Factors Associated with Relapse and Dependence on Glucocorticoids in Giant Cell Arteritis

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ABSTRACT. ***Objective.*** To identify characteristics and factors associated with relapse and glucocorticoid (GC) dependence in patients with giant cell arteritis (GCA).

Methods. We retrospectively analyzed 326 consecutive patients with GCA followed for at least 12 months. Factors associated with relapse and GC dependence were identified in multivariable analyses.

Results. The 326 patients (73% women) were followed up for 62 (12–262) months. During followup, 171 (52%) patients relapsed, including 113 (35%) who developed GC dependence. Relapsing patients had less history of stroke (p = 0.01) and presented large-vessel vasculitis (LVV) more frequently on imaging (p = 0.01) than patients without relapse. During the first months, therapeutic strategy did not differ among relapsing and nonrelapsing patients. GC-dependent patients were less likely to have a history of stroke (p = 0.004) and presented LVV on imaging more frequently (p = 0.005) than patients without GC-dependent disease. In multivariable analyses, LVV was an independent predictive factor of relapse (HR 1.49, 95% CI 1.002–2.12; p = 0.04) and GC dependence (OR 2.19, 95% CI 1.19–4.05; p = 0.01). Conversely, stroke was a protective factor against relapse (HR 0.21, 95% CI 0.03–0.68; p = 0.005) and GC-dependent disease (OR 0.10, 95% CI 0.001–0.31; p = 0.0005). Patients with a GC-dependent disease who received a GC-sparing agent had a shorter GC treatment duration than those without (p = 0.008).

Conclusion. In this study, LVV was an independent predictor of relapse and GC dependence. Further prospective studies are needed to confirm these findings and to determine whether patients with LVV require a different treatment approach. (First Release August 15 2019; J Rheumatol 2020;47:108–16; doi:10.3899/jrheum.181127)

Key Indexing Terms:
GIANT CELL ARTERITIS GLUCOCORTICOIDS RELAPSE
GLUCOCORTICOID DEPENDENCE LARGE-VESSEL VASCULITIS

Giant cell arteritis (GCA) is the most frequent form of vasculitis in patients over the age of 50[1]. Large- and medium-sized vessels are mainly affected, especially the cranial branches of the external carotid. The aorta and its branches are also involved in 30–60% of patients[2,3,4]. Glucocorticoids (GC) are the mainstay of treatment and should be initiated rapidly after diagnosis to reduce the risk of serious ischemic complications, especially ophthalmic or cerebrovascular involvement. However, during GC tapering, patients with GCA are exposed to a risk of relapse, which may affect two-thirds of patients[5,6,7]. GC doses have to be increased in this setting, with a risk of developing GC dependence, which is characterized by the inability to reduce GC below a certain fixed dose without relapse. Longterm GC administration exposes patients to several side effects and increases the risk of cardiovascular (CV) events, osteoporosis, infections, and metabolic complications[8]. To reduce the risk of side effects, GC-sparing strategies have been developed. Early identification of patients at risk of relapse and subsequent GC dependence would help physicians to better manage GC schedules and use GC-sparing agents earlier. Scant information has been published in this setting. We conducted a retrospective study aiming to describe and identify predictive factors of relapse or GC dependence in a large cohort of consecutive GCA patients with a minimum followup of 12 months.

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MATERIALS AND METHODS

Study design. This is an observational study describing a monocentric cohort of 403 consecutive patients diagnosed with GCA between 2000 and 2016 in a department of internal medicine in a tertiary hospital in western France.

All patients were identified through a centralized hospital diagnostic database and through the Department of Histology, which analyzed temporal artery biopsies (TAB) performed in 2000–2016.

In all patients, GCA diagnosis was retained after an evaluation by a physician expert in GCA, and with the presence of at least 3 criteria from the American College of Rheumatology (ACR)[9] or 2 ACR criteria associated with large-vessel vasculitis (LVV), which was demonstrated on imaging or an extratemporal vascular biopsy sample.

For the purpose of our study, which aimed to describe factors associated with relapse and GC dependence, we enrolled only patients with a minimum followup of 12 months. All patients with followup < 12 months were excluded from the study.

This study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki principles. In accordance with French public health law (Art. L 1121-1-1, Art. L 1121-1-2), written consent from the patient is not required for this type of retrospective study. Our local institutional ethics committee approved the study (CPPNOIII06092018).

