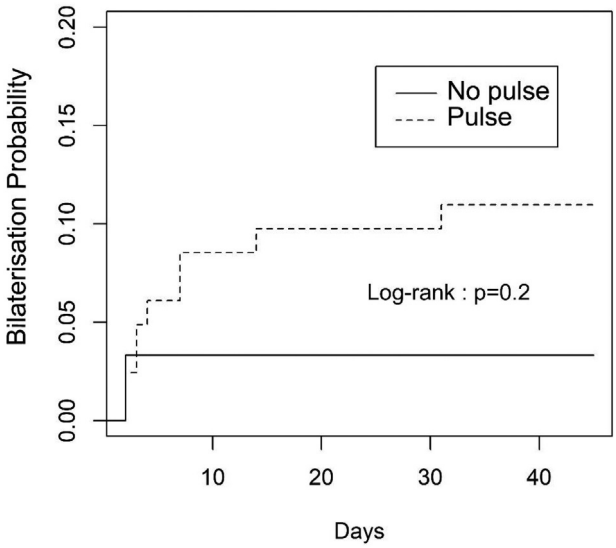

Fig. 2. Time to bilateralisation onset (for patients with data for the day; $n = 10/14$). Day 1 = first day of treatment, intravenous methylprednisolone, or direct prednisone therapy. Analyse was performed in 10 patients.

not prevent bilateralisation and does not improve the regression of the initial damage. We find the same results with a larger number of patients and greater precision. However, in the absence of a prospective study, we recommend discussing the use of IV-MP in cases of very early management (< 24 h), evaluating the benefit/risk.

In this study, the average time that elapsed before setting up appropriate management was four days from onset of PVI. This is in line with previously published large studies [3,8,12,28,29]. Half of our patients presented with bilateral damage before the fifth day of treatment. In the literature, bilateral involvement most often occurs within the first five days of treatment, irrespective of the treatment route (e.g., pulse IV-MP or direct prednisone therapy) [10,12,30,31]. All the investigators agreed that visual prognosis is more closely related to the time to treatment than to corticosteroid treatment regimens. It should be noted that ischemia of the optic nerve lasting several hours may be sufficient to cause permanent retinal damage [32].

As the population with GCA is elderly, with an average age of 77 years, and therefore more comorbidities, it is legitimate to question the use prescription of pulse IV-MP in complicated GCA, irrespective of patient history, notably the presence of multiple comorbid conditions. Moreover, in view of the results of this study and the lack of indisputable arguments justifying the use of pulse IV-MP to prevent contralateral PVI, the merit of the international therapeutic recommendations issued by EULAR and the ACR should be queried.

In addition to its retrospective nature, with the inherent biases of this type of study, the relatively small size of the direct prednisone group, therapeutic heterogeneity, and the small number of bilateralisation cases limit the significance of our results.

GCA was diagnosed in 15 patients despite the absence of histological confirmation and imaging of the aorta or temporal arteries. However, imaging examinations were not routinely performed a few years ago. Retrospectively, by analysing the patients from this cohort using the new 2022 ACR/EULAR classification criteria [33], all patients fulfilled the criteria for GCA.

One of the strengths of our study lies in the short-term evaluation of complications and tolerance of corticosteroid therapy in elderly patients with GCA pointing to poorer tolerance of IV-MP compared to direct prednisone therapy. Not surprisingly, although no category of complications emerged, there was a trend towards more neuropsychiatric complications, as in a previous study by Chibane et al. [34]. Cardiovascular and infectious complications were similar in both groups, but the small numbers of such patients precluded any firm conclusion. However, pulse IV-MP is fraught with complications, particularly in the elderly, particularly cardiovascular complications [35]. Also, many longer hospitalizations occurred in the IV-MP group, partially due to glycaemic imbalance. Although the difference was not statistically significant in our study, higher doses of corticosteroids are associated with higher and greater glycaemic imbalance. Due to the lack of power in our study, this cannot be confirmed, but diabetologists are aware of this association. As in our study, the extend of glycaemic imbalance increased the length of hospitalization. Subjects with type 2 diabetes need careful blood glucose monitoring and have a high probability of requiring therapeutic adjustments if their glycosylated haemoglobin level is 8.3% or higher [36–38].

5.

We do not recommend routine use of pulse IV-MP in GCA complicated by unilateral PVI. It might be safer to not give pulse glucocorticoids to selected patients with high risks of glucocorticoids side effects. A prospective randomised multicentre study comparing the early results and tolerance of pulse IV-MP and direct prednisone at 1 mg/kg per day is highly desirable. Until then, the international therapeutic recommendations from EULAR and ACR on the use of IV-MP in complicated GCA require some qualifications.

Disclosure of interest

The authors declare that they have no competing interest.

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Analysis and interpretation of data: R.F., G.G., S.D.
Drafting the manuscript: R.F., G.G., E.L., A.L.F, K.H.L., S.D.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jbspin.2023.105641.

