Autoimmunity Reviews 18 (2019) 714–720

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Large-vessel vasculitis diagnosed between 50 and 60 years: Case-control study based on 183 cases and 183 controls aged over 60 years

Laure Delaval[a,1], Aurélie Daumas[b], Maxime Samson[c], Mikael Ebbo[b], Hubert De Boysson[d], Eric Liozon[e], Henry Dupuy[f], Mathieu Puyade[g], Daniel Blockmans[h], Ygal Benhamou[i], Karim Sacré[j], Alice Berezne[k], Hervé Devilliers[l], Grégory Pugnet[m], François Maurier[n], Thierry Zénone[o], Claire de Moreuil[p], François Lifermann[q], Laurent Arnaud[r], Olivier Espitia[s], Alban Deroux[t], Vincent Grobost[u], Estibaliz Lazaro[f], Christian Agard[s], Alexandre Balageas[v], Kevin Bouiller[w], Cécile-Audrey Durel[x], Sébastien Humbert[w], Virginie Rieu[u], Mélanie Roriz[y], Odile Souchaud-Debouverie[g], Stéphane Vinzio[z], Yann Nguyen[a], Alexis Régent[a], Loïc Guillevin[a], Benjamin Terrier[a,*]

[a] National Referral Center for Rare Autoimmune and Systemic Diseases, Hopital Cochin, AP-HP, Université Paris Descartes, Paris, France
[b] Department of Internal Medecine, La Timone University Hospital, Marseille, France
[c] Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France
[d] Department of Internal Medecine, Caen University Hospital, University of Caen-Basse Normandie, France
[e] Department of Internal Medecine, Limoges University Hospital, France
[f] Department of Internal Medicine, Haut-Lévêque Hospital, Pessac, France
[g] Department of Internal Medicine, University Hospital of Poitiers, Poitiers, France
[h] Clinical department of general internal medicine department, University Hospitals Leuven, Belgium
[i] Department of Internal Medecine, 1 rue de Germont, Rouen, France
[j] Department of Internal Medecine, Bichat Hospital, Paris, France
[k] Department of Internal Medecine, CHR Annecy-Genevois, Annecy, France
[l] Department of Internal Medicine and Systemic Diseases, CHU Dijon Bourgogne, Inserm CIC 1432, Clinical Epidemiology Unit, Dijon, France
[m] Department of Internal Medecine, CHU de Toulouse, UMR 1027 Inserm-Université de Toulouse, France
[n] Department of Internal Medicine, Hôpital Belle Isle, Metz, France
[o] Internal Medicine Department, Valence Hospital, Valence, France
[p] Department of Internal Medecine and pneumology, CHU Brest, La Cavale Blanche Hospital, Brest Cedex, France
[q] Department of Internal Medecine, CH Dax, France
[r] Department of Rheumatology, CHU Strasbourg, INSERM UMR-S1109, RESO, Strasbourg University, F-67000 Strasbourg, France
[s] Department of Internal Medicine, Nantes University Hospital, Nantes, France
[t] Grenoble University Hospital, Division of Internal Medicine, Grenoble F-38043, France
[u] Internal Medicine Department, University Hospital, Clermont-Ferrand, France
[v] Department of Rheumatology, CH Pau, France
[w] Department of internal medicine, CHU Jean Minjoz, Besancon, France
[x] Department of Internal Medicine, Edouard Herriot Hospital, Lyon, France
[y] Department of Internal Medicine, Hôpital Lariboisière, Paris, France
[z] Department of Internal Medicine Groupe Hospitalier Mutualiste of Grenoble, Grenoble, France

ARTICLE INFO

Keywords:
Large-vessel vasculitis
Giant cell arteritis
Takayasu arteritis
Outcome measures
Refractory disease

ABSTRACT

Background: Age at onset of large-vessel vasculitis (LVV) is commonly used to distinguish giant cell arteritis (GCA) and Takayasu arteritis (TA). However, LVV between age 50 and 60 years may be difficult to classify.
Methods: We conducted a retrospective study including LVV aged between 50 and 60 years at onset ($LVV_{50–60}$, cases) and compared them to LVV aged over 60 years ($LVV_{>60}$, controls). LVV was defined histologically and/or morphologically. Controls fulfilled ACR 1990 criteria for GCA or presented isolated aortitis.
Results: We included 183 $LVV_{50–60}$ and 183 gender-matched $LVV_{>60}$. $LVV_{50–60}$ had more frequent peripheral

* Corresponding author at: Department of internal Medicine, National Referral Center for Rare Systemic Autoimmune Disease, Cochin Hospital, Paris Descartes University (Paris 5), 24 rue du Faubourg Saint-Jacques, 75014 Paris, France.
E-mail address: benjamin.terrier@aphp.fr (B. Terrier).
[1] for the French Vasculitis Study Group and the French Giant Cell Arteritis Study Group (GEFA).

https://doi.org/10.1016/j.autrev.2019.05.008
Received 11 February 2019; Accepted 16 February 2019
Available online 04 May 2019
1568-9972/

limb manifestations (23 vs. 5%), and less frequent cephalic (73 vs. 90%) and ocular signs (17 vs. 27%) than $LVV_{>60}$. Compared to $LVV_{>60}$, CT angiography and PET/CT scan were more frequently abnormal in $LVV_{50–60}$ (74 vs. 38%, and 90 vs. 72%, respectively), with aorta being more frequently involved (78 vs. 47%). By multivariate analysis, absence of cephalic symptoms, presence of peripheral limb ischemia and aorta involvement, and increased CRP level were significantly associated with $LVV_{50–60}$ presentation compared to $LVV_{>60}$. At last follow-up, compared to $LVV_{>60}$, $LVV_{50–60}$ received significantly more lines of treatment (2 vs. 1), more frequent biologics (12 vs. 3%), had more surgery (10 vs. 0%), and had higher prednisone dose (8.8 vs. 6.5 mg/d) at last follow-up,

Conclusion: LVV onset between 50 and 60 years identifies a subset of patients with more frequent aorta and peripheral vascular involvement and more refractory disease compared to patients with LVV onset after 60.