Patients and definitions. For all included patients, we collected demographic characteristics (age, sex), body mass index, CV risk factors (tobacco use, diabetes mellitus, dyslipidemia, hypertension, previous coronary disease, or stroke), laboratory tests (including erythrocyte sedimentation rate, C-reactive protein, hemoglobin, and platelet levels), TAB status, results of another vascular sample when available, the results of imaging searching for LVV, and administered treatments (including the dose of GC in mg/kg of body weight at initiation and at 3, 6, 12, and 18 months, if ongoing). All patients were treated with prednisone.

Cranial manifestations included headaches, temporal artery pulse absence, jaw claudication, scalp tenderness, and visual symptoms. GCA-related visual symptoms were secondary to anterior ischemic optic neuropathy or central retinal artery occlusion. Extracranial vascular symptoms included heart murmurs or peripheral vascular bruits and pulseless or painful limbs.

Relapse was defined as (1) a reoccurrence of clinical symptoms attributable to GCA or polymyalgia rheumatica (PMR); (2) an increase of acute-phase reactants; (3) a favorable response to an increase or a change of GCA-related treatment(s); or (4) the absence of another identifiable cause. In patients with a systemic presentation of GCA (e.g., isolated fever or isolated inflammatory variables), relapse was defined as the combination of all the above criteria except the clinical criterion, which can be missing.

GC dependence was defined as the presence of > 2 relapses and at least 2 of the following criteria: (1) a daily dose of oral prednisone > 20 mg/day (or 0.30 mg/kg) at 6 months; (2) a daily dose of oral prednisone > 10 mg/day (or 0.20 mg/kg) at 12 months; and (3) a treatment maintained > 24 months because of a relapsing disease course.

In our center, large-vessel imaging is performed at diagnosis to search for LVV in most patients, even in the absence of LVV symptoms. However, given the absence of guidelines regarding this practice, and according to the preferences of each treating physician, some patients did not undergo such imaging at diagnosis. Moreover, imaging performed during followup was not analyzed in this study.

Imaging results were extracted from the Nuclear Medicine and Radiology reports. In all procedures 8 vascular territories were analyzed: the thoracic and abdominal aorta and subclavian, carotid, axillary, upper limb, iliofemoral, and lower limb arteries. A vascular territory was considered to be affected on aortic computed tomography (CT) angiography when showing a circumferential and homogeneous thickening > 2 mm of the vascular wall. On 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT, all vascular uptakes of equal or superior intensity to that of liver physiologic uptake were considered positive, as defined by Meller, *et al*[10]. Circumferential and homogeneous vascular uptakes were suggestive of vasculitis. In contrast, focal (noncircumferential) FDG uptakes were considered to be atherosclerotic lesions and were thus classified as negative PET/CT in the setting of GCA. Isolated uptake from the infrarenal abdominal aorta and/or from the iliac/femoral and/or lower limb arteries was arbitrarily considered to indicate a negative result, because atherosclerosis is a more prevalent mimicker in these locations. Imaging was considered to be performed at diagnosis if the procedure was performed before or within the first 10 days of treatment.

Statistical analyses. Categorical variables were expressed as numbers (%), and quantitative variables were expressed as medians (range). Categorical variables were analyzed using the Pearson or Fisher's chi-square test, as appropriate. Quantitative variables were analyzed using the Wilcoxon rank-sum test.

A Cox proportional hazards model was used to assess predictive factors associated with relapse-free survival. HR and 95% CI were computed for each predictor in the univariable analysis and in the multivariable model using the backward stepwise approach, with variables that reached $p < 0.1$ in univariable analyses. Relapse-free survival was analyzed using life tables and the Kaplan-Meier method, and these were compared using the log-rank test.

A logistic regression model was used to assess predictive factors associated with GC dependence. OR and 95% CI were computed using the same strategy for the multivariable analysis. The statistical analyses were computed using JMP 9.0.1 (SAS Institute Inc.). $P < 0.05$ defined statistical significance.

RESULTS

Characteristics of the cohort at diagnosis and during followup. We enrolled 326 patients [239 (73%) women; median age at diagnosis: 74 (range 48–92) yrs] whose median followup was 62 (12–262) months. Detailed characteristics at diagnosis are shown in Table 1. Twelve patients had a systemic presentation of GCA with isolated fever and increased acute-phase reactants without any other symptoms.