References

[1] Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1–11.
[2] Hayreh SS. Ophthalmic features of giant cell arteritis. Baillière's Clin Rheumatol 1991;5:431–59.
[3] Hayreh SS, Zimmerman B, Kardon RH. Visual improvement with corticosteroid therapy in giant cell arteritis. Report of a large study and review of literature. Acta Ophthalmol Scand 2002;80:355–67.
[4] Liu GT, Glaser JS, Schatz NJ, et al. Visual morbidity in giant cell arteritis. Clinical characteristics and prognosis for vision. Ophthalmology 1994;101:1779–85.
[5] Font C, Cid MC, Coll-Vinent B, et al. Clinical features in patients with permanent visual loss due to biopsy-proven giant cell arteritis. Br J Rheumatol 1997;36:251–4.
[6] Aiello PD, Trautmann JC, McPhee TJ, et al. Visual prognosis in giant cell arteritis. Ophthalmology 1993;100:550–5.
[7] Hayreh SS, Podhajsky PA, Zimmerman B. Ocular manifestations of giant cell arteritis. Am J Ophthalmol 1998;125:509–20.
[8] Dumont A, Lecannuet A, Boutemy J, et al. Characteristics and outcomes of patients with ophthalmologic involvement in giant-cell arteritis: a case-control study. Semin Arthritis Rheum 2020;50:335–41.
[9] Chan CC, Paine M, O'Day J. Steroid management in giant cell arteritis. Br J Ophthalmol 2001;85:1061–4.
[10] Hayreh SS, Zimmerman B. Visual deterioration in giant cell arteritis patients while on high doses of corticosteroid therapy. Ophthalmology 2003;110:1204–15.
[11] Danesh-Meyer H, Savino PJ, Gamble GG. Poor prognosis of visual outcome after visual loss from giant cell arteritis. Ophthalmology 2005;112:1098–103.
[12] González-Gay MA, Blanco R, Rodríguez-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.
[13] Hellmich B, Agueda A, Monti S, et al. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19–30.
[14] Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399–424.
[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;33:1122–8.
[16] Dejaco C, Duftner C, Buttgereit F, et al. The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. Rheumatology (Oxford) 2017;56:506–15.
[17] Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017;377:317–28.
[18] Horvitz DG, Thompson DJ. A generalization of sampling without replacement from a finite universe. J Am Stat Association 1952;47:663–85.
[19] McCaffrey DF, Ridgeway G, Morral AR. Propensity score estimation with boosted regression for evaluating causal effects in observational studies. Psychol Methods 2004;9:403–25.
[20] Buuren S van, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. J Stat Software 2011;45:1–67.
[21] Curumthaullee MF, Liozon E, Dumonteil S, et al. Features and risk factors for new (secondary) permanent visual involvement in giant cell arteritis. Clin Exp Rheumatol 2022;40:734–40.
[22] 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.
[23] Hočevar A, Ješe R, Tomšič M, et al. Risk factors for severe cranial ischaemic complications in giant cell arteritis. Rheumatology (Oxford) 2020;59:2953–9.
[24] Berger CT, Wolbers M, Meyer P, et al. High incidence of severe ischaemic complications in patients with giant cell arteritis irrespective of platelet count and size, and platelet inhibition. Rheumatology (Oxford) 2009;48:258–61.
[25] Cid MC, Font C, Oristrell J, et al. Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. Arthritis Rheum 1998;41:26–32.
[26] González-Gay MA, García-Porrúa C, Llorca J, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine (Baltimore) 2000;79:283–92.
[27] Nesher G, Berkun Y, Mates M, et al. Risk factors for cranial ischemic complications in giant cell arteritis. Medicine (Baltimore) 2004;83:114–22.
[28] Foroozan R, Deramo VA, Buono LM, et al. Recovery of visual function in patients with biopsy-proven giant cell arteritis. Ophthalmology 2003;110:539–42.
[29] Sené T, Clavel G, Villeneuve D, et al. Delays in the management of ocular complications of giant cell arteritis: a retrospective monocentric study of 33 patients. Rev Med Interne 2020;41:661–6.
[30] Loddenkemper T, Sharma P, Katzan I, et al. Risk factors for early visual deterioration in temporal arteritis. J Neurol Neurosurg Psychiatry 2007;78:1255–9.
[31] Cornblath WT, Eggenberger ER. Progressive visual loss from giant cell arteritis despite high-dose intravenous methylprednisolone. Ophthalmology 1997;104:854–8.
[32] Hayreh SS, Jonas JB. Optic disk and retinal nerve fiber layer damage after transient central retinal artery occlusion: an experimental study in rhesus monkeys. Am J Ophthalmol 2000;129:786–95.
[33] Ponte C, Grayson PC, Robson JC, et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. Ann Rheum Dis 2022;81:1647–53 [Epub 2022 Nov 9. Erratum in: Ann Rheum Dis. 2023;82:e52].
[34] Chibane S, Feldman-Billard S, Rossignol I, et al. Short-term tolerance of three days pulse methyprednisolone therapy: a prospective study in 146 patients. Rev Med Interne 2005;26:20–6.
[35] Feldman-Billard S, Héron E. Systemic tolerance of corticosteroid therapy in ophthalmology depending on the route of administration. J Fr Ophtalmol 2008;31:1026–36.
[36] Crawford K. Guidelines for care of the hospitalized patient with hyperglycemia and diabetes. Crit Care Nurs Clin North Am 2013;25:1–6.
[37] Chebane L, Tavassoli N, Bagheri H, et al. Le réseau des Centres régionaux de pharmacovigilance français. Hyperglycémies d'origine médicamenteuse: étude dans la Base nationale française de pharmacovigilance (BNPV). Therapie 2010;65:447–58.
[38] Feldman-Billard S, Lissak B, Benrabah R, et al. Intravenous pulse methylprednisolone therapy in eye disease: effect on glucose tolerance. Ophthalmology 2003;110:2369–71.