1. Introduction

The 2012 International Chapel Hill Consensus Conference (CHCC2012) subdivides vasculitides based on a combination of features, including the type of vessel affected [1]. Thereby, primary vasculitides may be distinguished into large vessel vasculitis (LVV), medium vessel vasculitis and small vessel vasculitis [1]. Primary LVV, involving the aorta and its major branches, are represented by two major variants, i.e. Takayasu arteritis (TA) and giant cell arteritis (GCA). According to the CHCC2012, histopathologic features of TA and GCA are indistinguishable, and TA is usually considered to predominantly involve young individuals whereas GCA predominantly involve older individuals [2–6].Thus, the age at onset of LVV is commonly used to distinguish both diseases, TA occurring before 50 years and GCA after 50 years [7–9]. However, GCA incidence peaks at 70–79 years [2,10,11], and only very few GCA appear before 60 years. In contrast, peak age for TA onset is usually between 20 and 30 years and the disease less commonly occurs after 50 years [6,12]. Therefore, patients diagnosed with LVV between 50 and 60 years of age can be difficult to classify.

Treatment of active forms of LVV is based on glucocorticoids, but therapeutic regimens that could be used in case of relapsing or refractory disease may differ between TA and GCA. Tumor necrosis factor (TNF)-α blockers were constantly found to be ineffective in prospective trials in GCA [13–15], whereas they showed some efficacy in retrospective studies in TA [16–19]. In contrast, tocilizumab, an anti-interleukin (IL)-6 receptor monoclonal antibody, was shown to be effective in GCA in a large prospective randomized trial [20], whereas data from a small prospective trial failed to achieve the primary endpoint in TA but tended to favour tocilizumab [21,22].

In the present study, we describe the clinical pictures and outcomes of LVV occurring between the ages 50 and 60 ($LVV_{50–60}$) years, and compares them to LVV diagnosed after 60 years ($LVV_{>60}$).

2. Patients and methods

2.1. Patients

We conducted a nationwide retrospective multicenter study from January 2000 to February 2017, supported by the French Vasculitis Study Group (FVSG) and French Giant Cell Arteritis Study Group (GEFA), in 24 French and one Belgian departments of Internal Medicine and Rheumatology. Inclusion criteria for cases were: 1) patients with LVV as defined below, and 2) patients aged between 50 and 60 years ($LVV_{50–60}$). This study was conducted in compliance with the Good Clinical Practice protocol and the Declaration of Helsinki principles. The study was approved by local ethics committee, who waived the requirement for informed consent.

2.2. LVV definition

LVV was defined histologically (positive temporal artery biopsy, TAB) and/or morphologically (circumferential thickening of large vessels on computed tomography angiography and/or magnetic resonance angiography, or large vessel hypermetabolism on 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography).

2.3. Control group

Cases ($LVV_{50–60}$) were compared to controls, i.e. patients with LVV as defined above but aged over 60 years ($LVV_{>60}$). Controls fulfilled the American College of Rheumatology (ACR) 1990 criteria for GCA [8] or presented an isolated aortitis without argument for a secondary aortitis. In case of missing erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) levels (> 10 mg/L) was used as a criterion. Controls were taken from databases of three French Internal Medicine departments (Cochin Hospital in Paris, Dijon Hospital, La Timone Hospital in Marseille) and were randomly matched on gender with a 1:1 ratio.

2.4. Clinical, laboratory, radiological and pathological assessment

For each patient, cases and controls, clinical, biological, radiological and pathological data were retrospectively collected from the initial diagnosis of LVV throughout follow-up by physicians in charge of the patients. Clinical and biologic assessments included clinical manifestations, serum CRP levels, blood count, TAB, computed tomography angiography (CTA), magnetic resonance angiography (MRA) and 18F-FDG-PET/CT at time of diagnosis. Diagnosis of LVV variant by physicians in charge (TA or GCA), based on the clinical and morphological presentation, was recorded. Aortitis was defined as thickening > 2 mm, parietal contrast enhancement, or large vessel hypermetabolism on 18F-FDG-PET/CT. For patients with TA presentation, extension of the disease was specified as previously described [23]. Treatments were also recorded.

2.5. Response to therapy and outcome

Response to therapy was evaluated by physicians in charge of the patients during the routine follow-up of these patients and retrospectively reviewed. Remission was defined as the absence of clinical manifestations consistent with active disease, normalization of inflammatory parameters, absence of morphological progression or appearance of new lesions, and a prednisone dose ≤ 0.1 mg/kg/day. Glucocorticoids (GCs) dependency was defined as the need to maintain a prednisone dose > 0.1 mg/kg/day and ≤ 0.5 mg/kg/day to control the disease (absence of clinical manifestations, normalization of inflammatory parameters, absence of morphological progression or appearance of new lesions). GCs resistance was defined as the lack of response with a prednisone dose > 0.5 mg/kg/day. Only patients with a follow-up greater than twelve months were retained for follow-up analysis.