GCA diagnosis was biopsy-proven in 206 (65%) patients, including 203 who had TAB and 3 from an extratemporal vascular sample (2 aorta histology and 1 uterus histology). Six patients did not show inflammatory variables but had a positive TAB. Fourteen patients had 2 ACR criteria along with LVV on imaging.

Large-vessel imaging was performed at diagnosis in 208 patients (CT angiography of the aorta in 87 and PET/CT in 121) and showed LVV in 67 of them (32%; 27 on CT angiography and 40 on PET/CT). The details of patients with LVV are shown in Supplementary Tables 1 and 2 (available from the authors on request).

All patients from the cohort received GC initially at a median dose of 0.75 (0.25–1.45) mg/kg of body weight.

Characteristics and predictive factors of relapse. During followup, 171 patients (52%) relapsed after a median time of 12 (1–78) months after diagnosis. One relapse occurred in 124 patients, while 2, 3, 4, and 5 relapses occurred in 27, 15, 4, and 1 patients, respectively. The comparison of patients with and without relapse is indicated in Table 2.

When compared to patients without relapse, patients who relapsed had a less frequent history of stroke (4% vs 12%; $p = 0.01$) but more frequent LVV on imaging (39% vs 23%, $p = 0.01$).

GC management did not differ in the 2 groups at GC initiation and at 3 and 6 months. Thereafter, relapsing patients kept higher GC doses ($p < 0.0001$). Relapse occurred at a median dose of 8 mg (0–35) per day of prednisone, and 140

Table 1. Characteristics of the cohort of 326 patients with GCA.

Characteristics	Total, n = 326
Demographics	
Female	239 (73)
Age, yrs	74 (48–92)
Cardiovascular risk factors	
Tobacco use	57 (17)
Hypertension	171 (52)
Dyslipidemia	103 (32)
Diabetes mellitus	34 (10)
History of coronary disease	24 (7)
History of stroke	25 (8)
Clinical manifestations	
BMI	25 (16–37)
Fever	66 (20)
Cranial manifestations	297 (91)
Headaches	270 (83)
Scalp tenderness	141 (43)
Jaw claudication	133 (41)
Ophthalmic trouble	79 (24)
Temporal pulse absence	78 (24)
Limb claudication	15 (5)
Polymyalgia rheumatica	165 (51)
Laboratory tests	
ESR, mm	67 (7–138)
CRP, mg/l	75 (3–424)
Hemoglobin, g/dl	11.5 (7.4–15.3)
Platelets, g/mm^3	415 (140–785)
Positive histology	206 (65)
Positive TAB	203/317 (64)
Large-vessel involvement on imaging	67/208 (32)
Treatment	
GC doses, mg/kg	
At onset	0.75 (0.25–1.45)
At Month 3	0.34 (0.12–1.04)
At Month 6	0.18 (0.06–1)
At Month 12	0.11 (0.01–0.56)
Discontinuation of GC	202 (63)
Duration of GC treatment, mos	23 (6–212)*

Values are n (%) or median (range). * In 205 patients who discontinued GC. GCA: giant cell arteritis; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TAB: temporal artery biopsy; GC: glucocorticoids.

patients (82%) had a dose < 10 mg/day at the time of relapse, whereas 10 (6%) received > 25 mg/day. Cranial symptoms were present at the time of relapse in 117 (68%) patients and PMR in 92 (54%). Six patients among the 12 with initial systemic presentation of GCA relapsed without any clinical symptoms.

At the time of this analysis, fewer relapsing patients had discontinued their treatment (56% vs 71%, p = 0.004), and median GC duration was longer in relapsing patients [29 (10–212) mos vs 18 (6–156) mos in patients without relapses; p < 0.0001]. No differences were observed regarding the occurrence of CV events (stroke, acute coronary syndrome, aortic dissection) or deaths between the 2 groups during followup.

Baseline variables associated with relapse in uni- and multivariable Cox proportional hazard models are shown in Table 3. In multivariable analyses, previous stroke was found to be protective against relapse with an HR of 0.21 (95% CI 0.03—0.68; p = 0.005). Conversely, LVV was an independent predictive factor associated with relapse (HR 1.49, 95% CI 1.002–2.12; p = 0.04).

