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Original article

Evaluation of damage in giant cell arteritis

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Abstract

Objectives. To evaluate damage and variables associated with damage in GCA.

Methods. Patients with GCA enrolled in a prospective, multicentre, longitudinal study were included. Per-protocol assessments were made with the Vasculitis Damage Index and the Large-Vessel Vasculitis Index of Damage.

Results. The study included 204 patients: 156 women (76%), mean age at diagnosis 71.3 years (S.D. 8.3), mean follow-up of 3.5 years (S.D. 1.9). One or more damage item was present in 54% at baseline and 79% at the last follow-up on the Vasculitis Damage Index, and 60% at baseline and 82% at the last follow-up on the Large-Vessel Vasculitis Index of Damage. The most frequently observed damage items were large-artery complications (29% cohort) and ocular (22%). Among 117 patients with new damage, most new items were ocular (63 patients), cardiac/vascular (48) and musculoskeletal (34). Of these, treatment-associated items were frequently observed, including cataracts (46 patients), osteoporosis (22) and weight gain (22). Disease-associated new damage included ischaemic optic neuropathy (3 patients), limb claudication (13), arterial occlusions (10) and damage requiring vascular intervention (10). In univariate analysis, the risk of damage increased 22% for every additional year of disease duration [odds ratio (OR) 1.22 (95% CI 1.04, 1.45)]. In 94 patients enrolled within $\leqslant$90 days of diagnosis of GCA, the risk of new damage at the last follow-up decreased 30% for each additional relapse [OR 0.70 (95% CI 0.51, 0.97)].

Conclusions. Large-artery complications and ocular manifestations are the most commonly occurring items of damage in GCA. Most new damage is associated with treatment. These findings emphasize the cumulative burden of disease in GCA.

Key words: giant cell arteritis, vasculitis, large-vessel vasculitis, damage, large-artery manifestations

CLINICAL SCIENCE

Rheumatology key messages

- Most patients with GCA (>75%) have at least one damage item at follow-up.
- The most frequent items of damage in GCA are in the ocular, cardiac, peripheral vascular and musculoskeletal categories.
- Most new items of damage in patients with GCA are attributable to treatment.

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Introduction

GCA is a chronic, granulomatous, large-vessel vasculitis [1]. Damage in GCA may occur secondary to the underlying vasculitis and/or treatment for the disease. Visual impairment and permanent vision loss are particularly dreaded complications of GCA [2, 3]. Additionally, vascular inflammation may lead to large-vessel complications such as arterial stenosis, occlusion, aneurysm or dissection [2, 4–9]. Glucocorticoids remain the mainstay of treatment for patients with GCA but glucocorticoid-associated adverse effects and morbidity are common [10, 11].

Given the morbidity from vasculitis and treatment, damage assessment is an important component in the evaluation of patients with GCA. The Vasculitis Damage Index (VDI) is a validated tool to evaluate damage in systemic vasculitis [12]. It contains 64 items grouped into 11 organ-based systems. Only items that have been present for at least 3 months are scored. The VDI has also been shown to have prognostic value, with increased mortality in patients with granulomatosis with polyangiitis (Wegener's) with high VDI or damage in multiple organ systems [13]. However, validation studies of the VDI included only a small number of patients with large-vessel vasculitis (six with Takayasu's arteritis and one with GCA) [12]. The Large-Vessel Vasculitis Index of Damage (LVVID) (supplementary Fig. S1, available at *Rheumatology* Online) was developed to specifically catalogue damage in GCA and Takayasu's arteritis. Compared with the VDI, the LVVID contains additional items in the ocular, cardiac and peripheral arterial categories that are germane to patients with large-vessel vasculitis and are missing on the VDI, which was designed to address all forms of vasculitis.

The aim of this study was to assess damage and predictors of damage in a longitudinal cohort of patients with GCA using the VDI and LVVID and to inform future efforts to develop and validate standardized measures of damage for use in clinical trials in GCA [14].

