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New insights into the role of imaging in large vessel vasculitis

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Published in
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-8325-5786-0
DOI 10.3389/978-2-8325-5786-0

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New insights into the role of imaging in large vessel vasculitis

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Citation
Schmidt, W., De Miguel, E., Dejaco, C., Bosch, P., Molina-Collada, J., eds. (2024). *New insights into the role of imaging in large vessel vasculitis*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5786-0

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frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 03 December 2024
DOI 10.3389/fmed.2024.1528452

OPEN ACCESS

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RECEIVED 14 November 2024
ACCEPTED 19 November 2024
PUBLISHED 03 December 2024

CITATION
Molina-Collada J, Bosch P, de Miguel E, Schmidt WA and Dejaco C (2024) Editorial: New insights into the role of imaging in large vessel vasculitis. *Front. Med.* 11:1528452. doi: 10.3389/fmed.2024.1528452

Editorial: New insights into the role of imaging in large vessel vasculitis

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KEYWORDS

imaging, ultrasound, MRI, PET-CT, large vessel vasculitis, giant cell arteritis, polymyalgia rheumatica, Takayasu arteritis

Editorial on the Research Topic
New insights into the role of imaging in large vessel vasculitis

Due to the heterogeneity of clinical manifestations, diagnosing, monitoring, and stratifying risk in large vessel vasculitis (LVV) can be challenging. As a result of technological progress, imaging plays an increasing role in the management of LVV. Ultrasound (US), 18-FDG positron emission tomography/computed tomography (PET/CT), magnetic resonance imaging (MRI), and CT have proven diagnostic value and yielded promising data for the assessment of disease activity in giant cell arteritis (GCA) and Takayasu arteritis (TAK) (1). Since the first description of the use of US in GCA in 1995 (2), numerous studies have confirmed the diagnostic value of imaging for LVV, and the latest 2023 EULAR recommendations (3) reinforce the use of imaging for diagnosis, as well as its potential role in monitoring and assessment of vascular damage. Moreover, imaging was included for the first time in the new 2022 ACR/EULAR classification criteria for GCA (4) and TAK (5). Temporal artery (TA) US carries the same weight as TA biopsy for GCA classification, and evidence of vasculitis by imaging is an absolute requirement for the application of the TAK classification criteria.

However, several unmet needs remain, such us investigating the value of imaging composite scores for diagnosing, monitoring and prognosis of LVV, the prognostic value of positive imaging in patients in clinical remission, and the optimal timing for using imaging to detect vessel wall damage. In addition, as technological advances require constant validation of new imaging applications, this field is continuing to evolve. The articles included in the current Research Topic provide new insights and potential applications of imaging in LVV management.

Recently, interest has grown in using US to quantify vascular inflammation in GCA, and several US scores have been proposed for diagnosis and monitoring (6–10). However, they require extensive validation before they can be applied in research and clinical practice (3). In the current Research Topic, Conticini et al. investigated the diagnostic accuracy of three scores [Southend halo score, halo count, and OMERACT GCA US Score (OGUS)]

in 79 patients with suspected GCA. All three scores showed good sensitivity (>70%) and excellent specificity (97%). In particular, for OGUS, a threshold of 0.81 could be employed for diagnostic purposes, although this score was primarily developed for monitoring.

Schweiger et al. retrospectively investigated the incidence and predictors [including US determined intima-media thickness (IMT)] of glucocorticoid related side effects in 138 patients with GCA. Chronic kidney disease, fractures, cataracts, dementia, and hypertension were the most frequent events. In multivariable analysis, relapses during follow-up predicted diabetes, likely due to increased glucocorticoid use. However, analytical parameters of inflammation and endothelial dysfunction, including pulse-wave velocity and IMT by US were not linked with adverse events of glucocorticoids.

The diagnosis of GCA by US relies on traditional elementary lesions such us the halo sign (inflammatory concentric thickening of the arterial wall). The halo sign is normally determined on a visual basis applying the OMERACT criteria (11). However, there are ongoing efforts to establish cut-offs for the measurement of the arterial wall thickness (IMT) in different territories for diagnostic and monitoring purposes (12–15). Seitz et al. studied cut-off values and the diagnostic accuracy of IMTs of TA segments measured by US in GCA, using for the first time a dual reference standard, namely clinical diagnosis at the patient level and MRI of the head at the segmental level. Optimal US IMT cut-offs (of both walls measured together with complete compression) were 1.01 mm for the common superficial TA, 0.82 mm for the frontal branch and 0.69 mm for the parietal branch, with 79.7% sensitivity and 90.0% specificity for the diagnosis of GCA. The authors demonstrated further in a sub-analysis that sensitivity and specificity of the cut-offs were lower in high cardiovascular risk patients suggesting that cut-offs might need to be adjusted based on the individual cardiovascular risk profile.

Nielsen et al. presented the protocol for the DANIsh VASculitis cohort (DANIVAS), a national multicenter study aiming to prospectively collect clinical data and biobank material from polymyalgia rheumatica (PMR) and GCA patients. Specific objectives include the evaluation of treatment needs in GCA patients with/without LV involvement, in PMR with/without subclinical GCA, and the prognostic role of imaging for aneurysm formation.

In a groundbreaking study, Skoog et al. evaluated the role of superb microvascular imaging (SMI) to visualize neovascularization in TA and assessed its diagnostic performance alongside US in patients with suspected GCA. SMI detected neovascularization in 14 (43%) of 33 GCA patients, and this finding was associated with more widespread cranial disease and a higher halo count. While SMI did not improve sensitivity or specificity of the exam, it might serve in future as a marker to stratify GCA patients for disease severity.

In this Research Topic, two narrative reviews focusing on the role of PET/CT in the management of LVV are also presented. Collada-Carrasco et al. focused on the use of PET/CT in the diagnosis and follow-up of LVV, including a valuable comparison of the most relevant diagnostic PET/CT scales for LVV and PMR. Thibault et al. examined the value of PET/CT in the diagnosis and follow-up of GCA, including all studies on its role in predicting relapses. Moreover, Ni and Kohler reviewed recent advances in LVV imaging, highlighting the combination of imaging modalities, and newer techniques like contrast-enhanced US, shear wave elastography and ocular US.

Another interesting aspect in this Research Topic is the multicenter retrospective study of patients with vasculitis in Poland (POLVAS) presented by Milchert et al. They demonstrated an increase in GCA diagnosis from 2008 to 2019, reaching 8.38 per 100,000 in patients 50 years or older, which can in part be attributed to the introduction of fast-track diagnostic pathways in several centers.

Petzinna et al. reviewed the pathophysiological role of vascular adhesion protein-1 (VAP-1) in vascular inflammation, focusing on GCA and PMR. They highlighted VAP-1′s involvement in immune cell adhesion, migration, and its enzymatic contributions to oxidative stress and tissue damage, as well as recent imaging advances targeting VAP-1, such as [68Ga]Ga-DOTA-Siglec-9 PET/CT, offering new insights into VAP-1′s role in GCA and PMR pathogenesis.

In summary, this Research Topic provides a collection of articles offering new insights into LVV imaging, and we believe it represents a valuable contribution to a constantly evolving field of research.

Author contributions

JM-C: Writing – original draft, Writing – review & editing. PB: Writing – review & editing. EM: Writing – review & editing. WS: Writing – review & editing. CD: Writing – review & editing.

Conflict of interest

JM-C has received consultancy/speaker's fees from AbbVie, Lilly, Janssen, Novartis, Pfizer, UCB, MSD, and BMS; trial participation as principal investigator for Novartis. None of these fees were related to the present manuscript. PB has received speaker and add board fees from Janssen and AbbVie, speaker fees from Lilly and projects grants from Pfizer. EM speakers bureau: AbbVie, Novartis, Pfizer, MSD, BMS, UCB, Roche, Grünenthal, Janssen, and Sanofi; paid instructor for: Janssen, Novartis, and Roche; consultant of: AbbVie, Novartis, Pfizer, and Galapagos; Grant/research support from: AbbVie, Novartis, and Pfizer. WS has received speaker honoraria from AbbVie, Amgen, Bristol Myers Squibb, Chugai, GlaxoSmithKline, Johnson & Johnson, Medac, Novartis, Roche, and UCB; advisory board honoraria from AbbVie, Amgen, Boehringer Ingelheim, Fresenius Kabi, GlaxoSmithKline, Novartis, and Sanofi; trial participation as principal investigator for AbbVie, GlaxoSmithKline, Novartis, and Sanofi. CD has received consulting/speaker's fees from Abbvie, Eli Lilly, Janssen, Novartis, Pfizer, Roche, Galapagos, Sparrow, Boehringer, and Sanofi; grant support from AbbVie and Novartis, all unrelated to this manuscript.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 26 January 2024
DOI 10.3389/fmed.2024.1320076

OPEN ACCESS

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RECEIVED 11 October 2023
ACCEPTED 09 January 2024
PUBLISHED 26 January 2024

CITATION
Conticini E, Falsetti P, Al Khayyat SG, Grazzini S, Baldi C, Bellisai F, Gentileschi S, Bardelli M, Fabiani C, Cantarini L, Dasgupta B and Frediani B (2024) Diagnostic accuracy of OGUS, Southend halo score and halo count in giant cell arteritis.
Front. Med. 11:1320076.
doi: 10.3389/fmed.2024.1320076

Diagnostic accuracy of OGUS, Southend halo score and halo count in giant cell arteritis

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Objectives: Ultrasound has a paramount role in the diagnostic assessment of giant cell arteritis (GCA); Southend halo score (HS), halo count (HC), and OMERACT GCA Ultrasonography Score (OGUS) are the first quantitative scores proposed in this setting. The aim of this study was therefore to assess the diagnostic accuracy of these scores in a real-life scenario, as well as to evaluate their optimal cutoff, also with respect to disease extent, sex, and age.

Methods: We retrospectively collected clinical, serological, and US findings of all patients referred for the first time to our vasculitis clinic in the suspicion of GCA.

Results: A total of 79 patients were included, and a definite diagnosis of GCA was made in 43 patients. For OGUS, the ROC curve showed an optimal cut point of 0.81 (sensitivity 79.07% and specificity 97.22%). For HC and HS, the optimal cutoff values were > 1.5 (sensitivity 76.7% and specificity 97.2%) and > 14.5 (sensitivity 74.4% and specificity 97.2%), respectively. No relevant differences were assessed when patients were stratified according to disease extent, age, and sex. Compression sign (CS) was positive in 34 of 38 patients with cranial GCA and negative in all controls and LV-GCA.

Conclusion: All three scores display good sensitivity and excellent specificity, although the cutoff was slightly different than proposed. In particular, for OGUS, a threshold of 0.81 could be employed for diagnostic purposes, although it was developed solely for monitoring. Due to its high sensitivity and specificity, CS should be always assessed in all patients referred with a suspicion of cranial GCA.

KEYWORDS

ultrasonography, vasculitis, giant cell arteritis, Horton arteritis, diagnosis

Highlights

- Southend halo score (HS) and halo count (HC) have a good diagnostic accuracy, which is not influenced by disease extent, age, and sex.

- Even though the OMERACT GCA Ultrasonography Score (OGUS) was developed for disease monitoring, our study suggests its potential diagnostic role.
- Compression sign (CS) has the highest sensitivity and specificity for cranial GCA: Temporal arteries US should always comprise a dynamic evaluation.

Introduction

Giant cell arteritis (GCA) is a large-vessel vasculitis affecting the aorta and its major branches. Due to the high morbidity arising from irreversible, organ-threatening complications, an early diagnosis and prompt adequate treatment are mandatory. In this regard, in contradistinction to the temporal artery (TA) biopsy advocated in ACR 1990 criteria (1), imaging has a paramount role in the diagnosis and assessment of GCA. An ultrasound (US) of TA and axillary (AxA) arteries, due to its wide availability, rapidity, and lack of ionizing radiation, is most employed for both large vessels (LV) and cranial GCA.

Nevertheless, despite growing evidence supporting its routine use for diagnosis (2) and follow-up (3–6), US has several shortcomings in clinical practice: first the poor training of specialists facing the first symptoms of GCA, including rheumatologists; second, the paucity of studies that include also the LV-GCA phenotype in addition to the more common cranial one (7); third, the lack of validated quantitative scores, which limits its use for clinical trials (8) and multicenter studies.

The first quantitative score reports using the Southend Halo score (HS) (9) found an association with male sex, disease activity, ocular ischemia, and intimal hyperplasia on temporal artery biopsy. Thereafter, the Outcome Measures in Rheumatology (OMERACT) ultrasonography large-vessel vasculitis working group, after defining and testing elementary lesions in GCA (10, 11), has recently developed a novel, provisional score for disease monitoring (12). Both the HS and OMERACT GCA Ultrasonography Score (OGUS) displayed an excellent agreement and proved to be sensitive to changes during follow-up as well as to correlate with markers of inflammation and Birmingham Vasculitis Activity Score (BVAS) in one study (13).

Thus, we aimed to evaluate the quantitative halo scores (9, 12) in a real-life setting in order to assess their diagnostic accuracy and feasibility.

The primary endpoint of the study was a retrospective assessment of the specificity and sensitivity of OGUS, as well as to determine its optimal cutoff values, in a cohort of patients referred to our clinic with suspected GCA.

Secondary endpoints were to retrospectively assess the accuracy of the halo scores with respect to disease extent (LV and cranial) and to compare it with semiquantitative and quantitative scores already employed in our clinical practice.

Materials and methods

Study population

We retrospectively collected clinical, serological, and US findings of all patients referred to Vasculitis Clinic, Rheumatology Unit, University Hospital of Siena, in the suspicion of GCA from January 2020 to January 2023.

Patients could be referred by other clinicians or through our fast-track pathway, in which patients suffering from sudden visual impairment and/or other symptoms of GCA and an increase in erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) were immediately referred to our clinic.