Figure 1 shows the relapse-free survival (RFS) in our cohort. RFS at 3, 6, and 12 months after diagnosis was 94.4% (95% CI 91.9–96.9), 87.6% (95% CI 84–91.2), and 72.2% (95% CI 67.6–77.3), respectively.

Characteristics and predictive factors of GC dependence. Among the cohort, 113 (35%) patients developed a GC-dependent disease and had experienced at least 1 relapse. These patient characteristics are described in Table 4. Fifty-eight patients (51%) received a GC-sparing agent [51 received methotrexate, 3 received tocilizumab (TCZ), 2 received anakinra, 1 received a tumor necrosis factor-α blocker, and 1 received dapsone].

Patients with GC-dependent disease were significantly younger than patients without [median age 72 (53–87) yrs vs 76 (48–92) yrs; p = 0.0001] and showed less stroke in their medical history (2% vs 11%; p = 0.004). They also showed fewer visual symptoms (16% vs 29%; p = 0.01), more limb claudication (8% vs 3%; p = 0.03), and more LVV on imaging (44% vs 25%, p = 0.005).

GC doses at initiation and at 3 months were similar in both groups. In patients who discontinued GC, treatment duration was longer in patients with GC-dependent disease [51 (14–212) mos vs 20 (6–116) mos; p < 0.0001]. Thirty non–GC-dependent patients received GC for > 24 months, including 25 who continued a longterm dose of 5 mg/day of prednisone because they initially had an ophthalmic involvement; 5 patients were lost to followup for a few years with a 5-mg/day dose of prednisone before being readdressed to our department to discontinue GC.

In the 113 patients with GC-dependent disease, those who received a GC-sparing agent had a shorter GC therapy duration than those without: 36 (15–115) versus 61 (14–212) months (p = 0.008).

Uni- and multivariable analyses are described in Table 5. In the multivariable model, the best predictive factor of GC-dependent disease was the presence of LVV: OR 2.19, 95% CI 1.19–4.05 (p = 0.01). Conversely, a history of stroke was a protective factor against GC dependence: OR 0.10, 95% CI 0.001–0.31 (p = 0.0005).

DISCUSSION

Early identification of patients who will relapse and develop a GC-dependent disease is essential because the burden of GC-related side effects will be greater in this subset of patients. GC-sparing agents are particularly indicated in this setting[11,12,13].

Our relapse rate of 52% is in the range of what is observed in the literature[7,8,14,15,16,17]. Many slight differences might

Table 2. Characteristics of patients with GCA according to whether they relapsed.

Characteristics	Relapsing Patients, n = 171	Nonrelapsing Patients, n = 155	p
Demographics			
Female	128 (75)	111 (72)	0.51
Age, yrs	74 (53–89)	76 (48–92)	0.09
Cardiovascular risk factors			
Tobacco use	31 (18)	26 (17)	0.75
Hypertension	87 (51)	84 (54)	0.55
Dyslipidemia	50 (29)	53 (34)	0.34
Diabetes mellitus	15 (9)	19 (12)	0.30
History of coronary disease	14 (8)	10 (6)	0.55
History of stroke	7 (4)	18 (12)	0.01
Clinical manifestations			
BMI	25 (16–37)	25 (16–36)	0.20
Fever	38 (22)	28 (18)	0.35
Cranial manifestations	152 (89)	145 (94)	0.14
Headaches	136 (80)	134 (86)	0.1
Scalp tenderness	75 (44)	66 (43)	0.82
Jaw claudication	69 (40)	64 (41)	0.87
Ophthalmic trouble	38 (22)	41 (26)	0.37
Temporal pulse absence	38 (22)	40 (26)	0.45
Limb claudication	9 (5)	6 (4)	0.55
Polymyalgia rheumatica	92 (54)	73 (47)	0.23
Laboratory tests			
ESR, mm	68 (7–138)	66 (7–138)	0.71
CRP, mg/l	78 (3–398)	70 (3–424)	0.40
Hemoglobin, g/dl	11.2 (7.4–14.7)	11.5 (8.5–15.3)	0.15
Platelets, g/mm^3	404 (140–772)	439 (196–785)	0.46
Positive histology	105 (64)	101 (66)	0.71
Positive TAB	104 (63)	99 (66)	0.59
Large-vessel involvement on imaging	45/114 (39)	22/94 (23)	0.01
Treatment			
GC doses, mg/kg			
At onset	0.73 (0.25–1.45)	0.77 (0.29–1.45)	0.09
At Month 3	0.35 (0.12–1.04)	0.34 (0.14–0.83)	0.98
At Month 6	0.19 (0.08–0.7)	0.175 (0.06–0.65)	0.15
At Month 12	0.12 (0.02–0.53)	0.09 (0.01–0.56)	< 0.0001
Discontinuation of GC	95 (56)	110 (71)	0.004
Duration of GC treatment, mos	29 (10–212)	18 (6–156)	< 0.0001
Cardiovascular complications	29 (18)	31 (20)	0.48
Death	25 (15)	24 (15)	0.83