2.6. Statistical analysis

Data are presented as the mean ± standard deviation (SD) or as the median and interquartile range, as appropriate, for continuous variables and frequency (percentage) for qualitative variables. Quantitative variables were compared using Student's *t*-test or the nonparametric Mann-Whitney test, and categorical variables were compared using the chi-square test. Multivariable analysis was performed using a logistic regression. Clinical manifestations with $P \leq 0.20$ in the univariable analysis, CRP level, TAB and the presence of an aortitis on CT scan and/or FDG PET-CT were included in the multivariable logistic regression model to identify independent factors associated with LVV between 50 and 60 years and LVV aged over 60 years. All analyses were performed using the SAS software, version 9.4 and GraphPad Prism version 5.0. All statistical tests were two-sided, and significance was set at the 0.05 level.

3. Results

We included 183 cases ($LVV_{50–60}$) and 183 controls ($LVV_{>60}$) in this case-control study.

3.1. Clinical, biological and morphological characteristics of cases ($LVV_{50–60}$)

Clinical, biological and radiological characteristics of the 183 $LVV_{50–60}$ patients are indicated in Table 1. Median age at LVV diagnosis was 57 (54–58) years and 136 (74%) were female.

Initial vasculitis manifestations were constitutional symptoms in 144 (79%) cases (i.e. asthenia in 65%, weight loss in 45%, fever in 44%, night sweats in 18%), cephalic symptoms in 133 (73%) (i.e., headache in 68%, scalp tenderness in 27%, jaw claudication in 23% and decrease pulse in the temporal artery in 10%), *polymyalgia rheumatica* in 55 (30%), peripheral limb ischemic manifestations in 42 (23%), ocular manifestations in 32 (17%), stroke in 3 cases (2%) and mesenteric ischemia in 2 cases (1%). Peripheral limb ischemic manifestation consisted in a lack of pulse and/or asymmetric blood pressure in 11% each, upper limb claudication in 6% and lower limb claudication in 5%. Median CRP level was 9.5 mg/dL (0.2–42), including 10 (5%) patients without any biological inflammatory syndrome. Temporal artery biopsy was performed in 132 (72%) and showed evidence of LVV in 78 (59%) cases.

Computed tomography angiography was performed in 102 (56%) cases and was abnormal in 75 (74%) cases. Abnormalities on CTA involved aorta in 62 cases (61%, with thoracic involvement in 29%, abdominal involvement in 8%, and both in 63%), subclavian artery in 26 (25%), iliofemoral artery in 18 (18%) and carotid artery in 14 (14%). Isolated aortitis was noted in 29 (28%) patients. 18F-FDG-PET/CT was performed in 105 (57%) cases, showing evidence of large vessel hypermetabolism in 94 (90%) cases. Abnormalities on 18F-FDG-PET/CT involved aorta in 89 cases (95% of abnormal 18F-FDG-PET/CT and 85% of all 18F-FDG-PET/CT performed, including isolated thoracic involvement in 31 cases, isolated abdominal involvement in 1 case, and both in 57 cases), subclavian artery in 61 cases (58%), carotid artery in 48 (46%) and iliofemoral artery in 32 (30%). Isolated aortitis was noted in 21 (20%) cases. MRA was performed in 15 (8%) cases and was abnormal in all cases. Abnormalities on MRA involved aorta in 9 cases (60%) and its major branches in 11 (73%) cases including carotid artery in 9 (60%), subclavian artery in 7 (47%) and iliofemoral artery in 2 (13%). In 13 cases, CTA and 18F-FDG-PET/CT were also performed and were abnormal. In the 2 remaining cases, MRA was the only imaging performed.

Overall, aortitis was noted on CTA and/or 18F-FDG-PET/CT in 113/145 (78%) cases, without any cephalic symptoms in 41 (28%) patients. Finally, 15 patients had evidence for aortitis on 18F-FDG-PET/CT with no abnormalities on CTA.

Some patients underwent concomitant diagnostic investigations: 101 patients had concomitant TAB and an imaging test, including TAB and CTA in 70, TAB and 18F-FDG-PET/CT in 70, and TAB and MRA in 9. Positive diagnostic contribution in both investigations (TAB and imaging tests) was noted in 25 (36%) with CTA, 35 (50%) 18F-FDG-PET/CT and 3 (33%) with MRA. Fifty-six patients had both CTA and 18F-FDG-PET/CT, and investigations were concordant in 45 patients (80%), suggesting that TAB could underestimate LVV in patients between 50 and 60 years.

3.2. Treatments, response to therapy and outcome of the cases ($LVV_{50–60}$)

Among the 183 cases, 179 had at least one follow-up visit and 150 $LVV_{50–60}$ patients were followed-up for > 12 months and were included in the follow-up analysis. All cases received GCs at a dose between 0.5 and 1 mg/kg/day of prednisone, alone in most cases and in combination with immunosuppressive agents in 11 (6%) patients, i.e. methotrexate (n = 9), cyclophosphamide (n = 1) and mycophenolate mofetil (n = 1) as first-line therapy (Table 2). Nine patients received methylprednisolone intravenously. After a median follow-up of 43.8 months (range 12–187), 78/150 (52%) patients required at least a 2nd-line therapy. Overall, 52 (35%) patients received methotrexate and 18 (12%) patients received a biological agent (including tocilizumab in 15 patients and TNF-alpha blockers in 6) (Table 2). Fifteen (10%) patients required surgery (bypass surgery in 11 cases or angioplasty in 2 cases, and both in 2 cases). At the end of follow-up, only 68 patients (45%) had discontinued GCs and 63 (42%) all LVV-specific treatment.

Table 1
Characteristics of the 183 patients with LVV diagnosed between 50 and 60 years and the 183 controls with LVV aged over 60 years.