Methods

All data for this study were collected from patients enrolled between 2006 and 2014 in the Vasculitis Clinical Research Consortium Longitudinal Study of Giant Cell Arteritis, a multicentre, prospective, observational cohort from nine academic centres in North America. The study was approved by institutional review boards at each participating site. All participants provided informed consent.

All patients in this cohort meet the 1990 ACR classification criteria for GCA [15], modified to include patients with giant cell arteritis diagnosed by large-vessel angiography or biopsy. Inclusion criteria were age >50 years with the presence of two or more of the following features: new localized headache, temporal artery abnormality on examination, ESR >40 mm/h by the Westergren method, abnormal temporal artery biopsy and large vessel vasculitis by angiography or biopsy. All subjects were followed prospectively with standardized clinical assessments, including symptoms attributable to active vasculitis, laboratory findings and use of glucocorticoids and/or other immunosuppressive medications. Data from measures of damage (VDI and LVVID) were collected on all patients at study entry and every 6 months. Only items present for at least 3 months were captured in the damage assessment. Damage items were carried forward and were cumulative. Relapse was defined as any new disease activity since the last visit that was attributed to vasculitis by the treating physician after a period of remission (absence of any disease symptoms or findings attributable to vasculitis by the treating physician). The presence of any relapse and the number of relapses were recorded.

Descriptive statistics were used. Chi-square and Fischer's exact tests were used for comparison of categorical variables. Logistic regression analyses were performed to evaluate the association of clinical variables (age, sex, disease duration from diagnosis, presence of relapse as defined above and number of relapses) with the outcome of damage. Since this is not an inception cohort, risk factors for the presence of new damage during follow-up were also assessed in the subset of patients with newly diagnosed GCA (defined as enrolled into the cohort ⩽90 days from diagnosis).

Results

The Vasculitis Clinical Research Consortium GCA cohort

The study included 204 patients with GCA: 156 (76%) female, 197 (96%) Caucasian. The mean age at diagnosis of GCA was 71.3 years (S.D. 8.3). The median duration from diagnosis to entry into the cohort was 3.7 months (25th–75th quartile 1.0–16.5). A total of 117 subjects (57%) enrolled in the cohort within 6 months of diagnosis. The mean duration of follow-up for the cohort was 3.5 years (S.D. 1.9). Temporal artery biopsy was performed in 136 subjects (67%) and was positive in 116 (85%).

Damage at study entry

The median number of damage items at entry into the cohort was 1 (range 0–7) on the VDI and 1 (range 0–12) on the LVVID. At enrolment into the cohort, at least one damage item was present in 110 patients (54%) on the VDI and 123 (60%) on the LVVID. In the subset with one or more damage item on a given instrument, the median number of damage items was 2 (range 1–9) on the VDI and 3 (range 1–16) on the LVVID.

The most frequently observed items of damage at entry into the cohort are shown in Table 1.

At least one damage item was recorded in 46/114 (40%) patients diagnosed ⩽180 days prior to study entry on the VDI compared with 64/87 (74%) with a disease duration >180 days ($P < 0.0001$). Similarly, 55/116 (47%) patients diagnosed ⩽180 days prior to study entry had one or more item by the LVVID compared with 68/87 (78%) with a disease duration >180 days ($P < 0.0001$). The median damage in patients diagnosed ⩽180 days was 0 (range 0–5) on the VDI compared with 2 (range 0–7) in subjects with >180 days disease duration. The median

Table 1 Most frequently observed items of damage at study enrolment in 204 patients with GCA