Inclusion criteria were the availability of the following: a minimum core set of blood examinations (14), including hemoglobin (Hb), ESR, and CRP; US findings, including intima–media thickness (IMT), compressibility, and the presence of "halo sign" in AxA and common temporal, parietal, and frontal branches of both TA; a definite clinical diagnosis, which was performed by a single rheumatologist experienced in vasculitis and expressed as follows: cranial GCA, LV-GCA, cranial and LV-GCA, and no GCA.

Exclusion criteria were the unavailability of the abovementioned findings and a previous diagnosis of GCA in remission at the time of the assessment, as well as concomitant or previous treatment with anti-IL6 agents.

Ultrasonography

US examination was carried out by two rheumatologists experienced in US employing an Esaote MyLab X8, equipped with two linear (4–15 and 18–22 MHz) probes, and an Esaote MyLab Twice, equipped with two linear (4–13 and 6–18 MHz) probes. The vessels assessed were AxA and common temporal, parietal, and frontal branches of TA, the latter being evaluated only with high-frequency probes. Color Doppler frequency was set at 9–12.3 MHz and pulse repetition frequency at 2–3 KHz, while gain was adjusted at just below the threshold of artifacts. The burden of vascular inflammation was measured through IMT and scored using halo count (HC), HS (9), and OGUS (12). IMT measurements were manually performed evaluating the thickness from the luminal–intimal interface to the medial–adventitial one, in a longitudinal scan during systole and reported in millimeters (15, 16). The occurrence of low compressibility of any branch of TA was also recorded.

Statistical analysis

A binomial regression analysis was performed to obtain diagnostic cutoffs of different components of OGUS (total, LV, cranial, etc.). Various ROC curves were calculated comparing the halo score components with the diagnosis of GCA as the gold standard.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and its late amendments and approved by the local ethics committee (Rhelabus, protocol number 22271).

Results

A total of 79 subjects were evaluated with suspicion of GCA, and a clinical diagnosis was made in 43 of them (mean age 76.42 years; 24

TABLE 1 Clinical and serological features of GCA patients.

		GCA patients (n = 43)
Sex		24 women, 19 men
Mean age ± SD		76.42 ± 7.44 years
GCA subtype (*N*, %)	Cranial	29, 67%
	Cranial + LV	9, 21%
	LV	5, 12%
CRP (mean ± SD)		7.52 ± 5.74 mg/dL
ESR (mean ± SD)		69.28 ± 38.9 mm/h
Hb (mean ± SD)		11.08 ± 0.92 g/L
Ocular symptoms (*N*, %)		18, 41.9%
Headache (*N*, %)		19, 44.2%
Scalp tenderness (*N*, %)		12, 28%
Jaw claudication (*N*, %)		12, 28%
PMR (*N*, %)		10, 23.2%
B symptoms (*N*, %)		13, 30.2%
Relapsing patients (*N*, %)		8, 18.6%
Disease duration of relapsing patients (mean)		48 months
Treatment at the time of the first assessment (*N*, %)		6, 13.9%
	Prednisone (*N*, %)	6, 13.9%
	Methotrexate (*N*, %)	3, 6.9%
TA biopsy		0
PET (*N*, %)		6, 13.9%
PET uptake		
	Axillary and subclavian arteries	4, 66.6%
	Thoracic aorta	6, 100%
	Abdominal aorta	4, 66.6%
	Iliac arteries	2, 33.3%
US findings		
	IMT (mean values expressed in mm) ± SD	
	Right axillary artery	0.93 ± 0.4
	Left axillary artery	0.88 ± 0.34
	Right temporal artery: common branch	0.43 ± 0.19
	Left temporal artery: common branch	0.43 ± 0.21
	Right temporal artery: parietal branch	0.26 ± 0.19
	Left temporal artery: parietal branch	0.23 ± 0.12
	Right temporal artery: frontal branch	0.26 ± 0.16
	Left temporal artery: frontal branch	0.26 ± 0.16
	HC (mean ± SD)	2.86 ± 1.8
	HS (mean ± SD)	19.9 ± 7.42
	OGUS (mean ± SD)	1.01 ± 0.24
	CS+	34/38 cranial ± LV-GCA

(Continued)

TABLE 1 (Continued)

CRP, C-reactive protein; CS, compression sign; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; Hb, hemoglobin; HC, Halo count; HS, Halo score; LV, large vessels; OGUS, OMERACT GCA US Score; PET, positron emission tomography; PMR, polymyalgia rheumatica; SD, standard deviation; TA, temporal artery; US, ultrasonography.

women): 29 patients suffered from cranial GCA, 9 presented with involvement of both cranial and extracranial arteries, while 5 had only LV-GCA. Clinical and serological features of the patients, including PET findings, are reported in Table 1.

No patient underwent TA biopsy, while PET was requested in 6, in which an involvement of large vessels was suspected: In all of them, imaging displayed a pathological uptake (Meller scale 3) in the territory of the aorta and/or iliac vessels.

The area under the ROC curve (AUROC) for OGUS was 0.980 (95% confidence interval: 0.9534, 1). The ROC curve showed an optimal cut point of 0.81, with a sensitivity of 79.07%, a specificity of 97.22%, and a likelihood ratio (LR) of 28.47. Similar cutoffs were found also when patients were stratified according to disease extent (Table 2), while slightly lower values, although with 100% sensitivity, were reported when our cohort was subdivided for age and sex (Table 3).

For HC, AUROC was 0.979, with a CI of 0.944 to 1 and a $p < 0.0001$. The optimal cutoff value was set at >1.5 with a sensitivity of 76.7% (CI: 62.2–86.8%), a specificity of 97.2% (CI: 85.8–99.8%), and an LR of 27.63. A lower, although high, LR (17) was assessed with a cutoff >0.5 (sensitivity 100%, specificity 94.44%). The same cutoff (>1.5) was found to be the optimal one also for cranial, LV, and LV + cranial GCA, but the latter had the lowest sensitivity (66.6%), while the highest (100%) was found for cranial (Table 4). As for OGUS, these findings were not influenced by sex or age (Table 5). Finally, a positive, statistically significant correlation was found between HC and OGUS (Pearson's r: 0.841, $p < 0.001$).

For HS, a cutoff of >14.5 (AUROC: 0.95, sensitivity: 74.4%, specificity: 97.2, and LR: 26.7) was found for all GCA patients, but a lower sensitivity (65.5%) was found for cranial ones (Table 6). In contrast to HC and OGUS, a different optimal cutoff was evidenced for men, in whom an HS >8.5 was associated with 100% sensitivity and 83.3% specificity (Table 7).

Compression signs were positive in 34 of 38 patients with cranial and cranial + LV-GCA, while all controls and LV-GCA displayed negative CS (89% sensitivity and 100% specificity).

Discussion

The retrospective application of three different US scores to patients with suspected GCA allows for the first time a direct comparison of these methodologies. While some US scores and cutoff values have been proposed, their application is *de facto* restricted to the cohorts in which they were originally applied (9) and few other

TABLE 2 OGUS, stratification for GCA type.

	Cutoff	AUROC	Sensitivity (%) *CI*	Specificity (%) *CI*	LR	*p* value
All GCA	0.81	0.980 *0.95–1%*	79 *64.8–88.6%*	97.2 *85.8–99.8%*	28.47	<0.0001
Cranial	0.82	0.981 *0.95–1%*	79.3 *61.1–90.1%*	97.2 *85.8–99.8%*	28.5	<0.0001
LV	0.81	0.972 *0.92 – 1%*	80 *37.5–98.7%*	97.2 *85.8–99.8%*	28.8	0.0007
Cranial + LV	0.83	0.979 *0.98–1%*	77.7 *45.5–96%*	97.2 *85.8–99.8%*	24	<0.0001

AUROC, area under the ROC curve; CI, confidence interval; GCA, giant cell arteritis; LR, likelihood ratio; LV, large vessels; Sens, sensitivity; Spec, specificity.

TABLE 3 OGUS, stratification for sex and age.

	Cutoff	Sensitivity (%)	Specificity (%)	LR	*p* value
Male	>0.78	89.4	91.6	10.7	<0.0001
Female	>0.72	100	95.8	24	
Age ≥ 76	0.7	100	92.8	14	
Age < 76	0.73	100	92.3	13	

LR, likelihood ratio; Sens, sensitivity; Spec, specificity.

ones (6, 18). At the same time, OGUS, specifically designed for clinical trials and disease monitoring, is a consensus-based algorithm and has not been applied yet in clinical practice, except for assessing its sensitivity to change after treatment (13, 17), which appeared comparable to HS and HC, although only for TA.

In our sample population, comprising 79 subjects referred to in the suspicion of GCA, we evidenced positive US findings in the majority of patients who eventually were diagnosed with vasculitis, thus confirming the crucial role of US in its diagnostic work-up. Such findings were not influenced by age nor differed between first diagnosis and relapse; the only relevant difference was according to sex and disease extent, as the only GCA patient in whom US was negative had an exclusive involvement of the aorta. This is not surprising, because men have greater IMT than women (9), and at the same time, some vascular territories (i.e., aorta and iliac arteries) cannot adequately be detected by US and require different imaging procedures, such as PET, MRI, and CT. On the other hand, no patient with a final diagnosis of cranial GCA had a fully negative US.

When separately analyzing the three scores taken for examination, an overall good diagnostic accuracy was assessed, although with cutoffs slightly different than proposed.

In particular, OGUS had the best diagnostic performance at a threshold of 0.81, instead of 1.01: The latter resulted in an excellent specificity (100%) but a poor sensitivity (39.53%), while our cutoff displayed a slightly lower specificity (94.44%) but a significantly higher sensitivity (79.07%) with an LR of 28.47.

This finding was predictable, as OGUS was designed for clinical trials and research and not for being employed in a clinical setting nor for diagnostic purposes: In this context, a lower specificity, thus potentially leading to overtreatment of a patient with suspected vasculitis, should be preferred to a 100% specificity with a poor sensitivity, which in real life may lead to a hazardous and harmful undertreatment of a GCA.

On the other hand, our data confirm the excellent specificity of OGUS, applied for the first time in a real-life cohort, and strongly support its use in drug research and trials, in which the need to exclude mimickers is prevalent. Moreover, even though OGUS was developed only for disease monitoring, our study seems to suggest its potential diagnostic role.

For HC, our findings did not substantially differ from the cutoffs previously proposed: an HC ≥2 provided a 76.74% sensitivity and 97.22% specificity, with an LR of 27.63, which are values *de facto* comparable to the ones reported by Molina-Collada et al. (18) for an HC > 1 (sensitivity 80%; specificity 95%) and by van der Geest et al. (9) for an HC ≥ 2 in case of TAB positivity (sensitivity 85% and specificity 70%). On the other hand, despite a similar sensitivity (78%), van der Geest et al. (9) reported a much lower specificity (55%), for an optimal cutoff of 1. Curiously, a specificity comparable to ours (95%) was reported only for a cutoff of 6, 3-fold higher than the optimal one calculated in our cohort.

Such discrepancies are not easy to explain but are potentially due to the occurrence of a high HC in two non-GCA patients from the Southend cohort, which differed from ours in terms of F:M ratio (2.86 vs. 1.26).

On the other hand, it is noteworthy that all three cohorts evidenced a similar sensitivity, despite the differences existing among the three populations: the one by van der Geest et al. (9) and ours double the Spanish one (18) and include predominantly GCA patients, while in the latter, the controls are two thirds of the total. Moreover, and more importantly, we included cranial, LV, and cranial plus LV-GCA; the Southend cohort had only subjects with cranial vasculitis (headache was complained in up to 96% of subjects) and focused on the ischemic hazard, while, conversely, only 5 patients from the study by Molina-Collada et al. (18) fulfilled 1990 ACR criteria. Finally, at the time of the US assessment, four patients were relapsing, while both previous studies included only subjects referred for the first time.

That has a paramount importance in clinical terms, which is the ground of this study: Indeed, despite the application of this score in cohorts composed of different patients, comparable only for sex and age, HC presents the same good sensitivity, also for low or very low cutoffs. This confirms the potential application of HC in daily clinical practice, in which the prevention of ischemic complications prevails over the need to minimize the immunosuppressive treatment. In summary, it is not necessary to reach an HC ≥ 6, which can be assessed

TABLE 4 Halo count, stratification for GCA type.

	Cutoff	AUROC	Sensitivity (%) *IC*	Specificity (%) *IC*	LR	*p* value
All GCA	>1.5	0.979 *0.94–1%*	76.6 *62.2–86.8%*	97.2 *85.8–99.8%*	27.63	<0.0001
Cranial	>1.5	0.980 *0.94–1%*	75.8 *57.8–87.7%*	97.2 *85.8–99.8%*	27.3	<0.0001
LV	>1.5	0.972 *0.92 – 1%*	100 *56.5–100%*	97.2 *85.8–99.8%*	36	0.0007
Cranial + LV	>1.5	0.979 *0.94–1%*	66.6 *35.4% – 87 0.9%*	97.2 *85.8–99.8%*	24	<0.0001

TABLE 5 Halo count, stratification for sex and age.

	Cutoff	Sensitivity (%)	Specificity (%)	LR	*p* value
Male	≥1	100	91	12	<0.0001
Female	≥1	100	95	24	<0.0001
Age ≥ 76	≥1	100	100		
Age < 76	≥1	100	92	13	

only in a minority of patients, to reasonably start glucocorticoids in a patient with suspected GCA.

More relevant discrepancies were conversely evidenced for HS: Lower values resulted in very poor specificity, particularly when compared with the cohort by Molina-Collada et al. (18), who reported a sensitivity and specificity of 86.7 and 95.3%, respectively, for HS ≥ 2.

Conversely, our results found an optimal cutoff of 15, displaying an excellent specificity (97.22%) and a good sensitivity (74.22%), far higher than the one (21%) reported by van der Geest et al. (9) for an HC ≥ 10.

Such a difference is not easy to explain but can be presumably determined by the inclusion of relapsing patients in our cohort, therefore presenting a higher IMT of AxA, and by the higher numbers of LV-GCA. A lower HS can be considered prudentially.