Characteristics	$LVV_{50–60}$ (n = 183)	$LVV_{>60}$ (n = 183)	P value
Demography			
Female	136 (74)	136 (74)	–
Age at diagnosis, median (IQR), years	57 (54–58)	75 (68–82)	–
Clinical manifestations			
Constitutional symptoms	144 (79)	146 (80)	0.80
Cephalic symptoms	133 (73)	164 (90)	< **0.0001**
Polymyalgia rheumatica	55 (30)	71 (39)	0.08
Peripheral limb ischemia	42 (23)	10 (5)	< **0.0001**
Ocular signs	32 (17)	49 (27)	**0.03**
Cough	22 (12)	22 (12)	1
Stroke	3 (2)	5 (3)	0.50
Mesenteric ischemia	2 (1)	2 (1)	1
C-reactive protein, median, mg/dL	9.5 (5.4–14.7)	7.1 (4.4–135)	0.09
TAB	132 (72)	152 (83)	–
Positive TAB	78 (59)	109 (72)	**0.03**
Imaging tests			
Abnormal CT-angiography	75/102 (74)	44/117 (38)	< **0.0001**
Aorta involvement	62 (61)	42 (36)	**0.0002**
Thoracic	18	5	
Abdominal	5	2	
Both	39	35	
Subclavian artery involvement	26 (25)	7 (6)	< **0.0001**
Iliofemoral artery involvement	18 (18)	4 (3)	**0.0005**
Carotid artery involvement	14 (14)	5 (4)	**0.01**
Isolated aortitis	29 (28)	31 (26)	0.70
Abnormal 18F FDG PET-CT	94/105 (90)	50/69 (72)	**0.01**
Aortitis (CT scan and/or FDG PET–CT)	113/145 (78)	65/139 (47)	< **0.0001**
Aortitis without cephalic signs	41/145 (28)	11/139 (8)	< **0.0001**

Values are expressed as n (%) of patients or median (interquartile range).
IQR, interquartile range; CT, computed tomography.
PET, positron-emission tomography; TAB: temporal artery biopsy.
Bold represents significant differences.

Table 2
LVV medical therapeutic management of the 150 patients with LVV diagnosed between 50 and 60 years and the 150 controls with LVV aged over 60 years.

Characteristics	$LVV_{50–60}$ (n = 150)	$LVV_{>60}$ (n = 150)	P value
1st-line			
GCs	150 (100)	150 (100)	1
Methotrexate	9	1	
Cyclophosphamide	1	0	
Mycophenolate mofetil	1	0	
2nd-line	78 (52)	60 (40)	0.049
Methotrexate	38	37	
Cyclophosphamide	8	0	
Azathioprine	6	0	
Mycophenolate mofetil	1	0	
TNF-alfa blockers	3	0	
Tocilizumab	3	0	
≥3rd-line	27 (18)	9 (6)	0.002
Methotrexate	13	6	
Cyclophosphamide	2	0	
Azathioprine	2	0	
TNF-alfa blockers	1	0	
Tocilizumab	5	1	
Anakinra	3	0	
Leflunomide	0	1	
≥4th-line	10 (7)	1 (1)	0.01
Methotrexate	6	0	
TNF-alfa blockers	2	0	
Tocilizumab	2	1	

Values are expressed as n (%) of patients.
GCs, glucocorticoids; IVIg, intravenous immunoglobulin.

3.3. Case-controls comparisons ($LVV_{50–60}$ versus $LVV_{>60}$)

Compared to $LVV_{>60}$ controls, $LVV_{50–60}$ cases had significantly more frequent peripheral limb ischemia (23 vs 5%, P < 0.0001) and less frequent cephalic symptoms (73 vs 90%, P < 0.0001) (including scalp tenderness, jaw claudication and decreased pulse of temporal artery in respectively 27%, 23%, 10% versus 50%, 43% and 18%) and ocular signs (17 vs 27%, P = 0.03) (Table 1).

Number of imaging tests (i.e. CTA and 18F-FDG-PET/CT) was similar between cases and controls (145 versus 139, respectively; P = 0.53). In $LVV_{50–60}$ cases, CTA and 18F-FDG PET/CT were more frequently abnormal (74 vs 38%, P < 0.0001; and 90 vs 72%, P = 0.01, respectively), and the aorta was more frequently involved (78 vs 47%, P < 0.0001). There was also significantly more frequent aortitis without any cephalic symptoms (28% vs 8%, P < 0.0001). By multivariate analysis, absence of cephalic symptoms, presence of peripheral limb ischemia and aorta involvement, and increased CRP level were significantly associated with $LVV_{50–60}$ presentation compared to $LVV_{>60}$ (Table 3).

Regarding therapeutic management and outcome (Tables 2 and 4), $LVV_{50–60}$, compared to $LVV_{>60}$, received a median number of two lines (range 1–5) of treatment compared to one (range 1–4) (P = 0.006). Indication to second line of treatment was relapse, GCs dependency and GCs resistance in 26%, 21% and 4% of $LVV_{50–60}$, respectively, and 17%, 21% and 2% of $LVV_{>60}$, respectively. Compared to $LVV_{>60}$, $LVV_{50–60}$ required more frequently surgery (10 vs 0%, P < 0.0001) and biological agents (12 vs 3%, P = 0.003). At last follow-up, $LVV_{50–60}$ had a significantly higher median prednisone dose (8.8 vs 6.5 mg/d, P = 0.048) and lower percentage of patients on prednisone < 7.5 mg/d (71 vs 83%, P = 0.01) compared to $LVV_{>60}$.