Organ system	VDI,[a] *n* (%)	LVVID,[a] *n* (%)
Peripheral arterial	58 (29)	53 (26)
Arm claudication	NR[b]	37
Leg claudication	NR[b]	8
Limb claudication	39	NR[b]
Arterial thrombosis/occlusion	NR[b]	11
Absent pulse	39	NR[b]
Aortic aneurysm	NR[b]	7
Ocular	45 (22)	54 (26)
Ischaemic optic neuropathy	NR[b]	25
Low vision	NR[b]	25
Cataract	20	24
Blindness	18	18
Visual impairment/diplopia	18	NR[b]
Cardiac	21 (10)	33 (16)
Hypertension	NR[b]	31
Diastolic BP $\geqslant$ 95 mm Hg or requiring treatment	18	NR[b]
Musculoskeletal	25 (12)	25 (12)
Osteoporosis	16	16

[a]Percentage is the number of subjects with at least one abnormality divided by the total number of patients with GCA. [b]Item not queried on index. BP: blood pressure; NR: not reported.

damage in patients diagnosed $\leqslant$180 days was 0 (range 0–7) on the LVVID compared with 2 (range 0–12) in subjects diagnosed >180 days.

Damage accrual during follow-up

After a mean follow-up of 3.5 years, 161 (80%) patients had one or more item of damage [median 2 (range 0–9)] on the VDI while 166 (82%) patients had one or more damage item [median score 3 (range 0–16)] on the LVVID. At least one new item of damage was recorded in 112 (55%) patients on the VDI [median number of new items 1 (range 0–8)] and in 117 (60%) patients on the LVVID [median number 1 (range 0–8)]. The number of patients with three or more damage items on the VDI was 39%, with 13% of patients having five or more damage items [16]. A comparison of the frequency of damage items at enrolment and the last follow-up is shown in Table 2. Most new damage items were in the ocular [63 patients (54%)], cardiac/arterial [48 patients (41%)], musculoskeletal [34 patients (29%)], haematology/oncology [4 patients (3%)] and other [19 patients (16%)] categories on both damage indices (Table 2). The most frequently observed new items of damage are shown in Fig. 1.

Predictors of damage in patients with GCA

Predictors for the presence of any damage at the last follow-up for the whole cohort were evaluated using univariate analyses. Disease duration was the only predictor of the presence of any damage at the last follow-up; the risk of damage increased 22% for every additional year of disease duration [OR 1.22 (95% CI 1.04, 1.45)] (Table 3).

Predictors of damage in patients diagnosed with GCA $\leqslant$90 days

Risk factors for the presence of new damage during follow-up was assessed in the subset of 93 patients with newly diagnosed GCA (defined as enrolled into the cohort $\leqslant$90 days from diagnosis). In this subset, the risk of new damage at the last follow-up decreased 30% for each additional relapse [OR 0.70 (95% CI 0.51, 0.97)] (Table 3).

The distribution of relapses among the 93 newly diagnosed patients was as follows: zero relapses in 32 patients (34%), one relapse in 32 (34%), two relapses in 8 (9%) and three or more relapses in 21 (23%). Clinical variables were compared between 93 patients with newly diagnosed GCA (diagnosed $\leqslant$90 days) (i) with and without new items of damage and (ii) with and without relapses (Table 4).

Medication use also did not differ in 93 patients with newly diagnosed GCA with or without new damage. Among patients diagnosed $\leqslant$90 days, use of glucocorticoid at the time that new damage was observed was noted in 55 of 60 (92%) patients with new damage compared with 17 of 17 (100%) patients without new damage. Additional immunosuppressive therapies during follow-up were used in 12 of 60 (20%) patients with new damage compared with 4 of 17 (24%) patients without new damage.

Performance of the outcome measures

There were multiple items in the different categories on both the VDI and LVVID that never applied to any patient with GCA in this cohort (Table 5). The LVVID provided more granularity on the different components of damage that are frequently observed in patients with GCA, especially the ocular and peripheral arterial categories (Table 1). Specifically, for the ocular manifestations, ischaemic optic neuropathy, a dreaded complication of GCA, was captured on the LVVID but not on the VDI. While the VDI captures data on limb claudication, the peripheral vascular damage items on the LVVID separated them into upper and lower extremity claudication. Other large-vessel damage items, including arterial occlusions/thrombosis and aneurysms, were also captured on the LVVID. Additionally, weight gain (>10 lb) was systematically queried on the LVVID, which led to more complete capture of this frequently observed adverse effect of glucocorticoid therapy in patients with GCA.