However, regardless of the difference existing for the optimal cutoff, which may also be due to the heterogeneity of the patients included in the studies, both HC and HS, as well as OGUS, proved to be reliable US scores, with comparable sensitivity and specificity, suggesting that they can be variously and alternatively employed for the diagnosis of GCA and its relapses (6).

Nevertheless, some difference was assessed when our patients were distinguished according to sex: for OGUS, men displayed poorer specificity and sensitivity, even with an optimal cutoff higher than women.

Conversely, statistical analysis evidenced a lower cutoff value for HS in men, which nevertheless led to a poorer LR and a statistically significant lower specificity.

Those findings presumably mean that in men with suspected GCA, OGUS and HS are by far less specific (and OGUS less sensitive, too) than in women, presumably due to a physiological increase of IMT in men.

On the opposite, no difference was assessed for HC, whose cutoff remained the same, with identical specificity, sensitivity, and LR, in men and women: Regardless of sex and age, an HC ≥1 is strongly associated with a diagnosis of GCA.

When patients were stratified for age, no difference was evidenced for any of the scores: This, at least for HS, is in contradiction with previous findings, displaying a higher IMT in older patients, but can be explained by the reduced age range of our cohort, as well as by the high diagnostic accuracy of US, regardless of age.

When patients were stratified according to disease extent, no relevant differences were assessed for optimal cutoff, which remained the same for HC and HS. At the same time, specificity did not vary for any of the three scores, ranging from 94 to 97%; conversely, at our cutoffs, sensitivity appeared lower for HC and, particularly, HS (65%) in patients affected by cranial GCA.

In this specific subset of patients, the application of compressibility sign resulted, in our cohort, in higher sensitivity (89%) and a 100% specificity. Such findings are substantially in line with previous studies (19–21), which nevertheless did not distinguish between cranial and LV-GCA. Our findings remark that a dynamic US evaluation, comprising compression sign, is mandatory for achieving a higher sensitivity: Reduced compressibility of any segment of TA markedly increases the diagnostic value of US and should be routinely employed in a patient with suspected GCA. Further scores should therefore include compression sign and add it to the assessment of IMT and halo, thus resulting in a semiquantitative score comprehensive in all these three aspects.

Our study has some limitations: First, the relatively low numbers do not allow any definite conclusions. Second, the number of "pure" LV-GCA, is low in comparison with cranial and cranial and LV combination, thus potentially leading to an incorrect assessment of specificity and sensitivity in this subset of patients. Third, we did not evaluate subclavian (22, 23) nor vertebral arteries, which in our clinical practice are assessed only in patients with suspected Takayasu arteritis. Fourth, we employed two different US machines, although from the same factory and with comparable features. Fifth, we did not assess the echo-texture of the vessels: We suspect that in the case of subjects referred for disease relapse or with long-term disease, a chronic thickening of IMT can be misleadingly interpreted as inflammatory, instead of a fibrotic, reparatory process; hence, the inclusion of relapsing patients may be a confounder. Nevertheless, in the context of a real-life study, we could not exclude such an important subtype of patients referred to our centers.

In conclusion, all proposed scores appear feasible and reliable not only for studies or clinical trials but also in clinical practice. The high specificity assessed in all of them confirms the excellent diagnostic value of US in suspected GCA, in a clinical setting like ours which does not employ TA biopsy nor routinely requests radiological imaging procedures, such as MRI or PET, as first-line test for GCA. Despite the lack of direct comparison among OGUS, HS, and HC, the latter could be potentially preferred, as it is not influenced by age or sex.

TABLE 6 Halo score, stratification for GCA type.

	Cutoff	AUROC	Sensitivity (%) *IC*	Specificity (%) *IC*	LR	*p* value
All GCA	>14.5	0.950 *0.89–1%*	74.4 *59.7–85%*	97.2 *85.8–99.8%*	26.7	<0.0001
Cranial	>14.5	0.931 *0.82–1%*	65.5 *45.3–80%*	97.2 *85.8–99.8%*	23.5	<0.0001
Cranial + LV	15	0.986 *0.95–1%*	88.8 *56.5–99.4%*	97.2 *85.8–99.8%*	32	<0.0001

TABLE 7 Halo score, stratification for sex and age.

	Cutoff	Sensitivity (%)	Specificity (%)	LR	*p* value
Male	>8.5	100	83.3	6	<0.0001
Female	>14.5	70.8	95.8	17	<0.0001
Age ≥ 76	>9	95.2	92.3	13	
Age < 76	>9.5	85	92.3	11.1	

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Comitato Etico Area Vasta Sudest Toscana. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

EC: Conceptualization, Data curation, Methodology, Supervision, Writing – original draft. PF: Conceptualization, Data curation, Methodology, Supervision, Writing – original draft. SA: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. SiG: Conceptualization, Data curation, Investigation, Writing – review & editing. CB: Investigation, Supervision, Writing – review & editing. FB: Investigation, Validation, Writing – review & editing. StG: Investigation, Supervision, Writing – review & editing. MB: Investigation, Supervision, Writing – review & editing. CF: Supervision, Writing – review & editing. LC: Supervision, Validation, Writing – review & editing. BD: Supervision, Validation, Writing – original draft. BF: Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The authors declare that this study received funding from AbbVie (protocol number 0068880). The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 09 April 2024
DOI 10.3389/fmed.2024.1389655

OPEN ACCESS

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RECEIVED 21 February 2024
ACCEPTED 25 March 2024
PUBLISHED 09 April 2024

CITATION
Seitz P, Lötscher F, Bucher S, Bütikofer L, Maurer B, Hakim A and Seitz L (2024) Ultrasound intima-media thickness cut-off values for the diagnosis of giant cell arteritis using a dual clinical and MRI reference standard and cardiovascular risk stratification. *Front. Med.* 11:1389655. doi: 10.3389/fmed.2024.1389655

Ultrasound intima-media thickness cut-off values for the diagnosis of giant cell arteritis using a dual clinical and MRI reference standard and cardiovascular risk stratification

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Objectives: To derive segmental cut-off values and measures of diagnostic accuracy for the intima-media thickness of compressed temporal artery segments for the diagnosis of giant cell arteritis (GCA) on the patient level. To examine the influence of cardiovascular risk.

Methods: Retrospectively, patients evaluated for GCA with an ultrasound of the temporal arteries and an MRI of the head, including a T1-fatsat-black blood (T1-BB) sequence, were identified and classified based on cardiovascular risk and a dual reference standard of T1-BB on the segmental level and the clinical diagnosis on the patient level. Intima-media thickness of the common superficial temporal artery (CSTA), frontal and parietal branches (FB, PB) were measured by compression technique. Statistically and clinically optimal (specificity of approx. 90% for the patient level) cut-offs were derived. Diagnostic accuracy was evaluated on the patient level.

Results: The population consisted of 144 patients, 74 (51.4%) with and 70 (48.6%) without GCA. The *statistically optimal* cut-offs were 0.86 mm, 0.68 mm and 0.67 mm for the CSTA, the FB and PB, respectively. On the patient level sensitivity and specificity were 86.5 and 81.4%. *Clinically optimal* cut-offs were 1.01 mm, 0.82 mm and 0.69 mm and showed a sensitivity of 79.7% and a specificity of 90.0%. For patients *without* high cardiovascular risk, statistically optimal cut-offs showed a sensitivity of 89.6% and a specificity of 90.5%.

Conclusion: Newly derived ultrasound intima-media thickness cut-offs with a dual reference standard show high diagnostic accuracy on the patient level for the diagnosis of GCA, particularly in patients without high cardiovascular risk.

KEYWORDS

giant cell arteritis, vasculitis, ultrasound, cut-off, intima-media thickness, cardiovascular risk, T1-fatsat-black-blood, vessel wall MRI

Introduction

Giant cell arteritis (GCA) often affects the temporal arteries (TAs) and other superficial cranial arteries (SCAs) (1, 2). Timely confirmation of the diagnosis by either imaging and/or biopsy is recommended, with imaging now playing the main role in many centers (3–6). An ultrasound of the SCAs and axillary arteries is the recommended initial imaging test according to the European Alliance of Associations for Rheumatology (EULAR) recommendations in patients with suspected GCA, which includes patients with polymyalgia rheumatica and possible vasculitis (6–8). For magnetic resonance imaging (MRI) of the SCAs, the EULAR recommendations suggest a post-contrast, high-resolution, fat-suppressed T1-weighted, black-blood sequence (T1-BB) on a 3-Tesla scanner, which has a higher diagnostic accuracy for GCA compared to other MRI sequences (6, 9, 10).

Until recently, the presence of a halo or a compression sign was used exclusively to diagnose GCA with ultrasound (6, 11). Although these qualitative signs harbor good diagnostic accuracies, in recent years the measurement of the intima-media thickness (IMT) has gained momentum for the diagnostic evaluation in suspected GCA. The halo and compression signs were defined consensus-based on data using mainly 15 to 18 MHz probes (11, 12). With modern 20 to 24 MHz probes, precise measurements of IMTs are now possible (13–15). The use of diagnostic IMT cut-offs has not yet been adopted widely and is not yet part of the 2023 EULAR recommendations for large vessel vasculitis imaging. Nevertheless, IMT measurements are the basis of the provisional OMERACT ultrasonography score for follow-up in GCA (16).

On the *level of the patient*, GCA can either be present or not. It does not matter whether only a single arterial segment or several arteries are affected. On the *level of the arterial segment,* each segment can possibly be diseased or not. Previous studies about diagnostic IMT cut-offs for the TAs in suspected GCA have used different patient populations and measurement methods (15, 17–19). In these studies, the cut-off values for each segment were derived with the clinical diagnosis of GCA as the diagnostic reference standard on the patient level. Since false positive findings from each individual segment will be added together, a lower specificity is to be expected on the patient level than if each segment is separately evaluated against the diagnostic reference. The situation is different with cranial T1-BB MRI, where the scoring method and the resulting diagnostic accuracy is based on the examination of all available segments together without individual segmental cut-offs (20–22). Ideally, a diagnostic reference should be available for each of the assessed arterial segments. A study with biopsies of each segment is not ethically feasible and would likely yield lower quality data because of the skippy manifestations of GCA. However, by using a double reference standard with the clinical diagnosis on the *patient level* and T1-BB grading on the *segmental level*, this becomes possible.

Using this approach, IMTs for SCAs can be assessed at the *segmental level* using segment-specific cut-off values, with diagnostic accuracy assessment at the *patient level*. Accordingly, at least one segment with an IMT above the segment-specific cut-off is sufficient for a GCA diagnosis. To make ultrasound and MRI examinations comparable, similar lengths of the arteries need to be examined. Most prior ultrasound studies performed IMT measurements only at one specific point or quite focally (15, 17–19). The IMTs were measured either without compression on a single arterial wall or including both walls in a compressed artery, which is the method requiring less time (15, 17–19). Since the examination of a large proportion of the total length of a SCAs is very time-consuming, measuring the IMT in a compressed artery seems more suitable (17).

In daily practice ultrasound is mostly used for ruling *in* the diagnosis of GCA (6). Ruling *out* GCA with an ultrasound of the TAs is not advisable in many cases due to multiple other vessels being possibly affected, e.g., the aorta. Quite often a combination of tests (multiple imaging modalities and/or SCA biopsy) are necessary to rule out GCA, depending on pre-test probability (6, 23). We therefore hypothesized that, from a clinical point of view, cut-off values with high specificity should be aimed for, while from a purely statistical point of view, sensitivity and specificity are usually maximized together for the derivation of optimal cut-off values (24).

Prior studies have shown higher IMT levels in patients with atherosclerosis, with at least one TA segment above published cut-off values in approximately 10–20% of patients at high to very-high cardiovascular risk (CVR) (according to the European Society of Cardiology (ESC) 2021 classification) (25–28). Higher halo scores have also been described in non-GCA patients with high to very-high CVR (28, 29). CVR is therefore expected to influence the diagnostic performance of IMT cut-off values, which is particularly relevant because high CVR is very prevalent in the age group of patients with GCA (28, 30).

The main objective of this study was to derive new segmental cut-off values for the IMT of compressed temporal artery segments [common superficial temporal artery (CSTA), frontal and parietal branches (FB, PB)] with a dual reference standard of T1-BB results on the segment level and the clinical GCA diagnosis on the patient level. These are evaluated together as one examination on the patient level – comparable to an MRI examination – with a sub analysis on the influence of CVR.

Materials and methods

This is a retrospective, monocentric study, conducted in accordance with the Declaration of Helsinki located at the University Hospital Bern, Switzerland, a tertiary referral center for vasculitis. All patients provided written informed consent for their data to be analyzed. The study was approved by the Ethics Committee Bern, Switzerland, in 2021 (2021–02169). The manuscript fulfills the "Standards for Reporting of Diagnostic Accuracy Studies" (STARD) guidelines (31).

Study population

Inclusion criteria: ≥ 50 years of age; evaluation for suspected GCA between January 1st 2018 and December 31st 2021; available results of an MRI scan of the head *and* an ultrasound of the SCAs. Exclusion criteria: no informed consent available; severe imaging artifacts; diagnosis of non-GCA vasculitis; missing T1-BB MRI sequence (vessel wall MRI); interval between MRI and ultrasound >7 days. Patients with no documented general consent were specifically contacted by phone and mail and only included if they signed a study-specific consent. The clinical diagnosis ≥6 months after the initial

evaluation was used as the diagnostic reference standard on the patient level. It was determined independently by two consultant rheumatologists (L.S., P.S. or F.L.) based on all available electronic medical records (classification as GCA or non-GCA was identical for both experts). Clinical data and ultrasound results were extracted from the electronic patient records and transferred to a coded REDCap database. If certain IMT measurements were missing or unclear on the written report, the archived ultrasound images were double checked to see if these IMT measurements were available or truly missing.