4. Discussion

To better characterize the spectrum of LVV, especially after 50 years, we analyzed the presentation and outcome of LVV occurring between the ages 50 and 60 years ($LVV_{50–60}$) compared to those occurring after 60 years ($LVV_{>60}$). Using current classification criteria, $LVV_{50–60}$ may be defined as GCA but lying at the interface with TA, while $LVV_{>60}$ characterize the "classic" form of GCA. In the present study, we identified $LVV_{50–60}$ as a subset of patients with more frequent peripheral limb ischemia and aorta involvement, and less frequent cephalic symptoms, than patients with $LVV_{>60}$, i.e. presenting more like TA than classical GCA. Mainly defined on their age at disease onset, as suggested by ACR classification criteria with an age ≤ 40 years for TA and ≥ 50 years for GCA [9,24], distinction between TA and GCA seems however more complicated in daily practice. To illustrate this complexity, TA and GCA may share some clinical, histopathologic and radiographic features, and some authors suggested that TA and GCA could be considered as a continuum into the spectrum of the same disease. Also, classification criteria for TA or GCA may be difficult to apply in many patients diagnosed between 40 and 60 years. In classification criteria for TA proposed by Ishikawa [25], 6% of patients were over 40 years, and in another series of LVV [26], among 28 patients aged between 40 and 55 years at disease onset, patients were classified as having TA in 21 and GCA in 7. Similarly, Polachek [27] reported 18 patients with LVV diagnosed after 50 years presenting with vascular involvement typical of TA, and showed that five of these patients fulfilled ACR criteria for GCA, five fulfilled criteria for TA, three fulfilled criteria for both disease, while five patients did not fulfill criteria for either disease. Thereby, distinguishing TA and GCA based on age distribution may be difficult because of the absence of substantial differences in their distribution of vascular involvement [26–28].

Furthermore, studies showed that patients with large vessels presentation of GCA (LV-GCA), compared to those without, were younger while remaining over 60 years old (median age of 66–68 years compared to 72–75 years) [29–31] and more likely affecting women [29], whereas others did not show any difference in age or gender [32]. De Boysson [29], Muratore [33] and Assie [34] also showed that LV-GCA patients had less frequent cranial and ophthalmologic symptoms but more frequent extra-cephalic vascular signs than patient with cranial GCA. Also, age at diagnosis may be different from age at onset, and some patients may have an age at onset of symptoms < 50 years old and, thus, not be classified as GCA. This shows how misleading an age-based classification is. However, in our study, the time between onset of symptoms and diagnosis was systematically < 1 year. Overall, these conflicting studies suggest that, even if TA and GCA could represent two distinct diseases, cut-offs at age of onset currently used to define the diseases are probably not totally appropriate in all cases, especially between the age of 50 and 60 years where the two diseases could overlap, as illustrated in Fig. 1 [5].

Identifying $LVV_{50–60}$ patients as a peculiar subset of patients raises the question of its relevance in terms of outcome and therapeutic management. In our study, $LVV_{50–60}$ patients exhibited more frequent aorta involvement, reported in 78% of $LVV_{50–60}$ patients compared to 47% of $LVV_{>60}$. Aorta involvement at diagnosis was shown to be a predictive factor of aortic dilatation [29,33], with a risk ranging from 6% to 47% to develop an aortic complication during follow-up ranging from 6% to 47% [29,35–38]. Aortic dilation or aneurism occurred habitually on an aorta segment shown to be inflammatory on previous imaging in 94% of patients [29]. Also, aortic dissection, which is the

Table 3
Factors associated with $LVV_{>60}$ in multivariate analysis.

	OR	CI 95%	P value
Cephalic symptoms	2.28	1.14–4.59	0.02
Polymyalgia rheumatica	1.15	0.66–2	0.6
Peripheral limb ischemia	0.34	0.15–0.79	0.01
Ocular signs	1.25	0.64–2.45	0.52
C-reactive protein level	0.996	0.99–1	0.04
Positive TAB	1.43	0.84–2.43	0.19
Aortitis	0.34	0.19–0.6	0.0002

TAB: temporal artery biopsy; OR: Odds ratio; CI: confidence intervals.

Table 4
Therapeutic management and response to therapy of the 150 patients with LVV diagnosed between 50 and 60 years and the 150 controls with LVV aged over 60 years.

Characteristics	$LVV_{50–60}$ (n = 150)	$LVV_{>60}$ (n = 150)	P value
Number of lines of treatment, median, n	2 (1–5)	1 (1–4)	**0.006**
Patients with ≥2 lines of treatment, n (%)	78 (52)	60 (40)	**0.049**
Vascular surgery, n (%)	15 (10)	0 (0)	**< 0.0001**
Biological agent use, n (%)	18 (12)	4 (3)	**0.003**
At last follow-up			
Prednisone dose < 7.5 mg/d, n (%)	106 (71)	125 (83)	**0.01**
Mean prednisone dose (SD)	8.8 (9.2)	6.5 (4.4)	**0.048**
Median follow-up, (SD), (months)	43.8 (39.9)	36.4 (35.5)	0.051

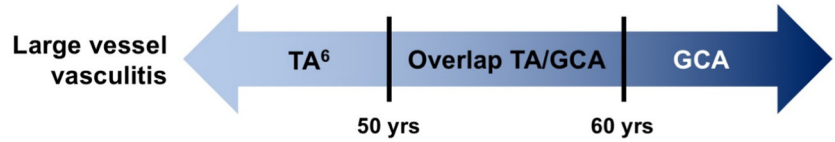
Values are expressed as n (%) of patients or median (range) or standard deviation (SD).
Bold represents significant differences.

most severe clinical condition that involves the aorta, occur in 6 to 24% of patients having an aneurysm [33,39–42]. Finally, even if aortic complications were shown to be maximal within the first 5 years after diagnosis, it continues to occur over time [35,41,43,44]. These findings suggest that $LVV_{50–60}$, exhibiting more frequent aorta involvement, are at higher risk of aortic complications than $LVV_{>60}$, and should particularly require a periodic evaluation to detect such complications. In our study, no patient presented with aortic dissection or rupture, but younger patients required more surgical procedures for the management of stenosis or vascular aneurysms. Unfortunately, we did not have follow-up CTA allowing us to analyze the frequency of occurrence of aneurysms.