Values are n (%) or median (range) unless otherwise specified. GCA: giant cell arteritis; CRP: C-reactive protein; BMI: body mass index; ESR: erythrocyte sedimentation rate; TAB: temporal artery biopsy; GC: glucocorticoids.

exist in the definition of relapse in different studies, which thus may explain the heterogeneity of rates.

Scant information has been published on factors associated with relapse or GC-dependent disease. Labarca, *et al* identified female sex, diabetes mellitus, and hypertension as factors associated with relapse[14]. Restuccia, *et al* showed that fever ≥ 38°C and the severity of inflammatory infiltrate on TAB at diagnosis were significantly associated with flares in GCA in a multivariable model[15]. In our study, fever was not associated with relapse and we did not have data regarding the severity of inflammatory infiltrate on TAB.

Alba, *et al* showed that patients with relapse more frequently showed scalp tenderness and PMR at diagnosis, and a higher level of haptoglobin than patients without relapse[16]. Martinez-Lado, *et al* observed that anemia (hemoglobin < 12 g/dl) was an independent predictive factor of relapse[17]. We did not observe such results in our study, but these previous studies did not analyze LVV as a possible factor influencing GCA outcomes. Indeed, considering LVV, as in our study, Espitia, *et al* suggested that the presence of aortitis was predictive of a more frequently relapsing disease[18]. Some pathophysiological studies suggest that patients with LVV are more difficult to treat, and thus have a greater likelihood of relapsing or developing GC dependence. Different cytokine profiles have been identified according to GCA pattern. While Th17 cells might be highly responsive to GC, Th1 cells, which produce interferon-γ, are less responsive. In large-vessel histological samples, a high

Table 3. Baseline variables associated with relapse in giant cell arteritis in a univariable and multivariable Cox proportional hazards model.

Characteristics	Univariable HR (95% CI)	p	Multivariable HR (95% CI)	p
Female	1.14 (0.82–1.63)	0.44		
Age, yrs	0.75 (0.35–1.62)	0.47		
Tobacco use	1.21 (0.80–1.75)	0.36		
Hypertension	0.90 (0.66–1.21)	0.47		
Dyslipidemia	0.87 (0.62–1.20)	0.39		
Diabetes mellitus	0.74 (0.42–1.21)	0.24		
History of coronary disease	1.19 (0.66–1.98)	0.54		
History of stroke	0.43 (0.18–0.84)	0.01	0.21 (0.03–0.68)	0.005
Fever	1.24 (0.85–1.75)	0.26		
Cranial manifestations	0.67 (0.43–1.12)	0.12		
Headaches	0.65 (0.46–0.96)	0.03		
Scalp tenderness	1.06 (0.78–1.44)	0.69		
Jaw claudication	0.97 (0.71–1.31)	0.84		
Ophthalmic trouble	0.89 (0.61–1.26)	0.51		
Temporal pulse absence	0.93 (0.64–1.32)	0.69		
Limb claudication	1.22 (0.58–2.25)	0.57		
Polymyalgia rheumatica	1.12 (0.83–1.52)	0.46		
ESR, mm	0.97 (0.48–1.95)	0.93		
CRP, mg/l	1.02 (0.45–2.19)	0.96		
Hemoglobin, g/dl	0.64 (0.22–1.85)	0.42		
Platelets, g/mm^3	0.58 (0.19–1.76)	0.34		
Positive histology	1 (0.73–1.38)	0.98		
Positive TAB	0.96 (0.71–1.33)	0.82		
Large-vessel involvement on imaging	1.53 (1.04–2.22)	0.03	1.49 (1.002–2.12)	0.04
Initial GC dose	0.56 (0.17–1.81)	0.34		

GC: glucocorticoids; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TAB: temporal artery biopsy.