Patients were classified according to CVR. The exact classification into different CVR categories according to ESC 2021 is quite demanding (32). Calculating reliable SCORE2 or SCORE2-OP scores during an assessment in a GCA fast-track clinic is unrealistic, as reliable values on proteinuria, blood lipids and systolic blood pressure must be available, which are very difficult to obtain during an emergency examination in patients who are frequently in pain and under stress (32). Therefore, a pragmatic approach was chosen for the classification into two different groups, which is feasible in the context of a fast-track outpatient assessment. Patients with established atherosclerotic disease (according to available medical records), diabetes mellitus (unless it was of <10 years duration and without known end organ damage or additional known cardiovascular risk factors), moderate to severe chronic renal insufficiency or known familial hypercholesterolemia were classified directly into the high to very-high CVR category according to the ESC 2021 guidelines (32). For all other "apparently healthy" patients (regarding cardiovascular diseases), CVR estimation using ESC-scores would be necessary for classification. This was the second patient group: patients who were not directly allocated to the high/very high CVR group according to ESC 2021 guidelines (32).

Ultrasound examination technique and scoring

Two different ultrasound machines were used; Logiq E9 from GE (18 MHz transducer) and Canon Aplio i800 (22 MHz transducer) for 27.8 and 72.2% of patients, respectively. Ultrasound examinations were performed by two vasculitis experts (L.S. for 104 patients; F.L. for 40 patients). L.S. and F.L. have performed >1,000 and > 500 vascular ultrasound examinations. The TAs were examined in a supine position, starting in the pretragal region where the TA rises from deep to the parotid gland to approximately the level of the central frontal hair line, for both the PBs and FBs, including sections covered with scalp hair. Ultrasound settings were at the discretion of the examining physician with an aim at maximal resolution and precision for the measurements. Due to artifacts from scalp hair, the B-Mode frequency sometimes had to be lowered to 19 or 20 MHz for the 22 MHz Canon transducer. Doppler was only used for faster identification of the arteries, IMT measurements were exclusively performed in B-Mode images. The bilateral CSTAs, FBs and PBs of the TA were examined in each patient. The segments were completely compressed, i.e., no pulsations and no flow detectable, on transverse view with multiple measurements taken along the length of the examined segment. In a frozen image, the cursor was positioned at both interfaces between the echogenic adventitia and the echo poor combined intima-media as defined by OMERACT; i.e. both single-sided intima-media complexes are combined by the compression and then measured together (16). Clearly atherosclerotic lesions were excluded from measurements, which comprised particularly sites with obvious calcifications. The thickest combined IMT per segment was recorded for each individual segment, i.e., the IMT of both walls were measured together. No additional single sided IMT measurements were carried out in the longitudinal axis, as this would have been too time-consuming due to the length of the examined segments and the number of measurements.

MRI acquisition, image evaluation, and rating of arteries

All images were acquired on 3-Tesla scanners (Skyra, Prisma and Vida from Siemens Healthineers, Erlangen, Germany) with 20-or 64-channel phased-array head and neck coils. The post-contrast T1-BB sequence was performed as recommended by EULAR and covered the volume from the hard palate to the vertex (6, 33). The sequence parameters were: 30 slices with slice thickness of 3 mm, TR of 500 ms, TE of 22 ms, acquisition matrix of 1′024 × 768, field of view of 200 × 200 mm, axial resolution 0.195 × 0.260 mm (6, 21). The time-of-flight MR-angiography (TOF-MRA) had a slice thickness of 0.5 mm. Readers were blinded to the reference diagnosis and all clinical information apart from age and sex. The coded MRI scans were scored by L.S. (134 scans) and P.S. (10 scans), both senior rheumatologists and vasculitis imaging experts with 13 and 12 years of work experience. The CSTAs, FBs, and PBs were identified bilaterally with the crosshair on corresponding TOF-MRA images, excluding the possibility of accidental identification of a vein (9). Each arterial segment was rated on T1-BB images according to the rating-scheme by Bley et al. (semiquantitative scoring 0 to 3; scores 2 and 3 considered to represent vasculitis) (21). This was used as the diagnostic reference standard on the segmental level.

Statistics

Statistical analysis was performed using Stata (version 18.0), figures were made with R (version 4.3.1). Patient characteristics are reported as median with interquartile range (IQR) or as absolute and relative frequencies for continuous and categorical variables, respectively. Comparison for continuous and categorical variables was made using the Mann–Whitney-Wilcoxon and Fisher's exact tests, respectively. Absolute and relative frequencies with Wilson 95%-confidence interval (CI) were used to report the proportion of correct classifications, sensitivity, and specificity. Likelihood ratios are reported with Katz 95%-CIs. *Statistically* optimal cut-offs for the segmental level were determined using the method by Youden (24). The area under the curve (AUC) of the receiver-operating-characteristic (ROC) is reported with asymptotic DeLong 95%-CIs. For the determination of the *statistically optimal* segmental cut-offs, only the data of the following segments were used: as normal segments, all segments of patients without a reference diagnosis of GCA; for pathological segments, only segments from patients with a clinical reference diagnosis of GCA *and* a pathological T1-BB score of 2 or 3. For the determination of the *clinically optimal* segmental cut-offs, the following procedure was chosen: For each of the three segments (CSTA, FB, PB) separately, cut-off values were determined

for each 1%-step between a minimum specificity of 85% and a specificity of 100% on the segmental level (for example: the cut-offs giving a minimum specificity of 95% for the CSTA on the segmental level and the cut-offs giving a minimum specificity of 95% for the FB and PB on the segmental level.) Every one of these 16 sets of three cut-offs (one combination for each 1% step of minimum specificity on the segmental level) were then evaluated on the patient level against the reference diagnosis according to the following rule: If at least one segment with an IMT above the cut-off was present, the patient was considered to have GCA. The *clinically optimal* set of three cut-off values was then selected according to the prespecified specificity of approximately 90% at the patient level. The level of 90% specificity was chosen due to the need of a test with high specificity in clinical practice. The same combined evaluation on the patient level was also done for the *statistically optimal* cut-offs.

Results

From a total of 223 retrospectively identified consecutive patients, 79 patients were excluded from the analysis (Supplementary Figure S1 shows the patient flow chart). The final total patient population included 144 patients, 74 (51.4%) with GCA and 70 (48.6%) with other diagnoses (Supplementary Table S1), of which 23 (32.9%) had polymyalgia rheumatica. The patients with polymyalgia rheumatica all received at least one additional imaging test to screen for possible large vessel vasculitis (22 (95.7%) received an ultrasound of the arm arteries, 13 (56.5%) an ultrasound of the neck arteries, 19 (82.6%) an MRI of the thorax and abdomen and 4 (17.4%) an FDG-PET-CT). None of the 23 included PMR patients had accompanying large vessel vasculitis. Median age was 71 years, and 85 (59.0%) patients were female. Upon clinical presentation, 117 (81.2%) patients had cranial manifestations and 27 (18.8%) patients had only non-cranial signs or symptoms. Patients with GCA were significantly more likely to experience jaw claudication (40.5 vs. 10.0%, $p < 0.01$), new onset headache (75.7 vs. 55.7%, $p = 0.014$) and had higher CRP-levels (mean 82 vs. 54 mg/L, $p = 0.020$). Median time between symptom onset and imaging was 39 days (IQR 15–79 days) for ultrasound and 38 days (IQR 16–78) for MRI. Median duration of therapy with glucocorticoids before imaging was 0 days. For the total population, the median daily prednisolone-equivalent glucocorticoid dose was 0 mg (IQR 0–15 mg) at the time point of US. For the 51/144 (35.4%) patients with glucocorticoid therapy at the time point of US, the median daily prednisolone-equivalent glucocorticoid dose was 45 mg (IQR 14–82 mg). From 144 patients, 43 (29.9%) had documented established atherosclerotic disease. A total of 54 (37.5%) patients belonged to the high/very-high CVR group. There were no significant differences in cardiovascular risk factors and rate of established atherosclerotic disease between GCA and non-GCA cases. Of the 79 (54.9%) patients with a TA biopsy, 42 (53.2%) had vasculitis, defined by the presence of an inflammatory wall infiltrate on histopathology. Table 1 shows the patients' characteristics for the total population.

TABLE 1 Patients' characteristics.

Characteristic[a]	Total ($N = 144$)	No GCA[g] ($N = 70$)	GCA ($N = 74$)	p-value
Age (years)[b]	71 (65–76)	69 (62–76)	72 (67–76)	0.07
Female patients	85 (59.0%)	37 (52.9%)	48 (64.9%)	0.18
2022 – ACR/EULAR criteria fulfilled	72 (50.0%)	n.a.[d]	72 (97.3%)	n.a.
New-onset headache	95 (66.0%)	39 (55.7%)	56 (75.7%)	0.014
Scalp tenderness	45 (31.3%)	19 (27.1%)	26 (35.1%)	0.37
Jaw claudication	37 (25.7%)	7 (10.0%)	30 (40.5%)	<0.001
Vision loss[c]	25 (17.4%)	13 (18.6%)	12 (16.2%)	0.11
PMR symptoms	80 (55.6%)	43 (61.4%)	37 (50.0%)	0.18
CRP (mg/L)[b]	64 (22–126)	54 (5–120)	82 (39–130)	0.020
GC therapy at ultrasound	51 (35.4%)	29 (41.4%)	22 (29.7%)	0.17
Duration GC before ultrasound (days)[b]	0 (0–2)	0 (0–3)	0 (0–1)	0.08
GC therapy at MRI	48 (33.3%)	24 (34.3%)	24 (32.4%)	0.86
Duration GC before MRI (days)[b]	0 (0–3)	0 (0–20)	0 (0–1)	0.027
Established atherosclerotic disease[e]	43 (29.9%)	23 (32.9%)	20 (27.0%)	0.47
Diabetes mellitus	12 (8.3%)	6 (8.6%)	6 (8.1%)	1.00
CKD ≥ Grade 3[f]	9 (6.2%)	6 (8.6%)	3 (4.1%)	0.32
Arterial hypertension	73 (50.7%)	36 (51.4%)	37 (50.0%)	0.87
Hypercholesterolemia	37 (25.7%)	21 (30.0%)	16 (21.6%)	0.26

[a]n (%) unless stated otherwise.
[b]median (inter quartile range).
[c]persistent vision loss (complete or incomplete, unilateral or bilateral).
[d]classification criteria are not met if vasculitis is not present.
[e]clinically manifest disease.
[f]chronic kidney disease with KDIGO grading 3 to 5.
[g]see Supplementary Table S1 for listing of diagnosis.
CKD, chronic kidney disease; CRP, C-reactive protein; GC, glucocorticoids; MRI, magnetic resonance imaging; n.a., not applicable; PMR, polymyalgia rheumatica.

Segment level

Eleven patients with GCA but normal T1-BB-MRI dropped out of the analysis for the derivation of optimal cut-offs. Six of these eleven patients had other pathological test results for vasculitis of the SCA (ultrasound or biopsy); five patients had only extracranial large vessel vasculitis upon imaging. For the total study population, the median IMTs for CSTAs, FBs and PBs were larger for patients with GCA versus without GCA (0.98 mm versus 0.60 mm, 0.91 mm versus 0.48 mm and 0.70 mm versus 0.41 mm, respectively). There were no relevant differences for the IMT between those with and those without cranial symptoms (median IMT for patients with GCA and cranial symptoms: CSTA 1.0 mm, FB 0.99 mm, PB 0.71 mm; no formal testing performed) (Table 2). The *statistically optimal* cut-off for the CSTA was 0.86 mm, with a sensitivity of 86.2% and a specificity of 93.1%; for the FB 0.68 mm, with a sensitivity of 93.3% and a specificity of 88.3%; for the PB 0.67 mm with a sensitivity of 76.2% and a specificity of 95.3%. For all segments together, the *statistically optimal* cut-off was 0.68 mm with a sensitivity of 86.4% and a specificity of 85.3% (Table 3 and Figure 1).

Figure 2 illustrates the trade-off between sensitivity and specificity depending on the cut-off chosen for each segment and Supplementary Table S2 tabulates these measures of diagnostic accuracy for each 0.1 mm step in the cut-off for each segment and for all segments combined. It can be appreciated that a 0.1 mm step can lead to quite large differences. Table 4 shows the segment-specific cut-offs in millimeters to reach specificities between 85 and 100%: 100% specificity is reached at 1.05 mm, 1.04 mm and 0.88 mm for the CSTA, the FB and the PB, respectively. Supplementary Figure S2 shows positive and negative likelihood ratios depending on the cut-off chosen for each segment. It shows very pronounced likelihood ratios already close to the cut-offs but also the increasing confidence intervals with more extreme cut-offs due to progressively smaller numbers of patients.

Patient level

Measures of diagnostic accuracy for the patient level, are shown in Table 5 (a more comprehensive version including source data is included in the supplementary material as Supplementary Table S3). The *statistically optimal* segmental cut-offs, derived from the analysis of individual segments against the clinical reference diagnosis, showed a sensitivity of 86.5% and a specificity of 81.4% for the total study population and a sensitivity of 92.1% and a specificity of 87.0% for the group with cranial manifestations. As

TABLE 2 Intima-media-thickness measurements by ultrasound on segmental level.

Segment	Total ($N = 288$)[a]	No GCA ($N = 140$)[a]	GCA ($N = 148$)[a]	*p*-value
CSTA				
N[b]	212	107	105	
Median (IQR)	0.70 (0.55, 1.00)	0.60 (0.50, 0.71)	0.98 (0.70, 1.30)	<0.001
Mean (sd)	0.81 (0.36)	0.61 (0.17)	1.0 (0.39)	
TA frontal branch				
N[b]	281	138	143	
Median (IQR)	0.60 (0.45, 0.93)	0.48 (0.40, 0.58)	0.91 (0.66, 1.10)	<0.001
Mean (sd)	0.72 (0.36)	0.50 (0.15)	0.93 (0.37)	
TA parietal branch				
N[b]	272	130	142	
Median (IQR)	0.51 (0.40, 0.71)	0.41 (0.35, 0.53)	0.70 (0.49, 0.92)	<0.001
Mean (sd)	0.60 (0.31)	0.44 (0.13)	0.74 (0.35)	

Values for the intima-media thickness are in millimeters, using the compressed lumen technique (combining both walls).
[a]each patient can have two segments, i.e., the total N is twice the number of patients.
[b]number of non-missing observations for this segment.
CSTA, common superficial temporal artery; GCA, giant cell arteritis; IQR, interquartile range; sd, standard deviation; TA, temporal artery.