Some patients also underwent various concomitant diagnostic investigations, including TAB, CTA, 18F-FDG-PET/CT and/or MRA. Based on the data from our study, in $LVV_{50–60}$, vascular imaging was found to be abnormal in majority of cases whereas diagnostic value of TAB was poor, suggesting that TAB could underestimate LVV in patients between 50 and 60 years. CTA and 18F-FDG PET/CT were concordant in 80% of cases, strengthening the performance of these examinations in this age group. The choice between CTA and 18F-FDG-PET/CT was left to the discretion of the clinician [45,46].

Besides this increased risk of aortic complications, $LVV_{50–60}$ patients were characterized by more frequent refractory disease (i.e more lines of treatment and more GCs at the last follow-up), requiring more immunosuppressive agents, especially methotrexate and/or biological agents. Given the retrospective nature of our study, it remains unclear if the use of immunosuppressive or biological agents was more related to the refractoriness or to the peculiar presentation of these patients at the time of diagnosis. However, refractoriness could itself be related to the younger age of patients or to their peculiar presentation, especially the higher frequency of extra-cranial manifestations. However, only 6% of $LVV_{50–60}$ patients received a combination of GCs and immunosuppressants as first-line, supporting the refractoriness of $LVV_{50–60}$. Muratore et al. have shown that LV-GCA experienced more relapses [33], whereas de Boysson and al. [29,47] did not show any difference in relapse rate but the patients were receiving more GCs-sparing agents. Otherwise, as in our study, more patients without aortitis had discontinued GCs, and median GCs duration of these patients was lower [29] or similar [47] than that of those with aortitis. Overall, our study raises the question of treating more aggressively patients aged between 50 and 60 years of age, using combination of GCs and immunosuppressive agents and/or biological agents, to decrease GCs exposure and possibly the incidence of long-term aortic complications. So far, there is no recommendation supporting the use of TNF-α blockers in GCA [13,48], whereas they showed some efficacy in TA [49]. Considering patients between 50 and 60 years as an overlapping form between TA and GCA, TNF-α blockers could however be discussed in some situations of refractory disease. Nevertheless, tocilizumab, which demonstrated more evidence of its efficacy in both LVV variants [20,21,50], could be preferentially used in these $LVV_{50–60}$ forms, and TNF-α blockers only in case of failure or intolerance of tocilizumab.

Naturally, our study has some limitations, related to its retrospective design that may limit completeness of data, especially during follow-up, the lack of comparable imaging available for all patients at diagnosis, and the absence of centralized reviewing of imaging tests to look for aortitis. Furthermore, $LVV_{>60}$ patients were followed-up 8 months less than $LVV_{50–60}$, but this difference was not significant and could not explain, on its own, the difference between the two groups. A recent French study had shown that patients with large vessel involvement were not treated differently than those with cephalic



Female	83 %	74%	80%
Cranial signs	40%	73%	90%
Ocular signs	22%	17%	27%
Extra-cranial signs	100%	64%	58%
Positive TAB	0%	59%	72%
Aortitis	75%	78%	47%
Refractory disease	68%	52%	40%
MTX or biologics	68%	40%	27%
Vascular surgery	49%	10%	0%

Fig. 1. Description of large vessel vasculitis according to age at onset. Descriptive analysis from TA patients was obtained from data of a French cohort (Arnaud and et al. [5]). Data from the «Overlap TA/GCA» phenotype are from our $LVV_{50–60}$ patients, and those from the «GCA» phenotype are from our $LVV_{>60}$ patients.

involvement [47]. In contrast, we describe here a very large population of LVV diagnosed between 50 and 60 years, and the multicenter study design reflects the wide spectrum of therapeutic management commonly used in France.

In conclusion, primary LVV diagnosed between 50 and 60 years identifies a subset of patients with more frequent aorta and peripheral limb vascular involvement than patients diagnosed after 60 years, and with more refractory disease requiring more frequent use of methotrexate and/or biological agents. Patients with $LVV_{50–60}$ should be probably treated more aggressively in first-line, especially those with large vessels involvements, and be monitored more closely, especially for aortic complications.

Authors contribution

Study conception and design: Delaval, Terrier.

Acquisition of data: Laure Delaval, Aurélie Daumas, Maxime Samson, Mikael Ebbo, Hubert De Boysson, Eric Liozon, Henry Dupuy, Mathieu Puyade, Daniel Blockmans, Ygal Benhamou, Karim Sacré, Alice Berezne, Hervé Devilliers, Grégory Pugnet, François Maurier, Thierry Zénone, Claire de Moreuil, François Lifermann, Laurent Arnaud, Olivier Espitia, Alban Deroux, Vincent Grobost, Estibaliz Lazaro, Christian Agard, Alexandre Balageas, Kevin Bouiller, Cécile-Audrey Durel, Sébastien Humbert, Virginie Rieu, Mélanie Roriz, Odile Souchaud-Debouverie, Stéphane Vinzio, Yann Nguyen, Alexis Régent, Loïc Guillevin, Benjamin Terrier. Analysis and interpretation of data: Delaval, Terrier.

Drafting and writing of the manuscript: Delaval, Terrier.

All authors were involved in revising the manuscript, and all authors approved the final version to be published. Dr. Terrier has full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure statement

All authors have declared no conflicts of interest.

Funding support

None.