Discussion

This is the largest longitudinal study to assess damage in patients with GCA. After a median observation of 3.5 years, the majority of patients with GCA had at least one item of damage. New items of damage were observed in more than half of the patients in this cohort, with the majority of new damage items being related to treatment.

Table 2 Frequency and categories of damage captured on the damage indices at study enrolment and last follow-up

Organ system	VDI ($n = 204$)			LVVID ($n = 204$)		
	Baseline, *n* (%)	Follow-up, *n* (%)	*P*-value	Baseline, *n* (%)	Follow-up, *n* (%)	*P*-value
Cardiac	21 (10)	44 (22)	<0.01	33 (16)	51 (25)	0.04
Peripheral arterial	58 (29)	66 (32)	0.45	53 (26)	66 (32)	0.19
Musculoskeletal	25 (12)	51 (25)	<0.01	25 (12)	51 (25)	<0.01
Ocular	45 (22)	89 (44)	<0.01	54 (26)	92 (45)	<0.01
ENT	1 (0.5)	1 (0.5)	1.00	1 (0.5)	1 (0.5)	1
Gastrointestinal	1 (0.5)	2 (1)	1	0 (0)	1 (0.5)	1
Neuropsychiatric	4 (2)	8 (4)	0.38	5 (3)	6 (3)	1
Endocrine	8 (4)	10 (5)	0.81	11 (5)	9 (4)	0.81
Haematology/oncology	0 (0)	8 (4)	<0.01	0 (0)	7 (3)	<0.01
Skin	1 (0.5)	1 (0.5)	1	4 (2)	7 (3)	0.54
Pulmonary	4 (2)	5 (3)	1	NR[a]	NR[a]	NR
Renal	0 (0)	0 (0)	1	NR[a]	NR[a]	NR
Other	7 (3)	15 (7)	0.12	27 (13)	44 (22)	0.04

[a]Item not queried on index. *n*: total number of patients with at least one item of damage in that category; NR: not reported.

Fig. 1 Frequently observed new items of damage during follow-up as captured on either damage index, and, attribution