TABLE 3 Statistically optimal segment-specific cut-offs.

	Number of patients/ segments	Cut-off (mm)	AUC (95% CI)	Sensitivity	Specificity	Positive LR	Negative LR	Correctly classified
CSTA	101/159	0.86	0.92 (0.86–0.97)	86.2% (75.1–92.8%)	93.1% (86.4–96.6%)	12.44 (6.04–25.61)	0.15 (0.08–0.28)	90.6% (85.0–94.2%)
TA frontal branch	129/241	0.68	0.96 (0.94–0.98)	93.3% (86.8–96.7%)	88.3% (81.9–92.7%)	7.99 (5.02–12.69)	0.08 (0.04–0.16)	90.5% (86.1–93.6%)
TA parietal branch	117/209	0.67	0.90 (0.85–0.95)	76.2% (65.9–84.2%)	95.3% (90.2–97.9%)	16.39 (7.43–36.15)	0.25 (0.17–0.37)	88.0% (82.9–91.8%)
Overall[a]	133[b]/609	0.68	0.92 (0.89–0.94)	86.4% (81.5–90.1%)	85.3% (81.3–88.5%)	5.87 (4.57–7.55)	0.16 (0.12–0.22)	85.7% (82.7–88.3%)

Cut-offs for the compressed lumen technique (combining both walls), calculated using method by Youden.
[a]all segments combined.
[b]11 Patients with giant cell arteritis had a normal T1-BB-MRI for all segments and were not included in this analysis.
AUC; area under the curve; CSTA, common superficial temporal artery; LR, likelihood ratio; TA, temporal artery.

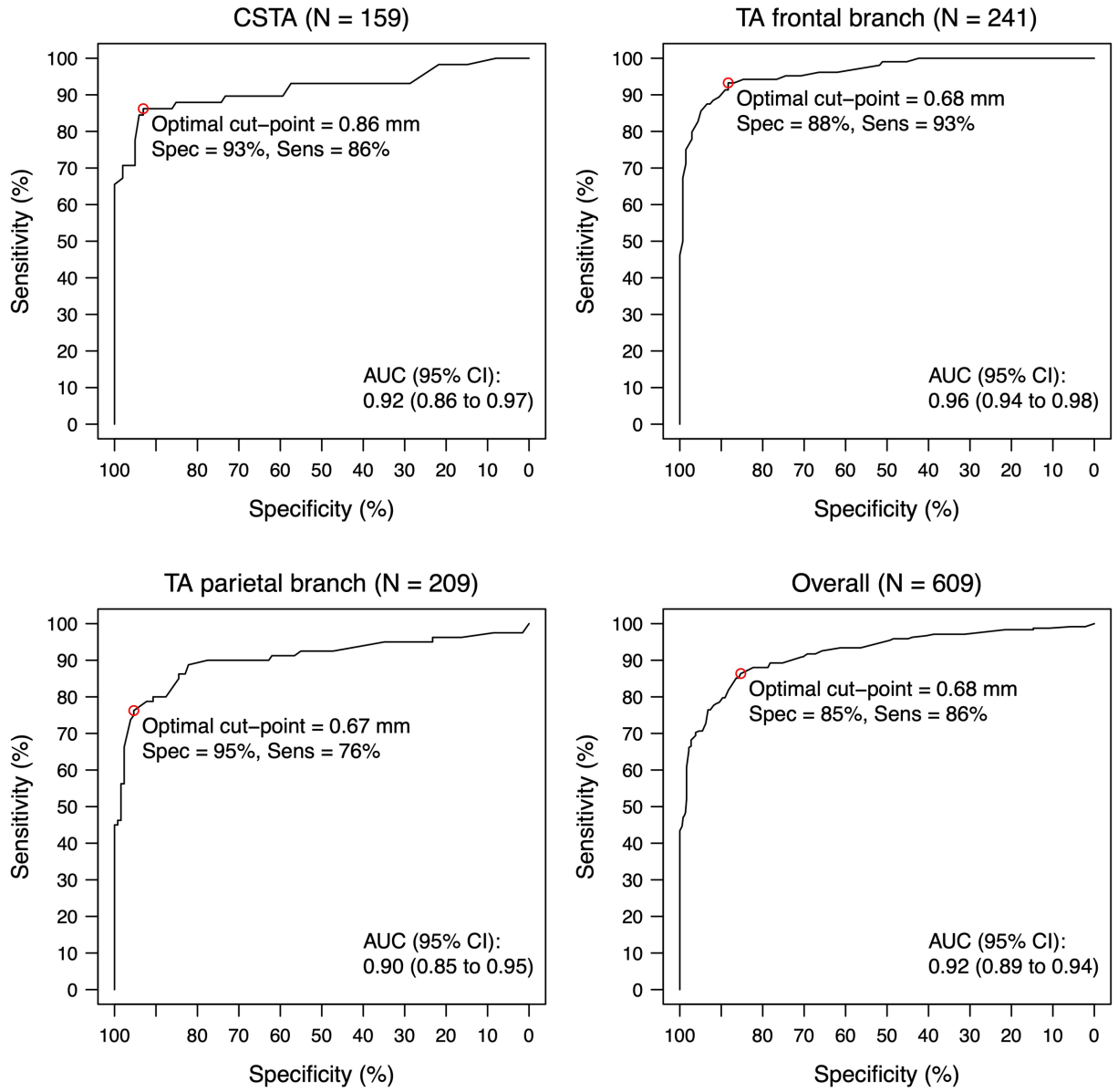

FIGURE 1
ROC-curve for intima-media thickness for each temporal artery segment and overall. Intima-media thickness values are shown for the compressed lumen technique (combining both walls). The circle indicates the statistically optimal cut-off. Eleven Patients with giant cell arteritis had a normal T1-BB-MRI for all segments and were not included in this analysis. N indicates the number of segments (a maximum of two per patient, left and right side). AUC, area under the curve; CI, confidence interval; CSTA, common superficial temporal artery; IMT, intima-media thickness; ROC, receiver operating characteristic; TA, temporal artery.

expected, the resulting specificities were lower than for the segmental level because results from up to six segments were combined. A specificity of approximately 90% on the patient level was prespecified as criterion for the *clinically optimal* cut-offs. For the total patient population this corresponded to the 96%-specificity cut-off values on the segment level in Table 4. These cut-offs were 1.01 mm for CSTAs, 0.82 mm for FBs and 0.69 mm for PBs. If the ultrasound examination is taken as a whole, at least one of these cut-off values needs to be met to be classified as GCA. These *clinically optimal* cut-off values result in a sensitivity of 79.7% and a specificity of 90.0% for the total study population and a sensitivity of 87.3% and specificity of 94.4% for the group with cranial manifestations. On the patient level the subsets according to CVR were analyzed as well with a clinically relevant advantage in measures of diagnostic accuracies for those patients which did not belong to the high/very-high CVR category. Using the statistically optimal cut-offs for both groups, 40/54 (74.1%) versus 81/90 (90%) were correctly classified; a difference of 15.9% (p-value 0.018). For patients with and without high/very-high CVR respectively, sensitivities were 80.8% versus 89.6% and specificities 67.9% versus 90.5%. For clinically optimal cut-offs for the CSTA, the FB and the PB respectively, for patients in the high/very-high CVR group cut-offs were 1.03 mm, 0.86 mm and 0.80 mm with a corresponding sensitivity of 73.1% and a specificity of 89.3%. For patients not in

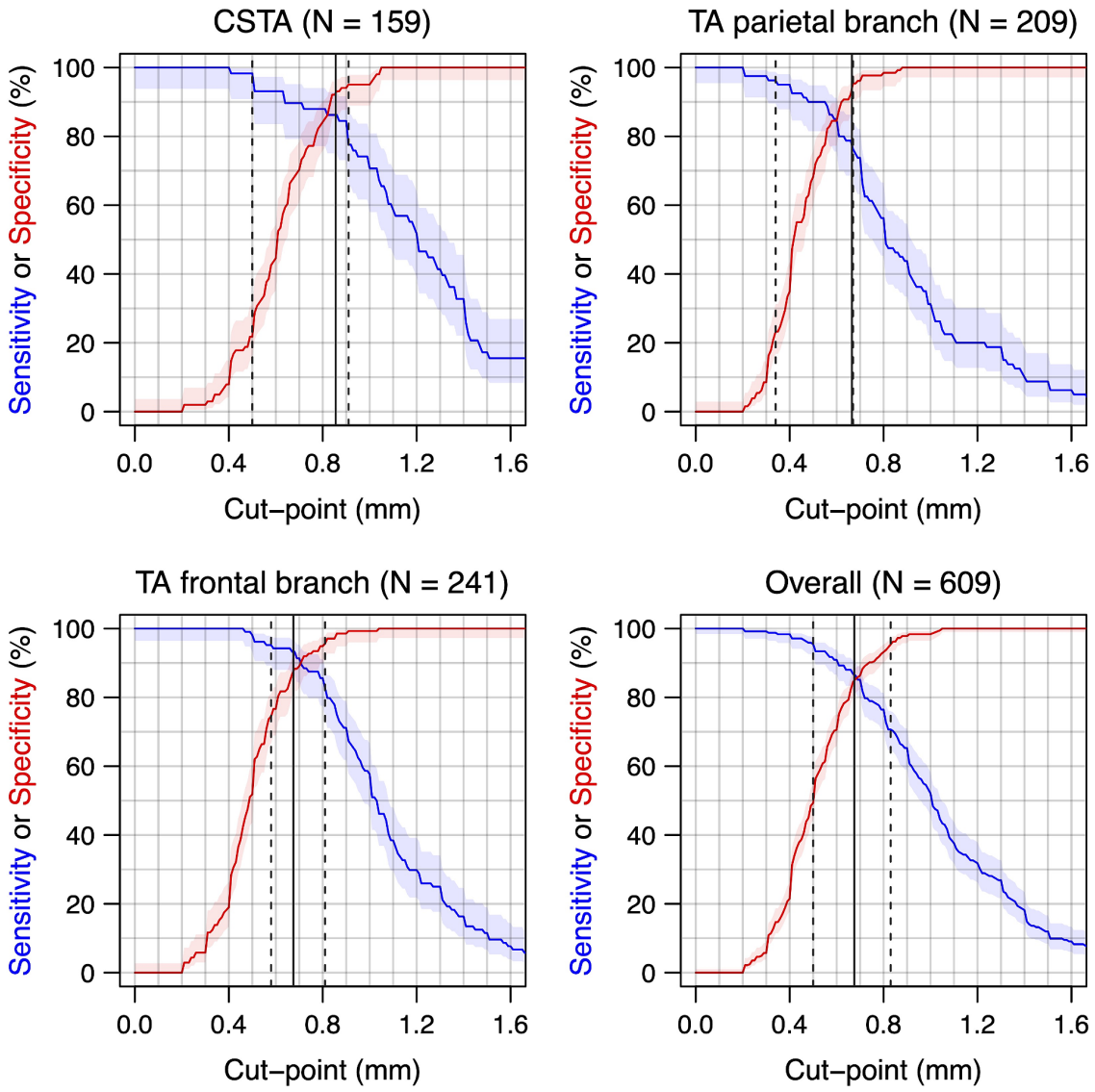

FIGURE 2
Sensitivity and specificity for different cut-offs for the intima-media thickness for each temporal artery segment and overall. Intima-media thickness values are shown for the compressed lumen technique (combining both walls). Curve for sensitivity: top left to lower right corner. Curve for specificity: lower left to top right corner. Eleven Patients with giant cell arteritis had a normal T1-BB-MRI for all segments and were not included in this analysis. N indicates the number of segments (a maximum of two per patient, left and right side). 95%-confidence regions in shaded areas. The vertical lines indicate the optimal cut-off (solid) and the cut-points to reach a sensitivity or specificity of 95% (dashed). CSTA, common superficial temporal artery; TA, temporal artery.

the high/very-high CVR group cut-offs were lower at 0.84 mm, 0.71 mm and 0.63 mm, respectively, with a corresponding sensitivity of 89.6% and specificity of 90.5%. The different sets of cut-off values are shown in Table 6 for easier comparison.

Discussion

This study evaluated patients with suspected GCA, *including isolated non-cranial presentations*, in a real-life scenario. Segmental cut-off values for the IMT of the TA segments were evaluated for the diagnosis of GCA at the patient level, comparable to the usual approach of cranial MRI. An innovative and novel approach with a double reference standard of expert clinical diagnosis at the patient level and T1-BB-MRI results at the segment level was used to identify normal and diseased segments for the derivation of new cut-off values.

In daily clinical practice, *ruling in* GCA is the focus of imaging studies as *ruling out* GCA with an ultrasound examination of the TAs is often not possible (6, 34). While in the case of a negative test, another test is usually performed depending on pre-test probability for GCA, the use of a test with high specificity is important to limit false-positive results. Therefore, in addition to *statistically optimal* cut-off values, we derived *clinically optimal* cut-off values with a predefined specificity of approximately 90% or higher on the patient level, which allows a GCA diagnosis with a high degree of certainty, particularly in patients with a high pretest probability.

TABLE 4 Segment-specific cut-offs to reach specificities of ≥ 85% for all segments.

Minimum specificity for each segment	Common superficial temporal artery	Temporal artery frontal branch	Temporal artery parietal branch
85%	0.81	0.67	0.61
86%	0.82	0.67	0.61
87%	0.83	0.68	0.61
88%	0.83	0.68	0.62
89%	0.83	0.70	0.62
90%	0.84	0.71	0.63
91%	0.84	0.72	0.66
92%	0.84	0.74	0.66
93%	0.86	0.76	0.67
94%	0.88	0.79	0.67
95%	0.91	0.81	0.67
96%	1.01	0.82	0.69
97%	1.02	0.82	0.71
98%	1.03	0.86	0.80
99%	1.05	0.91	0.86
100%	1.05	1.04	0.88

Cut-offs for the compressed lumen technique (combining both walls) are shown in millimeters.