Acknowledgements

The authors would like to thank the following authors that included some patients in this study: Audrey Benyamine, Philippe Blanche, Pascal Cohen, Nathalie Costedoat-Chalumeau, Laetitia Coutte, Bertrand Dunogue, Stéphane Gayet, Brigitte Granel, Matthieu Groh, Jean Robert Harlé, Claire Le Jeunne, Jonathan London, Alfred Mahr, Nathalie Morel, Luc Mouthon, Thomas Papo, Romain Paule, Xavier Puéchal, Nicolas Schleinitz, Jean Sibila and Stéphane Vinzio.

References

[1] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. Revised international Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65(1):1–11. Jan 1.

[2] Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Miranda-Filloy JA, Gonzalez-Juanatey C, Martin J, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Care Res 2009 Oct 15;61(10):1454–61.

[3] de Souza AWS, de Carvalho JF. Diagnostic and classification criteria of Takayasu arteritis. J Autoimmun 2014 Feb 1;48–49(Supplement C):79–83.

[4] Gudbrandsson B, Molberg Ø, Garen T, Palm Ø. Prevalence, incidence, and disease characteristics of Takayasu arteritis by ethnic background: data from a large, population-based cohort resident in southern Norway. Arthritis Care Res 2017 Feb;69(2):278–85.

[5] Arnaud L, Haroche J, Limal N, Toledano D, Gambotti L, Chalumeau NC, et al. Takayasu arteritis in France: a single-center retrospective study of 82 cases comparing white, north African, and black patients. Medicine (Baltimore) 2010 Jan 1;89(1):1–17.

[6] Watanabe Y, Miyata T, Tanemoto K. Current clinical features of new patients with Takayasu arteritis observed from cross-country research in Japan: age and sex specificity. Circulation 2015 Nov 3;132(18):1701–9.

[7] Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990 Aug;33(8):1129–34.

[8] Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990 Aug;33(8):1122–8.

[9] Kermani TA, Crowson CS, Muratore F, Schmidt J, Matteson EL, Warrington KJ. Extra-cranial giant cell arteritis and Takayasu arteritis: how similar are they? Semin Arthritis Rheum 2015 Jun;44(6):724–8.

[10] Salvarani C, Macchioni P, Rossi F, Castri C, Capozzoli N, Baricchi R, et al. Epidemiologic and immunogenetic aspects of polymyalgia rheumatica and giant cell arteritis in northern Italy. Arthritis Rheum 1991 Mar 1;34(3):351–6.

[11] Machado EBV, Michet CJ, Ballard DJ, Hunder GG, Beard CM, Chu C-P, et al. Trends in incidence and clinical presentation of temporal arteritis in olmsted county, Minnesota, 1950–1985. Arthritis Rheum 1988 Jun 1;31(6):745–9.

[12] Vanoli M, Daina E, Salvarani C, Sabbadini MG, Rossi C, Bacchiani G, et al. Takayasu's arteritis: a study of 104 Italian patients. Arthritis Care Res 2005 Feb 15;53(1):100–7.

[13] Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Ann Intern Med 2007 May 1;146(9):621–30.

[14] Seror R, Baron G, Hachulla E, Debandt M, Larroche C, Puéchal X, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial. Ann Rheum Dis 2014 Dec;73(12):2074–81.

[15] Martínez-Taboada VM, Rodríguez-Valverde V, Carreño L, López-Longo J, Figueroa M, Belzunegui J, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. Ann Rheum Dis 2008 May;67(5):625–30.

[16] Bonilla-Abadía F, Cañas CA, Echeverri AF. Outcomes of patients with Takayasu arteritis treated with infliximab. J Rheumatol 2013 Nov 1;40(11):1930–1.

[17] Mekinian A, Comarmond C, Resche-Rigon M, Mirault T, Kahn JE, Lambert M, et al. Efficacy of biological-targeted treatments in Takayasu arteritis: multicenter, retrospective study of 49 patients. Circulation. 2015 Nov 3;132(18):1693–700.

[18] Hoffman GS, Merkel PA, Brasington RD, Lenschow DJ, Liang P. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. Arthritis Rheum 2004 Jul;50(7):2296–304.

[19] Gudbrandsson B, Molberg Ø, Palm Ø. TNF inhibitors appear to inhibit disease progression and improve outcome in Takayasu arteritis; an observational, population-based time trend study. Arthritis Res Ther 2017;19 Internet. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5437509/.

[20] Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017;377(4):317–28. 27.

[21] Nakaoka Y, Isobe M, Takei S, Tanaka Y, Ishii T, Yokota S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). Ann Rheum Dis 2018 Mar;77(3):348–54.

[22] Ferfar Y, Mirault T, Desbois AC, Comarmond C, Messas E, Savey L, et al. Biotherapies in large vessel vasculitis. Autoimmun Rev 2016 Jun 1;15(6):544–51.

[23] Quéméneur T, Hachulla E, Lambert M, Perez-Cousin M, Queyrel V, Launay D, et al. Takayasu arteritis. Presse Medicale Paris 2006 May;35(5 Pt 2):847–56.

[24] Koster MJ, Warrington KJ. Classification of large vessel vasculitis: can we separate giant cell arteritis from Takayasu arteritis? Presse Medicale Paris Fr 1983. 2017 Aug;46(7–8 Pt 2):e205–13.

[25] Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's arteriopathy. J Am Coll Cardiol 1988 Oct;12(4):964–72.

[26] Grayson PC, Maksimowicz-McKinnon K, Clark TM, Tomasson G, Cuthbertson D, Carette S, et al. Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. Ann Rheum Dis 2012 Aug;71(8):1329–34.

[27] Polachek A, Pauzner R, Levartovsky D, Rosen G, Nesher G, Breuer G, et al. The fine line between Takayasu arteritis and giant cell arteritis. Clin Rheumatol 2014 Nov 23;34(4):721–7.