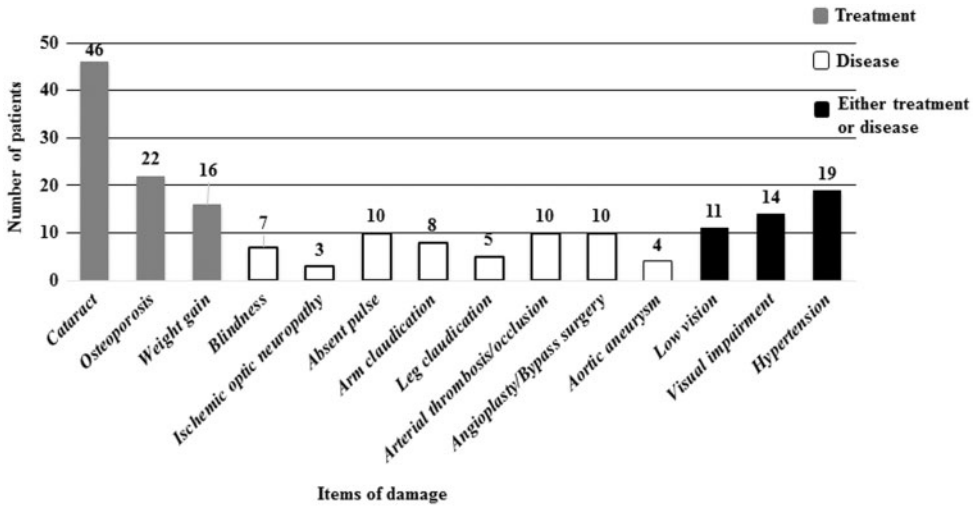

Table 3 Univariate analysis of predictors of damage in patients with GCA

Variable	Any damage at last visit[a] ($n = 204$)	New damage items during follow-up in recently diagnosed patients[b] ($n = 93$)
Age at diagnosis	1.01 (0.97, 1.06)	1.02 (0.97, 1.08)
Female sex	1.99 (0.90, 4.40)	0.82 (0.30, 2.25)
Disease duration	1.22 (1.04, 1.45)	1.17 (0.90, 1.52)
Any relapse	0.63 (0.29, 1.38)	0.90 (0.35, 2.30)
Number of relapses	0.88 (0.68, 1.13)	0.70 (0.51, 0.97)

All values are OR (95% CI). [a]Entire cohort. [b]Restricted to 93 patients enrolled within ⩽90 days of diagnosis.

Damage is the irreversible consequence of the condition and may represent the cumulative burden of the disease experienced by the patient [17, 18]. Patients with GCA may experience irreversible consequences of the disease, including permanent vision loss, chronic ischaemic symptoms and infarction or large-artery complications. Furthermore, in prospective observational studies, relapses were frequently observed in patients with GCA [19–22] and often necessitate an increase in glucocorticoid treatment. This is the first study to systematically assess damage in patients with GCA using the VDI, a validated tool, and the LVVID, an instrument that was specifically developed for use in large-vessel vasculitis.

More than 80% of patients in the cohort had one or more damage item at the last follow-up, which is similar to what has been reported in studies evaluating damage in

Table 4 Comparison of clinical variables in 93 patients with GCA ⩽90 days from diagnosis

Variable No (*n* = 31)	Presence of any damage during follow-up			Presence of any relapse during follow-up		
	Yes (*n* = 62)	*P*-value	No (*n* = 32)	Yes (*n* = 61)	*P*-value	
Age, mean (S.D.), years	70.9 (8.8)	72.3 (9.3)	0.49	73.0 (8.2)	71.2 (9.6)	0.35
Female sex	23 (74)	44 (71)	0.81	22 (69)	45 (73)	0.63
Positive biopsy	9/14 (64)	21/24 (88)	0.12	9/12 (75)	21/26 (81)	0.69
Duration follow-up, mean (S.D.), weeks	143 (95.4)	171 (83.5)	0.15	138.3 (81.2)	175.8 (89.1)	0.05
Cranial manifestations	28 (90)	53 (85)	0.75	29 (91)	53 (85)	0.75
Constitutional symptoms	8 (26)	24 (39)	0.25	9 (28)	23 (37)	0.50
Visual symptoms	10 (32)	26 (42)	0.50	15 (47)	22 (35)	0.37
Polymyalgia rheumatica	12 (39)	24 (39)	1.0	13 (41)	24 (39)	1.0
Arm claudication	3 (10)	10 (16)	0.14	6 (19)	7 (12)	0.36
Leg claudication	0 (0)	5 (8)	0.17	0 (0)	5 (8)	0.16

[A]ll results are presented as *n* (%) unless stated otherwise.

Table 5 Damage-related items never noted in the GCA cohort, arranged by organ system

Organ system	VDI, items not used /total number of items (%)	LVVID, items not used /total number of items (%)
Cardiac	3/7 (43)	6/12 (50)
Peripheral arterial	2/8 (25)	0/14 (0)
Musculoskeletal	2/5 (40)	0/4 (0)
Ocular	1/7 (14)	6/22 (27)
Neuropsychiatric	1/8 (50)	2/7 (29)
Skin	1/3 (33)	0/3 (0)
Endocrine	1/2 (50)	3/4 (75)
Haematology/oncology	1/2 (50)	2/8 (25)
Pulmonary	4/7 (57)	NR
Gastrointestinal	3/4 (75)	1/2 (50)
ENT	4/6 (67)	2/3 (56)
Renal	3/3 (100)	NR
Other	1/2 (50)	1/3 (33)

NR: not reported.