The *statistically optimal* segmental cut-offs for the total study population obtained using the compression technique are very similar to previously published cut-offs, which were mostly reported as single-sided measurements (our values would need to be divided by two for direct comparison) (15, 17–19).

The focus of this study was the combined assessment of all segments together on the patient level, which is the relevant test in daily practice. Using a combination of several segments together, a loss in specificity can be expected compared to an analysis with single segments because false positives become more likely. Using the newly derived *statistically optimal* cut-offs from the segment level analysis, a sensitivity and specificity of 86.7%/81.4 and 92.1%/87.0% was reached for the patient level for the total population and patients with cranial manifestations, respectively. The use of *clinically optimal* segmental cut-off values was associated with a slight drop in sensitivity to 79.7% at a specificity of 90.0% for the total study population. For patients with cranial manifestations, the diagnostic accuracy was higher and the drop in sensitivity to 87.3% less pronounced. The *clinically optimal* cut-offs are 0.02 to 0.15 mm higher than the *statistically optimal* cut-offs (compressed artery) (Table 6).

The mean IMT shows considerably lower values for the frontal and especially the parietal branches in both non-GCA and GCA cases compared to the CSTA (Table 2). This justifies the use of segment-specific cut-off values for the diagnosis of GCA.

Our cohort had a considerable proportion of patients with high/very-high CVR and subgroup analysis showed pronounced differences in measures of diagnostic accuracy. The 22.6% lower specificity for newly derived *statistically optimal* cut-offs for patients with high/very-high CVR is striking but corresponds well to our clinical experience. In other words, in order to achieve a specificity of around 90% for the patient level in individuals with high/very-high CVR, the cut-offs need to be raised considerably. However, for patients without high/very-high CVR, *clinically optimal* cut-offs are much lower and correspond approximately to the *statistically optimal* cut-offs for the total study population (Table 6 for direct comparison of different sets of cut-off values).

Using the data from our study, ultrasound results can be used in a Bayesian approach to the diagnosis of GCA, depending on clinical circumstances. Using *clinically optimal* cut-offs would allow to *rule in* a GCA diagnosis in cases with reasonably high pre-test probability but with some compromises in sensitivity. In the case of a negative ultrasound, other diagnostic tests such as cranial MRI, TA biopsy or FDG-PET-CT can be performed, and we have been using this stepwise approach successfully in clinical practice for several years (6). The measures of diagnostic accuracy from our study compare well to recent pooled estimates for the T1-BB MRI (sensitivity of 82%, specificity of 92%) (6, 35). Since a relevant proportion of patients with GCA do not have vasculitis of the TAs, the maximum attainable sensitivity of any diagnostic test for the TAs is expected to lie below 100% with an expected ceiling effect (34, 36).

When the results of this study are compared with previously published data, some important differences need to be considered. Comparison of this study to the only other study using IMT measurements in the compressed artery by Czihal et al. is complicated by the fact that they did not differentiate TA segments (17). Mean IMT for GCA patients was reported as 1.03 mm with a standard deviation (SD) of only 0.03 mm; for non-GCA cases it was 0.44 mm (SD 0.13 mm). Values for mean IMT are in line with our results but the SD for GCA cases is much smaller than in our cohort where SDs were more than ten times larger for GCA cases (see Table 2). Czihal et al. (17) One possible explanation of higher variability in IMT values could be that in our study multiple measurements were taken along a large section of the artery, compared to mostly defined single point or more limited measurements in previous studies, also in the study by Czihal et al. (15, 17–19). In addition, areas with scalp hair, where measurements can be challenging, were also included. Schäfer et al. used a very different patient population and selection procedure of relevant arterial segments, making a direct comparison to the present study difficult. They published the first estimates for cut-off values in 2017, which are similar to the *statistically optimal* cut-offs (divided by two) for the total study population from the present study, with only the PB having a relevantly lower value (15). Newer studies using single-sided measurements published very similar segmental cut-off values. Ješe et al. (18) used a comparable patient population but used a probe with non-adjustable 18 MHz and single-sided longitudinal IMT measurements (18). Despite generating an overall cut-off of 0.40 mm for all TA-segments combined, very high estimates for sensitivity and specificity were presented (97.9 and 99.0%) (18). The study by López-Gloria et al. from 2022 also used a similar population, an 18 MHz probe with longitudinal single-sided IMT measurements with focal measurements 1 cm distal to the TA bifurcation in the PB and FB and derived similar segmental cut-off values but with very high sensitivities and specificities (94.7–100%) (19). Measures of diagnostic accuracies for segmental and patient level (the latter only by Ješe et al.) analysis from these studies surpassed those from MRI studies and our data considerably (18, 19, 35). While the more comprehensive IMT measurement method in the present study is a

TABLE 5 Patient-level measures of diagnostic accuracy for statistically optimal cut-offs and range of possible cut-offs with *minimum* specificities per segment of 85 to 100%.

	Total study population (*N* = 144)			Patients with cranial manifestations (*N* = 117)			Patients without high/very high CVR (*N* = 90)			Patients with high/very high CVR (*N* = 54)		
	Sensitivity (95% CI)	Specificity (95% CI)	Correctly classified (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Correctly classified (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Correctly classified (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Correctly classified (95% CI)
Statistically optimal cut-offs	86.5% (76.9–92.5%)	81.4% (70.8–88.8%)	84.0% (77.2–89.1%)	92.1% (82.7–96.6%)	87% (75.6–93.6%)	89.7% (82.9–94.0%)	89.6% (77.8–95.5%)	90.5% (77.9–96.2%)	90.0% (82.1–94.5%)	80.8% (62.1–91.5%)	67.9% (49.3–82.1%)	74.1% (61.1–83.9%)
Specificity 85%	86.5% (76.9–92.5%)	75.7% (64.5–84.2%)	81.2% (74.1–86.8%)	92.1% (82.7–96.6%)	79.6% (67.1–88.2%)	86.3% (78.9–91.4%)	89.6% (77.8–95.5%)	85.7% (72.2–93.3%)	87.8% (79.4–93.0%)	80.8% (62.1–91.5%)	60.7% (42.4–76.4%)	70.4% (57.2–80.9%)
Specificity 86%	86.5% (76.9–92.5%)	75.7% (64.5–84.2%)	81.2% (74.1–86.8%)	92.1% (82.7–96.6%)	79.6% (67.1–88.2%)	86.3% (78.9–91.4%)	89.6% (77.8–95.5%)	85.7% (72.2–93.3%)	87.8% (79.4–93.0%)	80.8% (62.1–91.5%)	60.7% (42.4–76.4%)	70.4% (57.2–80.9%)
Specificity 87%	86.5% (76.9–92.5%)	77.1% (66.0–85.4%)	81.9% (74.9–87.4%)	92.1% (82.7–96.6%)	81.5% (69.2–89.6%)	87.2% (79.9–92.1%)	89.6% (77.8–95.5%)	88.1% (75.0–94.8%)	88.9% (80.7–93.9%)	80.8% (62.1–91.5%)	60.7% (42.4–76.4%)	70.4% (57.2–80.9%)
Specificity 88%	86.5% (76.9–92.5%)	77.1% (66.0–85.4%)	81.9% (74.9–87.4%)	92.1% (82.7–96.6%)	81.5% (69.2–89.6%)	87.2% (79.9–92.1%)	89.6% (77.8–95.5%)	88.1% (75.0–94.8%)	88.9% (80.7–93.9%)	80.8% (62.1–91.5%)	60.7% (42.4–76.4%)	70.4% (57.2–80.9%)
Specificity 89%	86.5% (76.9–92.5%)	77.1% (66.0–85.4%)	81.9% (74.9–87.4%)	92.1% (82.7–96.6%)	81.5% (69.2–89.6%)	87.2% (79.9–92.1%)	89.6% (77.8–95.5%)	88.1% (75.0–94.8%)	88.9% (80.7–93.9%)	80.8% (62.1–91.5%)	60.7% (42.4–76.4%)	70.4% (57.2–80.9%)
Specificity 90%	86.5% (76.9–92.5%)	78.6% (67.6–86.6%)	82.6% (75.6–88.0%)	92.1% (82.7–96.6%)	81.5% (69.2–89.6%)	87.2% (79.9–92.1%)	89.6% (77.8–95.5%)	90.5% (77.9–96.2%)	90.0% (82.1–94.6%)	80.8% (62.1–91.5%)	60.7% (42.4–76.4%)	70.4% (57.2–80.9%)
Specificity 91%	86.5% (76.9–92.5%)	80.0% (69.2–87.7%)	83.3% (76.4–88.5%)	92.1% (82.7–96.6%)	83.3% (71.3–91.0%)	88.0% (80.9–92.7%)	89.6% (77.8–95.5%)	92.9% (81.0–97.5%)	91.1% (83.4–95.4%)	80.8% (62.1–91.5%)	60.7% (42.4–76.4%)	70.4% (57.2–80.9%)
Specificity 92%	85.1% (75.3–91.5%)	80.0% (69.2–87.7%)	82.6% (75.6–88.0%)	92.1% (82.7–96.6%)	83.3% (71.3–91.0%)	88.0% (80.9–92.7%)	87.5% (75.3–94.1%)	92.9% (81.0–97.5%)	90.0% (82.1–94.6%)	80.8% (62.1–91.5%)	60.7% (42.4–76.4%)	70.4% (57.2–80.9%)
Specificity 93%	85.1% (75.3–91.5%)	85.7% (75.7–92.1%)	85.4% (78.7–90.3%)	92.1% (82.7–96.6%)	90.7% (80.1–96.0%)	91.5% (85.0–95.3%)	87.5% (75.3–94.1%)	95.2% (84.2–98.7%)	91.1% (83.4–95.4%)	80.8% (62.1–91.5%)	71.4% (52.9–84.7%)	75.9% (63.1–85.4%)
Specificity 94%	83.8% (73.8–90.5%)	85.7% (75.7–92.1%)	84.7% (78.0–89.7%)	92.1% (82.7–96.6%)	90.7% (80.1–96.0%)	91.5% (85.0–95.3%)	87.5% (75.3–94.1%)	95.2% (84.2–98.7%)	91.1% (83.4–95.4%)	76.9% (57.9–89.0%)	71.4% (52.9–84.7%)	74.1% (61.1–83.9%)
Specificity 95%	81.1% (70.7–88.4%)	85.7% (75.7–92.1%)	83.3% (76.4–88.5%)	88.9% (78.8–94.5%)	90.7% (80.1–96.0%)	89.7% (82.9–94.0%)	83.3% (70.4–91.3%)	95.2% (84.2–98.7%)	88.9% (80.7–93.9%)	76.9% (57.9–89.0%)	71.4% (52.9–84.7%)	74.1% (61.1–83.9%)
Specificity 96%	79.7% (69.2–87.3%)	90.0% (80.8–95.1%)	84.7% (78.0–89.7%)	87.3% (76.9–93.4%)	94.4% (84.9–98.1%)	90.6% (83.9–94.7%)	83.3% (70.4–91.3%)	97.6% (87.7–99.6%)	90.0% (82.1–94.6%)	73.1% (53.9–86.3%)	78.6% (60.5–89.8%)	75.9% (63.1–85.4%)
Specificity 97%	77.0% (66.3–85.1%)	91.4% (82.5–96.0%)	84.0% (77.2–89.1%)	84.1% (73.2–91.1%)	94.4% (84.9–98.1%)	88.9% (81.9–93.4%)	79.2% (65.7–88.3%)	97.6% (87.7–99.6%)	87.8% (79.4–93.0%)	73.1% (53.9–86.3%)	82.1% (64.4–92.1%)	77.8% (65.1–86.8%)
Specificity 98%	73.0% (61.9–81.8%)	94.3% (86.2–97.8%)	83.3% (76.4–88.5%)	79.4% (67.8–87.5%)	96.3% (87.5–99.0%)	87.2% (79.9–92.1%)	72.9% (59.0–83.4%)	97.6% (87.7–99.6%)	84.4% (75.6–90.5%)	73.1% (53.9–86.3%)	89.3% (72.8–96.3%)	81.5% (69.2–89.6%)
Specificity 99%	68.9% (57.7–78.3%)	98.6% (92.3–99.7%)	83.3% (76.4–88.5%)	74.6% (62.7–83.7%)	98.1% (90.2–99.7%)	85.5% (78.0–90.7%)	68.8% (54.7–80.1%)	100% (91.6–100%)	83.3% (74.3–89.6%)	69.2% (50.0–83.5%)	96.4% (82.3–99.4%)	83.3% (71.3–91.0%)
Specificity 100%	63.5% (52.1–73.6%)	100% (94.8–100%)	81.2% (74.1–86.8%)	68.3% (56.0–78.4%)	100% (93.4–100%)	82.9% (75.1–88.7%)	62.5% (48.4–74.8%)	100% (91.6–100%)	80.0% (70.6–87.0%)	65.4% (46.2–80.6%)	100% (87.9–100%)	83.3% (71.3–91.0%)

GCA, giant cell arteritis; CI, confidence interval; CVR, cardiovascular risk; N, number of patients in the subpopulation.

10.3389/fmed.2024.1389655

TABLE 6 Comparison of statistically optimal and clinically optimal cut-offs with associated sensitivities and specificities on the patient level.