[28] Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? Medicine (Baltimore) 2009 Jul;88(4):221–6.

[29] de Boysson H, Daumas A, Vautier M, Parienti J-J, Liozon E, Lambert M, et al. Large-vessel involvement and aortic dilation in giant-cell arteritis. A multicenter study of 549 patients. Autoimmun Rev 2018 Apr;17(4):391–8.

[30] Czihal M, Piller A, Schroettle A, Kuhlencordt P, Bernau C, Schulze-Koops H, et al. Impact of cranial and axillary/subclavian artery involvement by color duplex sonography on response to treatment in giant cell arteritis. J Vasc Surg 2015 May;61(5):1285–91.

[31] Schmidt WA, Moll A, Seifert A, Schicke B, Gromnica-Ihle E, Krause A. Prognosis of large-vessel giant cell arteritis. Rheumatology (Oxford) 2008 Sep;47(9):1406–8.

[32] Prieto-González S, Arguis P, García-Martínez A, Espígol-Frigolé G, Tavera-Bahillo I, Butjosa M, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. Ann Rheum Dis 2012 Jul 1;71(7):1170–6.

[33] Muratore F, Kermani TA, Crowson CS, Green AB, Salvarani C, Matteson EL, et al. Large-vessel giant cell arteritis: a cohort study. Rheumatology (Oxford) 2015 Mar;54(3):463–70.

[34] Assie C, Janvresse A, Plissonnier D, Levesque H, Marie I. Long-term follow-up of upper and lower extremity vasculitis related to giant cell arteritis: a series of 36 patients. Medicine (Baltimore) 2011 Jan;90(1):40–51.

[35] Nuenninghoff DM, Hunder GG, Christianson TJH, McClelland RL, Matteson EL. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum 2003 Dec;48(12):3522–31.
[36] de Boysson H, Lambert M, Liozon E, Boutemy J, Maigné G, Ollivier Y, et al. Giant-cell arteritis without cranial manifestations: working diagnosis of a distinct disease pattern. Medicine (Baltimore) 2016 Jun;95(26):e3818.
[37] Blockmans D, Coudyzer W, Vanderschueren S, Stroobants S, Loeckx D, Heye S, et al. Relationship between fluorodeoxyglucose uptake in the large vessels and late aortic diameter in giant cell arteritis. Rheumatology (Oxford) 2008 Aug;47(8):1179–84.
[38] García-Martínez A, Hernández-Rodríguez J, Arguis P, Paredes P, Segarra M, Lozano E, et al. Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: a cross-sectional screening of fifty-four prospectively followed patients. Arthritis Rheum 2008 Mar 15;59(3):422–30.
[39] Lie JT. Aortic and extracranial large vessel giant cell arteritis: a review of 72 cases with histopathologic documentation. Semin Arthritis Rheum 1995 Jun;24(6):422–31.
[40] Kebed DT, Bois JP, Connolly HM, Scott CG, Bowen JM, Warrington KJ, et al. Spectrum of aortic disease in the Giant cell arteritis population. Am J Cardiol 2018 Feb 15;121(4):501–8.
[41] Kermani TA, Warrington KJ, Crowson CS, Ytterberg SR, Hunder GG, Gabriel SE, et al. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. Ann Rheum Dis 2013 Dec;72(12):1989–94.
[42] Kermani TA, Warrington KJ, Crowson CS, Hunder GG, Ytterberg SR, Gabriel SE, et al. Predictors of dissection in aortic aneurysms from giant cell arteritis. J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis 2016 Jun;22(4):184–7.
[43] García-Martínez A, Arguis P, Prieto-González S, Espígol-Frigolé G, Alba MA, Butjosa M, et al. Prospective long term follow-up of a cohort of patients with giant cell arteritis screened for aortic structural damage (aneurysm or dilatation). Ann Rheum Dis 2014 Oct;73(10):1826–32.
[44] Robson JC, Kiran A, Maskell J, Hutchings A, Arden N, Dasgupta B, et al. The relative risk of aortic aneurysm in patients with giant cell arteritis compared with the general population of the UK. Ann Rheum Dis 2015 Jan;74(1):129–35.
[45] de Boysson H, Dumont A, Liozon E, Lambert M, Boutemy J, Maigné G, et al. Giant-cell arteritis: concordance study between aortic CT angiography and FDG-PET/CT in detection of large-vessel involvement. Eur J Nucl Med Mol Imaging 2017 Dec;44(13):2274–9.
[46] Lariviere D, Benali K, Coustet B, Pasi N, Hyafil F, Klein I, et al. Positron emission tomography and computed tomography angiography for the diagnosis of giant cell arteritis: a real-life prospective study. Medicine (Baltimore) 2016 Jul;95(30):e4146.
[47] de Boysson H, Liozon E, Lambert M, Dumont A, Boutemy J, Maigné G, et al. Giant-cell arteritis: do we treat patients with large-vessel involvement differently? Am J Med 2017 Aug;130(8):992–5.
[48] Samson M, Espígol-Frigolé G, Terrades-García N, Prieto-González S, Corbera-Bellalta M, Alba-Rovira R, et al. Biological treatments in giant cell arteritis & Takayasu arteritis. Eur J Intern Med 2018 Apr;50:12–9.
[49] Molloy ES, Langford CA, Clark TM, Gota CE, Hoffman GS. Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up. Ann Rheum Dis 2008 Nov;67(11):1567–9.
[50] Mekinian A, Resche-Rigon M, Comarmond C, Soriano A, Constans J, Alric L, et al. Efficacy of tocilizumab in Takayasu arteritis: multicenter retrospective study of 46 patients. J Autoimmun 2018;91:55–60.