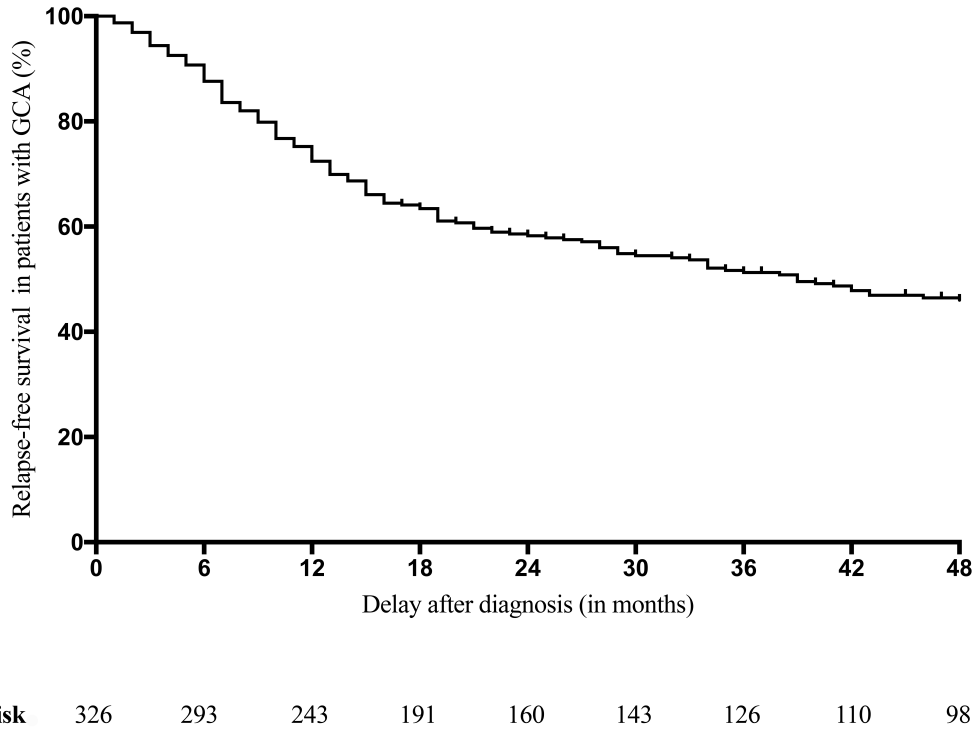

Figure 1. Relapse-free survival in the 326 patients with giant cell arteritis (GCA).

Table 4. Comparison of GCA patients with and without GC-dependent diseases.

Characteristics	GC-dependent Disease, n = 113	Non GC-dependent Disease, n = 213	p
Demographics			
Female	86 (76)	153 (71)	0.40
Age, yrs	72 (53–87)	76 (48–92)	0.0001
Cardiovascular risk factors			
Tobacco use	20 (18)	37 (17)	0.94
Hypertension	61 (54)	110 (52)	0.69
Dyslipidemia	31 (27)	72 (34)	0.24
Diabetes mellitus	12 (11)	22 (10)	0.93
History of coronary disease	7 (6)	17 (8)	0.56
History of stroke	2 (2)	23 (11)	0.004
Clinical manifestations			
BMI	25.3 (16.9–36.9)	24.65 (16–35.6)	0.05
Fever	21 (19)	45 (21)	0.59
Cranial manifestations	103 (91)	194 (91)	0.98
Headaches	94 (83)	176 (83)	0.90
Scalp tenderness	53 (47)	88 (41)	0.33
Jaw claudication	44 (39)	89 (42)	0.62
Ophthalmic trouble	18 (16)	61 (29)	0.01
Temporal pulse absence	24 (21)	54 (25)	0.41
Limb claudication	9 (8)	6 (3)	0.03
Polymyalgia rheumatica	60 (53)	105 (49)	0.51
Laboratory tests			
ESR, mm	73 (7–138)	66 (7–138)	0.15
CRP, mg/l	94 (3–310)	70 (3–424)	0.17
Hemoglobin, g/dl	11.3 (7.4–14.7)	11.5 (8.3–15.3)	0.31
Platelets, g/mm^3	391 (230–703)	426 (140–785)	0.74
Positive histology	75 (66)	131 (64)	0.70
Positive TAB	74 (69)	129 (62)	0.23
Large-vessel imaging performed	77 (68)	131 (62)	0.24
Large-vessel involvement on imaging	34/77 (44)	33/131 (25)	0.005
Treatment			
GC doses, mg/kg			
At onset	0.74 (0.25–1.22)	0.75 (0.29–1.45)	0.45
At Month 3	0.37 (0.12–1.04)	0.34 (0.14–0.9)	0.90
At Month 6	0.24 (0.08–0.7)	0.17 (0.06–0.65)	0.0007
At Month 12	0.14 (0.03–0.53)	0.09 (0.01–0.56)	< 0.0001
Discontinuation of GC	52 (46)	153 (72)	< 0.0001
Duration of GC treatment, mos	51 (14–212)	20 (6–116)	< 0.0001
GC-sparing agent	58 (51)	4 (7)	< 0.0001
Cardiovascular complications	19 (17)	41 (19)	0.59