	Statistically optimal cut-offs total study population	Clinically optimal[a] cut-offs total study population	Clinically optimal[a] cut-offs with high/very high CVR	Clinically optimal[a] cut-offs without high/very CVR
Common superficial TA	0.86 mm	1.01 mm	1.03 mm	0.84 mm
Frontal branch of TA	0.68 mm	0.82 mm	0.86 mm	0.71 mm
Parietal branch of TA	0.67 mm	0.69 mm	0.80 mm	0.63 mm
Sensitivity	86.5% (76.9–92.5%)	79.7% (69.2–87.3%)	73.1% (53.9–86.3%)	89.6% (77.8–95.5%)
Specificity	81.4% (70.8–88.8%)	90.0% (80.8–95.1%)	89.3% (72.8–96.3%)	90.5% (77.9–96.2%)

Cut-off values are shown for the compressed lumen technique (combining both walls).
[a]defined as sets of cut-offs with approximately 90% specificity on the patient level (from Tables 4, 5).
CVR, cardiovascular risk; TA, temporal artery.

likely explanatory factor, there may be unknown differences in study design or patient population as well. Furthermore, the exact handling of measurements at locations with possible atherosclerotic disease may have been a relevant source of heterogeneity between studies. OMERACT provides a definition of atherosclerotic vessel wall changes with an emphasis on echogenicity (11). Despite that, the clear differentiation of atherosclerosis and/or intima hyperplasia from vasculitis with ultrasound remains extremely challenging, especially in cases where atherosclerosis and vasculitis coexist, which is frequent in patients with high CVR. We believe it is particularly in patients with atherosclerosis, where it is the most difficult to differentiate diseased from non-diseased segments. The drop in specificity in the subgroup analysis with high/very-high CVR demonstrates this clearly.

This study has several limitations. Patients were retrospectively collected but represent a typical population from a tertiary referral center for suspected GCA. The combined IMT of both walls of a compressed artery is measured at our center because multiple measurements would be very time consuming with the single-sided longitudinal method and becomes even more difficult and sometimes impossible in areas with scalp hair. A direct comparison of IMT measurements of compressed arteries with single-sided IMT measurements seems reasonable, and OMERACT regards this method as equivalent, but, to our knowledge, it has not been proven that both methods result in equal results (16). Single-sided measurements with their shorter distances place considerably higher demands on the ultrasound equipment and may therefore be less widely applicable internationally. Both, ultrasound examinations and re-reading of MRI images, were not done by 2 independent readers because of the retrospective nature of the data for the former and time constraints for the latter. Therefore, no information on inter-rater reliability can be provided for the ultrasound measurements. For the T1-BB MRI, an inter-rater analysis for the same two readers was published previously for another study and showed substantial reliability (9). The pragmatic classification into two CVR groups is possibly imperfect, as some of the patients may be re-classified into the high/very-high CVR group after application of the SCORE2/SCORE2-OP-scores, especially elderly men in high-or very-high-risk countries (e.g., Eastern Europe; Switzerland is a low-risk country) (32). While a perfect classification into CVR groups would be ideal, in our opinion this is not feasible in the situation of a fast-track clinic. Even in the inpatient setting, the application of a SCORE-score is difficult because blood pressure measurements in patients with pain and high dose glucocorticoids are not reliable. The method proposed in this study allows a pragmatic classification at the bedside using readily available clinical information. The cut-offs were derived from and evaluated in the same population. Still, for the derivation of measures of diagnostic accuracy on the patient level all 765 available segments were used, while for the cut-off derivation only 609 segments were used. A formal prospective validation on another and eventually also external patient population is necessary.

Because of the segmental manifestation of the disease and the potential influence of sex, height, weight, age and CVR on IMT, the diagnostic approach using IMT cut-off values remains complex and still has its limitations (37). An even better conceptualization of the diagnostic process for GCA, including pertinent features from the patient history, the physical examination and laboratory values would be a multivariable model including IMTs as continuous variables. Including information on CVR would allow an estimation of the influence of the IMT on the probability of disease independent of this risk categorization. In such models, MRI data could be implemented as well. For adequate derivation of such multivariate models, larger number of patients in a prospective study design may be necessary, depending on the number of variables used.

In conclusion, our study provides four sets of segmental cut-offs with measures of diagnostic accuracy for the diagnosis of giant cell arteritis for direct application in clinical practice depending on the clinical situation and physician preference.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee Bern, Switzerland. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

PS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. FL: Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – review & editing. SB: Data

curation, Investigation, Writing – review & editing. LB: Formal analysis, Visualization, Writing – review & editing. BM: Funding acquisition, Resources, Writing – review & editing. AH: Resources, Writing – review & editing. LS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. Article processing charges for open access publication were covered by the Open Access Publication Fund at the University of Bern, Bern, Switzerland.

Conflict of interest

BM: Research: AbbVie, Protagen, Novartis Biomedical; patent mir-29 for the treatment of systemic sclerosis issued (US8247389, EP2331143); lecturing: Boehringer-Ingelheim, GSK, Novartis, Otsuka; consulting/advisory boards: Novartis, Boehringer Ingelheim, Janssen-Cilag, GSK; congress support: Medtalk, Pfizer, Roche, Actelion, Mepha, MSD.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1389655/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 22 May 2024
DOI 10.3389/fmed.2024.1382946

OPEN ACCESS

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RECEIVED 06 February 2024
ACCEPTED 07 May 2024
PUBLISHED 22 May 2024

CITATION
Schweiger L, Hafner F, Meinitzer A, Brodmann M, Dejaco C and Jud P (2024) Association of clinical, imaging and laboratory parameters with adverse effects of glucocorticoid therapy in patients with giant cell arteritis.
Front. Med. 11:1382946.
doi: 10.3389/fmed.2024.1382946

Association of clinical, imaging and laboratory parameters with adverse effects of glucocorticoid therapy in patients with giant cell arteritis

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Background: Giant cell arteritis (GCA) is characterized by inflammation of large and medium vessels. First-line therapy for the treatment of GCA are glucocorticoids, which are effective while potential adverse effects should be considered, especially during long-term use. The aim was to investigate the incidence of glucocorticoids' adverse effects and potential predictors for them.

Materials and methods: 138 GCA patients were retrospectively evaluated for newly developed glucocorticoid adverse effects in 2020. Potential predictors, defined as initial glucocorticoid pulse therapy, relapse of GCA and concomitant polymyalgia rheumatica as well as parameters of inflammation and endothelial dysfunction, including pulse-wave velocity and intima-media-thickness, were measured in 2012.

Results: Potential new glucocorticoid adverse effects per patient was 1 (25th-75th 0–3) of which chronic kidney disease progression (29%), bone fractures (23.2%), cataracts (18.1%), dementia, and arterial hypertension (each at 12.3%) were most commonly recorded. Significant associations were found between occurrence of any relapse and new diabetes mellitus and between initial glucocorticoid pulse therapy and new dementia (all with $p < 0.05$). In multivariate regression analysis, any relapse was a predictor for developing diabetes mellitus (OR 9.23 [95% CI 1.33–64.05], $p = 0.025$). However, no correlations were observed between endothelial dysfunction or inflammatory parameters and development of new glucocorticoid adverse effects.

Conclusion: GCA relapses may be associated for development of diabetes mellitus potentially by increasing glucocorticoid doses. Parameters of inflammation and endothelial dysfunction are not suited predictors for glucocorticoid adverse effects.

KEYWORDS

giant cell arteritis, adverse effects, glucocorticoids, inflammation, endothel dysfunction

Introduction

Giant cell arteritis (GCA) is classified as a large vessel vasculitis and is the most prevalent form of systemic vasculitis in adults with an annual incidence rate of 15–25 cases per 100,000 individuals (1). This condition primarily affects individuals over the age of 50 and it tends to be more common among women than men (2, 3). GCA is characterized by an inflammatory process that primarily affects large and medium-sized arteries, including the aorta and extracranial branches of the carotid arteries. This inflammatory process may lead to substantial damage, potentially resulting in complications like stenosis, occlusions, and even aneurysms in the affected arteries (4–6). The clinical presentation of GCA encompasses a range of symptoms, such as unilateral or bilateral temporal headaches, myalgia, jaw claudication, fatigue, and acute visual impairment (7).

In line with the recent recommendations from the European Alliance of Associations for Rheumatology (EULAR), glucocorticoids are the first-line therapy for GCA, particularly involving high doses when ocular complications are present (8). Although glucocorticoids are the most used therapy for GCA, this form of treatment is associated with a multitude of potential adverse effects exhibiting a dose-dependent pattern. Prolonged usage of glucocorticoids is associated with typical adverse effects, including osteoporosis, gastritis, arterial hypertension, and the onset of diabetes mellitus (9–11). Additionally, the risk for venous thromboembolism (VTE) is 3.5-fold higher during treatment with glucocorticoids and vascular dementia was also more likely to be diagnosed in those patients that had ever used long-lasting glucocorticoid treatment of more than two years (12, 13). Furthermore, it has been reported that adverse effects of glucocorticoid therapy may occur in up to 86% of GCA patients (10). Due to those adverse effects, glucocorticoid tapering need to done during an inactive phase of GCA, while relapse of GCA may occur during glucocorticoid tapering and relapse rates may be higher upon withdrawal of glucocorticoids (10, 14, 15). Therefore, determining the most effective treatment strategy to prevent relapse and minimize glucocorticoid adverse effects in GCA is challenging. Moreover, potential risk factors predicting glucocorticoid adverse effects are rarely described, especially GCA-specific parameters have been scarcely evaluated.

The aim of this study was to investigate the incidence of adverse effects caused by glucocorticoid therapy and find potential predictors for these effects in patients with GCA.

Materials and methods

Study design and patient cohort

This is a sub-study of a previously published study investigating cardiovascular diseases in patients with GCA (16). In brief, patients with a diagnosed GCA between 1993 and 2010 were identified by electronic search and invited to participate that study in 2012. At study inclusion between January and December 2012, blood sampling for parameters of endothelial dysfunction and inflammation, ultrasound measuring intima-media-thickness (IMT), and pulse-wave analysis measuring arterial stiffness were performed. All measurements were performed in a phase of inactive GCA and no subject had a disease relapse within a period of at least six months prior to study inclusion. After study inclusion, patients were followed-up by clinical routine. Charts review was performed in 2020 retrieving retrospectively patients' demographics and clinical parameters up to study inclusion and recording retrospectively potential newly developed glucocorticoid adverse effects and relapse of GCA after study inclusion.

Patients with GCA were diagnosed clinically by the treating angiologic or rheumatologic physician based on clinical parameters, laboratory data, imaging and/or biopsy. All patients had been diagnosed with GCA of at least two years prior study inclusion. The modified criteria from the American College of Rheumatology (ACR) proposed by Dejaco et al. (17) were fulfilled retrospectively in all GCA subjects. Exclusion criteria for GCA patients were active cancer, infections, or other types of vasculitis.

Laboratory parameters

Fasting blood samples for evaluation of inflammatory parameters, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, and white blood cells including lymphocyte subsets, were obtained from each patient at study inclusion in 2012. Additionally, CRP, ESR and fibrinogen from the time of GCA onset have been collected retrospectively. Peripheral blood mononuclear cells were isolated by Histopaque density gradient centrifugation and total cell number was determined by a Beckmann Coulter for measurement of lymphocytes subsets. Surface staining was performed according to routine protocols using appropriate combinations of antibodies for detection of CD3, CD4, CD8, CD28, CD45RA, CD45RO and appropriate isotype controls. Stained cells were measured using a fluorescence-activated cell sorter Canto II (Becton Dickinson), and data analysis was conducted with DIVA software and FlowJo. For the measurement of asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) by high-performance liquid chromatography as described by Meinitzer et al. (18), one tube of whole blood was collected at study inclusion and subsequently centrifuged at 4,000 g for 10 min at 15°C temperature within 1 h after blood sampling obtainment. The supernatant was collected and divided into aliquots of 1 mL, which were stored at −80°C until final analysis.

Imaging parameters

Details about measurements of IMT and arterial stiffness have been described previously (19). In brief, IMT of both common carotid, both subclavian and both common femoral arteries was measured by ultrasound using a linear transducer with 8–13 MHz (Siemens ACUSON S2000™, Siemens Healthcare Corp., Henkelstr., Erlangen, Germany) manually on magnified frozen longitudinal images and present carotid IMT of ≥0.9 mm in any

Abbreviations: ACR, American College of Rheumatology; ADMA, asymmetric dimethylarginine; Aix, augmentation index; CKD, chronic kidney disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; GCA, giant cell arteritis; IMT, intima-media-thickness; MEDOCS, Medical Documentation and Communication network of Styria; PMR, polymyalgia rheumatica; PWV, pulse-wave velocity; SD, standard deviation; SDMA, symmetric dimethylarginine; VTE, venous thromboembolism.

common carotid artery was defined as abnormal (20, 21). Subsequently, carotid-femoral pulse-wave velocity (PWV) and augmentation index (Aix) were measured and calculated by automated analysis via photo-plethysmographic device Vascular Explorer® (enverdis Ltd., Fürstenwall, Düsseldorf, Germany) using software version 1.0 defining PWV >10 m/s as pathologic (20).

Charts review of glucocorticoid adverse effects and clinical parameters

Charts review from all GCA subjects was performed between July and December 2020 via a fully electronic patient information system, called Medical Documentation and Communication network of Styria (MEDOCS), which is installed in the province of Styria, Austria, to provide electronic health data from all public Styrian hospitals and hospital alliances (22). Patient's demographics, clinical parameters, defined as initial glucocorticoid pulse therapy, relapse and concomitant polymyalgia rheumatica (PMR), and potential prevalent glucocorticoid adverse effects prior to study inclusion in 2012 were recorded. Additionally, potential newly developed glucocorticoid adverse effects and relapse during follow-up were recorded. Potential adverse effects of systemic glucocorticoid therapy were defined as arterial hypertension, diabetes mellitus, obesity, hyperlipidemia, including hypercholesterolemia and hypertriglyceridemia, chronic kidney disease (CKD), osteoporosis, bone fracture, cataract, glaucoma, hepatic steatosis and cirrhosis, VTE, depression, dementia, gastritis, peptic ulcer, esophagitis, and pancreatitis (22, 23). Definition of the respective glucocorticoid adverse effect was made by adoption of the respective diagnosis from another hospital and/or by respective investigation, like measurement of the estimated glomerular filtration rate with subdivision into CKD 1–5 according to the recent KDOQI classification for CKD, X-ray densitometry for osteoporosis or abdominal sonography for hepatic steatosis. Relapse was defined as major or minor relapse according to the EULAR recommendations for the management of large vessel vasculitis (8). The end of the follow-up period was patient's last documented medical report in MEDOCS.