other systemic vasculitides [17, 23–25]. However, the median VDI and LVVID scores in patients with GCA were lower than those reported in other forms of systemic vasculitis [13, 17, 23–25]. The majority of the damage items in patients with GCA were captured in four main categories: ocular, cardiac, peripheral vascular and musculoskeletal. Additionally, on the LVVID, many patients also had findings in the 'other' category due to the item of weight gain, which was included in this index. The burden of disease-associated manifestations at study entry was high, with limb claudication in 19%, ischaemic optic neuropathy in 12% (captured only on the LVVID) and permanent vision loss in 9%. Aneurysms were present in 3% patients (captured only on the LVVID), although this manifestation of disease may be underrecognized if imaging of the aorta is not performed routinely.

Similar to what has been reported for other forms of vasculitis, new damage items that may be related to disease or its treatment, particularly glucocorticoids, were observed in patients with GCA [17, 24–26]. Prior studies have also found a higher risk of treatment-related damage in older subjects [13, 16, 25]. Most of the new damage items in patients with GCA in the current study were associated with treatment. The disease-associated items of damage were predominantly large-vessel arterial events, including absent pulses, limb claudication, arterial occlusions and arterial damage requiring intervention, suggesting a higher burden of disease in patients with extracranial manifestations of GCA.

When evaluating the entire cohort, disease duration was associated with the presence of damage at the last follow-up. Given that most new damage items are glucocorticoid related, this likely reflects prolonged glucocorticoid exposure in these patients. In ANCA-associated vasculitis (AAV), disease relapses have been associated with increased damage [16, 24, 27, 28]. However, when evaluating the subset of 93 patients with newly diagnosed GCA (⩽90 days from entry into the cohort), a higher number of relapses was associated with a lower likelihood of new damage during follow-up. This finding was not well explained, especially since the majority of the new damage over time in this cohort was related to the toxicity of treatment with glucocorticoids. Symptoms at disease presentation or the frequency of a temporal artery biopsy positive for GCA was not different in subjects with or without relapses or new damage. Furthermore, the use of immunosuppressive medications other than glucocorticoids was not different in newly diagnosed patients with new damage items compared with newly diagnosed patients without new items of damage. While cumulative glucocorticoid doses were not available, glucocorticoid use at the time of new damage was no different between patients with or without new damage items when restricted to patients with newly diagnosed disease. In the future, tools such as the glucocorticoid toxicity index may be

helpful in better quantifying glucocorticoid-associated damage but warrant further investigation [29].

Many items that are queried on the VDI and LVVID did not apply to any patient with GCA. The LVVID systematically captured important damage items including ischaemic optic neuropathy, arterial occlusions, aneurysms and damage requiring surgery that were not present on the VDI. The LVVID did not include absent pulses, which was queried on the VDI; however, this finding is a proxy for arterial stenoses, which is captured on the LVVID.

The strengths of this study include the prospective design with standardized serial assessments. This cohort included subjects with the full range of manifestations of GCA, including a substantial number with large-artery disease, a now commonly recognized subgroup [5, 30–32]. The conduct of the study at multiple centres in North America adds to the generalizability of the results.

Potential limitations of the study include that the cohort includes patients evaluated at tertiary care referral centres and may include a higher proportion of patients with relapsing or severe disease compared with community practices; however, the multicentred nature of the cohort and the inclusion of so many patients at each site helps increase the range of disease and generalizability of the study. Additionally, data on the cumulative doses of glucocorticoids were not available and would have been of interest relative to several items of damage.

Patients with GCA should be monitored for cumulative disease and treatment-associated damage. This study provides information for data-driven development of damage-related outcomes for future use in clinical trials and clinical practice. These data also provide support to simplify the VDI/LVVID approach to damage assessment through removal of items not applicable to the vast majority of patients with GCA. Better therapeutics for GCA that target disease activity and reduce the cumulative burden of disease- and treatment-associated damage are needed. The present study highlights the importance of including damage assessment in future clinical trials of GCA.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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