Values are n (%) or median (range) unless otherwise specified. GCA: giant cell arteritis; GC: glucocorticoids; CRP: C-reactive protein; BMI: body mass index; ESR: erythrocyte sedimentation rate; TAB: temporal artery biopsy.

proportion of Th1 cells have been observed[19,20,21]. This may lead to persistent inflammation, thereby explaining why patients with LVV have a higher risk of relapse, GC dependence, or vascular complications. However, some studies also showed that Th1 response was increased in patients with GCA who developed GCA-related artery occlusion, suggesting a possible increased Th1 response in patients with GCA-related stroke[19]. Our observation of a protective effect of previous stroke on relapse or GC dependency could appear paradoxical. However, in our study cardioembolic origin or atherosclerosis, rather than GCA, are more likely responsible for the previous stroke observed in the medical history of some patients, precluding any interpretation.

This study questions the need to treat patients with LVV differently. In a previous work, we showed that patients with LVV did not receive a different therapeutic regimen in the clinical practice of tertiary centers[22]. However, the present study showed that patients with GC-dependent disease who received a GC-sparing agent were able to discontinue GC earlier than those who did not. This result may encourage prescribing a GC-sparing agent to patients at risk of developing GC dependence, especially those with LVV. Methotrexate or TCZ both showed a GC-sparing effect and

Table 5. Baseline variables associated with GC-dependent GCA in univariable and multivariable analyses.

Characteristics	Univariable OR (95% CI)	p	Multivariable OR (95% CI)	p
Female	1.24 (0.74–2.13)	0.40		
Age	0.95 (0.92–0.98)	0.0003		
Tobacco use	1.02 (0.54–1.85)	0.94		
Hypertension	1.10 (0.70–1.74)	0.69		
Dyslipidemia	0.74 (0.45–1.21)	0.24		
Diabetes mellitus	1.03 (0.47–2.14)	0.93		
History of coronary disease	0.76 (0.28–1.83)	0.55		
History of stroke	0.14 (0.02–0.52)	0.001	0.10 (0.001–0.31)	0.0005
Fever	0.85 (0.47–1.50)	0.58		
Cranial manifestations	1.01 (0.46–2.33)	0.98		
Headaches	1.04 (0.57–1.94)	0.90		
Scalp tenderness	1.25 (0.79–1.99)	0.33		
Jaw claudication	0.88 (0.56–1.41)	0.62		
Ophthalmic trouble	0.47 (0.26–0.83)	0.009		
Temporal pulse absence	0.79 (0.45–1.36)	0.40		
Limb claudication	2.98 (1.05–9.12)	0.04		
Polymyalgia rheumatica	1.16 (0.74–1.84)	0.51		
ESR, mm	0.41 (1.24–2.45)	0.11		
CRP, mg/l	0.74 (0.22–2.54)	0.63		
Hemoglobin, g/dl	0.39 (0.08–1.97)	0.26		
Platelets, g/mm^3	0.82 (0.14–4.47)	0.82		
Positive histology	1.10 (0.68–1.79)	0.70		
Positive TAB	1.35 (0.83–2.22)	0.23		
Large-vessel involvement on imaging	2.35 (1.29–4.29)	0.005	2.19 (1.19–4.05)	0.01
Initial GC dose	0.35 (0.06–2.13)	0.26		

GC: glucocorticoids; GCA: giant cell arteritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TAB: temporal artery biopsy.

could be used in this setting[11,12,13]. The increasing use of TCZ will probably modify future rates of relapse and GC dependence because this drug has shown significant efficacy in treating GCA[12].

In a study by Restuccia, *et al* aiming to analyze factors associated with longterm remission (defined as a permanent discontinuation of prednisone without recurrence of symptoms and elevation of inflammatory markers for at least 1 yr), they observed a lower cumulative dose of GC in patients with longterm remission, which is concordant with our study in which relapsing and GC-dependent patients received longer GC treatments and a subsequently higher cumulative dose[23].

We found that previous stroke was protective against relapse or GC dependence. These findings question the possible protective role of atherosclerosis or its associated treatments. Although not fully understood, a link between both conditions is possible, explaining why GCA affects the elderly, in whom atherosclerosis is highly prevalent. The effect of several CV treatments in GCA is not known. Alba, *et al* demonstrated that the addition of angiotensin receptor blocker (ARB) to the treatment of GCA was associated with less relapse[24]. This finding may be explained by a modulation of the Th1 response by ARB[24]. Schmidt, *et al*[25] showed that the use of statins may reduce the risk of developing GCA. However, statin use in patients with GCA was not associated with a modification of clinical presentation or disease course. Weyand, *et al* demonstrated the complementary effect of acetylsalicylic acid (ASA) with GC in suppressing proinflammatory cytokines in vascular lesions of GCA[26]. ASA currently is used for secondary prevention in patients with CV risk factors.

On the other hand, atherosclerosis has been shown to induce inflammatory disease with stimulation of proinflammatory cytokines[27]. Thus, some studies on GCA or other inflammatory diseases found an increased prevalence of atherosclerosis[28,29,30,31]. In GCA patients, Pujades-Rodriguez, *et al* and Gonzalez-Juanatey, *et al* did not show an increased risk of CV complications[32,33]. Finally, the links between GCA and atherosclerosis and their respective influences remain to be determined.

Some limitations in our study should be discussed. First, the retrospective design limits the completeness of data retrieval. The gradual tapering of GC was heterogeneous in our study. However, we monitored the doses of GC at onset and at 3 and 6 months and did not observe differences between patients, limiting the effect of GC doses on early relapse.

In GCA studies, definitions of relapse and GC dependence might slightly vary. Our results should thus be interpreted in light of these definitions.

Our study indicated that LVV was associated with a higher risk of relapse and GC dependence, which we did not observe in a previous work[22]. However, in this past study, patients were selected and probably not representative of all patients with GCA. Moreover, the design (multicenter enrollment) and the number of patients included (40 in the previous study) were also different.

The retrospective retrieval of imaging results, the absence of central reviewing and the absence of imaging in all our patients are limitations. However, imaging performed at diagnosis in our study was specifically done to search for LVV. Other studies replicating these results are needed to strengthen the value of our observations and confirm this finding. Because LVV was not searched for at diagnosis in all our patients, some patients without relapse or GC-dependent disease might have silent LVV, which could diminish the relevance of our findings. However, we did not observe any difference between relapsing or GC-dependent patients regarding the rate of large-vessel imaging performed at diagnosis. Moreover, our work provided information on large-vessel inflammation but did not analyze the other forms of GCA-related large-vessel involvement such as dilation or vascular stenosis.

No firm conclusion can be drawn regarding the protective effect of previous stroke on relapse and GC dependency because this result has not been replicated in other studies, the number of patients with previous stroke was small, and other factors not identified in this study might have confounded our results. Further studies are clearly warranted.

The absence of data regarding the use of statins or ARB in our patients is another limitation.

Our current study demonstrates that relapses and GC dependence are common in GCA. Large-vessel involvement was an independent predictive factor of relapse and GC dependence. Conversely, a previous stroke was protective against relapse and GC dependence. Future research is required to better understand the links between atherosclerosis and GCA. Finally, these results open up new perspectives for further studies that should analyze whether GCA patients with LVV require a different treatment regimen, including new GC-sparing agents.

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