Statistics

Normally distributed parameters were expressed as means ± standard deviation (SD), non-normally distributed parameters as median with interquartile range and categorical parameters as frequency and percentages. Normality of distribution was examined by the Kolmogorov–Smirnov test and visual inspection. Assessment for the association between glucocorticoid adverse effects and clinical parameters of GCA was done by chi-square test and by simple as well as multiple logistic regression analyses. Multiple regression analysis was adjusted for important confounding variables, including age, sex, active smoking, arterial hypertension, diabetes mellitus and obesity. Pearson's and Spearman's correlation coefficients were utilized for normally and for non-normally distributed variables, respectively. Given an exploratory study character no adjustment for multiple testing was applied. Statistical significance was assumed for p values <0.05. Statistical analyses were executed via SPSS version 27.0.

Ethic approval and informed consent

This study was approved by the local ethics committee of the Medical university of Graz (EK Nr. 32–469 ex 19/20) and was conducted in accordance with the recent Helsinki Declaration. All patients provided written informed consent at study inclusion.

Results

138 patients with GCA (106 female, 76.8%) with a mean age (± SD) of 74.5 ± 7.7 years were included in this study. Most common potential previously known glucocorticoid adverse effects at study inclusion were CKD (93.5%) followed by arterial hypertension (70.3%) and hyperlipidemia (66.7%). Further potential previous glucocorticoid adverse effects, concomitant medications at baseline and selected laboratory parameters at GCA onset are shown in Table 1.

Development of glucocorticoid adverse effects during follow-up

Mean follow-up (± SD) duration in the GCA cohort was 87.1 ± 21.7 months. Any potentially new glucocorticoid adverse effect occurred in 104 patients with GCA (75.4%). Median of potentially new glucocorticoid adverse effect was one with a 25th-75thpercentile range of 0–3. Among newly developed glucocorticoid adverse effects, CKD progression was the most prevalent, occurring in 29% of the patients, followed by bone fractures in 23.2% and by cataracts in 18.1% of the patients. Development of new-onset arterial hypertension (12.3%), dementia (12.3%) and hyperlipidemia (10.9%) were additional common glucocorticoid adverse events. Further details of newly developed glucocorticoid adverse events during the follow-up period are listed in Table 2.

Associations between clinical, laboratory and imaging parameters with glucocorticoid adverse effects

Significant association was observed between the occurrence of any relapse and new-onset diabetes mellitus ($p = 0.025$). Furthermore, a significant association was found between the initial glucocorticoid pulse therapy and the development of new-onset dementia ($p = 0.041$). No further significant associations were observed between initial glucocorticoid pulse therapy, any relapse, PMR and the occurrence of any other new adverse effects (Table 3). In simple logistic regression analysis, the occurrence of any relapse was significant associated with new-onset diabetes mellitus during follow-up (OR 9.58 [95% CI 1.50–61.37], $p = 0.017$) and remained a statistically significant predictor in multiple logistic regression analysis (OR 9.23 [95% CI 1.33–64.05], $p = 0.025$). Conversely, although the association between initial glucocorticoid pulse therapy and development of new-onset dementia was statistically significant in simple logistic regression analysis (OR 4.08 [95% CI 1.09–15.25], $p = 0.036$), no statistical significance could be achieved in multiple logistic regression analysis (OR 1.63 [95% CI 0.30–8.76], $p = 0.571$).

10.3389/fmed.2024.1382946

TABLE 1 Patients' characteristics and retrospectively collected potential glucocorticoid adverse effects.

Age (years), mean (± SD)	74.5 (±7.7)
Sex, *n* (%)	
Female	106 (76.8)
Male	32 (23.2)
BMI (kg/m²), mean (± SD)	26.47 (±4.65)
GCA subtype, *n* (%)	
Extracranial GCA	8 (5.8)
Cranial GCA	69 (50.0)
GCA without PMR	77 (55.8)
GCA with PMR	61 (44.2)
Ocular involvement, *n* (%)	12 (8.7)
Laboratory parameters at GCA onset, median (25th–75th percentile)	
CRP (mg/L)	56.0 (19.0–98.5)
ESR (mm/h)	69 (50–98)
Fibrinogen (mg/dL)	663 (536–883)
Drug therapy, *n* (%)	
Antiplatelet therapy	73 (52.9)
Oral anticoagulation	17 (12.3)
ACE inhibitors	43 (31.2)
Beta blockers	57 (41.3)
Calcium channel blockers	12 (8.7)
Diuretics	24 (17.4)
Other antihypertensives	15 (10.9)
Insulin	4 (2.9)
Metformin	12 (8.7)
Statins	45 (32.6)
DMARD	18 (13.0)
Methotrexate	15 (10.9)
Azathioprine	3 (2.2)
Relapse, *n* (%)	22 (15.9)
Major relapse	5 (3.6)
Minor relapse	17 (12.3)
Potential previous glucocorticoid adverse effects, *n* (%)	
Arterial hypertension	97 (70.3)
Diabetes mellitus	28 (20.3)
Obesity	24 (17.4)
Hyperlipidemia	92 (66.7)
Hypercholesterolemia	85 (61.6)
Hypertriglyceridemia	41 (29.7)
CKD	129 (93.5)
CKD 1	0 (0.0)
CKD 2	69 (49.3)
CKD 3	57 (41.3)
CKD 3a	48 (34.9)
CKD 3b	9 (6.5)
CKD 4	4 (2.9)
CKD 5	0 (0.0)
Osteoporosis	71 (51.4)
Bone fracture	25 (18.1)
Cataract	44 (31.9)
Glaucoma	13 (9.4)
Hepatic steatosis	14 (10.1)
Hepatic cirrhosis	0 (0.0)
VTE	12 (8.7)
Depression	8 (5.8)
Dementia	4 (2.9)
Gastritis	28 (20.3)
Peptic ulcer	6 (4.3)
Esophagitis	18 (13.0)
Pancreatitis	6 (4.3)
Number of potential previous glucocorticoid adverse effects, median (25th-75th percentile)	5 (3–6)

ACE, angiotensin-converting enzyme; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; GCA, giant-cell arteritis; PMR, polymyalgia rheumatica; VTE, venous thromboembolism.

No associations were identified between PWV >10 m/s or IMT ≥0.9 mm and the development of any new glucocorticoid adverse effects. Additionally, no significant association was noted between ESR >30 mm/h or CRP >5 mg/L, neither at study inclusion nor at GCA onset, and the development of any new glucocorticoid adverse effects (Table 4). In correlation analysis, no significant correlations were found between the number of newly developed glucocorticoid adverse effects and imaging or laboratory parameters of endothelial dysfunction and inflammation at study inclusion (Table 5). Significant correlations were found between the number of newly developed glucocorticoid adverse effects and CRP at GCA onset ($r = 0.297$, $p = 0.006$) and fibrinogen at GCA onset ($r = 0.351$, $p = 0.002$), but not for ESR at GCA onset ($r = 0.105$, $p = 0.387$).

Discussion

By our retrospective analysis of GCA patients, we demonstrated a high number of potential glucocorticoid adverse effects which was comparable to previous studies. Proven et al. (10) described glucocorticoid adverse effects in 86% of patients with GCA over a median follow-up period of ten years while we observed any new glucocorticoid adverse effect in 75% of patients with GCA over a mean follow-up period of 7.25 years. Regarding the total amount of newly developed glucocorticoid adverse effects, our study was also comparable to another previous study by Perrineau et al. (11), who reported the same median adverse effect event number but lower 25th-75th percentiles ranging from 0–1 adverse effects. In our study, 25th-75th percentiles ranged from 0–3 adverse effects, while the follow-up period was larger than by Perrineau et al. (11) (78.1 vs.

TABLE 2 Development of glucocorticoid adverse effects during the follow-up period.

Potential new glucocorticoid adverse effects, *n* (%)	
Arterial hypertension	17 (12.3)
Diabetes mellitus	5 (3.6)
Obesity	4 (2.9)
Hyperlipidemia	15 (10.9)
Hypercholesterolemia	13 (9.4)
Hypertriglyceridemia	10 (7.2)
New CKD	6 (4.3)
CKD stage progression	40 (29.0)
CKD 1	3 (2.2)
CKD 2	69 (50.0)
CKD 3	56 (40.6)
CKD 3a	38 (27.5)
CKD 3b	18 (13.0)
CKD 4	6 (4.3)
CKD 5	1 (0.7)
Osteoporosis	10 (7.2)
Bone fracture	32 (23.2)
Cataract	25 (18.1)
Glaucoma	3 (2.2)
Hepatic steatosis	3 (2.2)
Hepatic cirrhosis	0 (0.0)
VTE	10 (7.2)
Depression	5 (3.6)
Dementia	17 (12.3)
Gastritis	7 (5.1)
Peptic ulcer	1 (0.7)
Esophagitis	6 (4.3)
Pancreatitis	5 (3.6)
Patients with any potentially new glucocorticoid adverse effect, *n* (%)	104 (75.4)
Number of potentially new glucocorticoid adverse effects, median (25th-75th percentile)	1 (0–3)

CKD, chronic kidney disease; VTE, venous thromboembolism.

34 months). This may be also an explanation for the higher percentile range in our study. Other demographics, like gender or age which may influence and contribute to diseases as defined in our study as glucocorticoid adverse effects, were also comparable to previous studies (10, 11). Nevertheless, we observed some changes of each specific glucocorticoid adverse effects compared to previous studies. The most common glucocorticoid adverse effect in our analysis was CKD stage progression, occurring in 29% of the cases, although a clear reason for the high rate of CKD progression remains elusive due to the retrospective study design. One potential and probably the main cause for CKD progression was the aging process of the patient cohort during the observational period, as 93.5% of our GCA patients had CKD grade 2–5 at study inclusion. Other causes may be inadequate treatment of concomitant arterial hypertension or diabetes mellitus and also the intake of potential other nephrotoxic drugs during the observational period. Nevertheless, potential direct nephrotoxic effect of glucocorticoid therapy, but also indirect nephrotoxic effects of glucocorticoid therapy due to worsening of concomitant arterial hypertension or diabetes mellitus cannot be excluded. However, the overall rate of clinical relevant CKD was low in our cohort as only six patients and one other patient had CKD grade 4 and grade 5, respectively, at the end of the observational period. Nevertheless, the high rate of CKD progression sets our analysis apart from existing literature, where cataract and bone fracture were identified as the most prevalent adverse effect of glucocorticoid therapy (10, 11, 24). We recorded bone fracture in 23.2% of the patients as the second and cataract in 18.1% of the patients as the third most common adverse effect, followed by arterial hypertension and dementia which were recorded each in 12.3% of cases. Most rates of the respective glucocorticoid adverse effects were lower compared to Proven et al. (10) (38, 41, 22%, not recorded, respectively), but were higher to Perrineau et al. (11) (13, 8, 8%, not recorded, respectively). Regarding dementia, another study reported only a rate of 0.6% of GCA patients which is twentyfold lower than in our study (25). New-onset hyperlipidaemia were two-fold higher than in the cohort from Perrineau et al. (11) while new-onset diabetes mellitus were lower than in the cohort from Proven et al. (10). Rates of other new-onset specific glucocorticoid adverse effects, including VTE or gastrointestinal disorders, were not reported by both studies. Compared to other studies, however, we observed in our GCA cohort higher rates for VTE and gastritis with lower rates of glaucoma and peptic ulcers (25–27). To the best of our knowledge, no previously reported incidence rates for hepatic steatosis and cirrhosis, depression, esophagitis and pancreatitis in GCA patients were found.

The high rate of glucocorticoid adverse effects observed in our GCA cohorts can be explained on the one hand by the necessitated high doses, particularly in cases of ocular involvement and of GCA relapse, and on the other hand by the substantial proportion of older patients, which generally increases the likelihood for numerous diseases, including those which were defined in this study as glucocorticoid adverse effects. Causes for the different incidence rates of glucocorticoid adverse effects between our analysis and previous studies are various. Firstly, different rates of glucocorticoid adverse effects may be attributed to a stricter prevention regime for several glucocorticoid adverse effects, including calcium supplementation, administration of proton pump inhibitors or antihypertensive drugs. Especially, older studies on this topic, when knowledge of potential glucocorticoid adverse effects and their prevention was sparse, may report higher adverse effect rates than newer studies. Also the increasing use of disease-modifying anti-rheumatic drugs in GCA with their glucocorticoid sparing effect may cause a decrease of glucocorticoid adverse effects (28). Another aspect may be the missing awareness of less typical glucocorticoid adverse effects like VTE or glaucoma, which have been reported only occasionally for other diseases or in newer studies. Furthermore, some glucocorticoid adverse effects have not been investigated yet in GCA, like pancreatitis or a worsening of renal insufficiency. It must be, however, noted that especially CKD stage progression but also gastritis or hepatic steatosis may be caused also by several other factors including aging, smoking, or secondary to other drugs and other diseases.

TABLE 3 Associations of new glucocorticoid adverse effects with clinical parameters of GCA with exact *p*-values of chi-square test.

	Initial glucocorticoid pulse therapy	Any relapse	PMR
Arterial hypertension	0.320	0.294	0.206
Diabetes mellitus	0.658	**0.025**	0.383
Obesity	>0.999	0.487	>0.999
Hyperlipidemia	>0.999	>0.999	0.421
Hypercholesterolemia	0.320	0.691	0.774
Hypertriglyceridemia	>0.999	>0.999	>0.999
CKD	>0.999	0.590	0.694
CKD stage progression	0.349	0.189	0.349
Osteoporosis	0.686	0.179	>0.999
Bone fracture	0.609	0.782	0.689
Cataract	0.279	>0.999	0.664
Glaucoma	0.267	>0.999	>0.999
Hepatic steatosis	0.341	0.393	0.583
Hepatic cirrhosis	-	-	-
VTE	0.333	0.359	0.337
Depression	0.546	>0.999	0.655
Dementia	**0.041**	0.469	0.801
Gastritis	>0.999	>0.999	0.464
Peptic ulcer	0.341	>0.999	>0.999
Esophagitis	>0.999	0.226	0.070
Pancreatitis	>0.999	0.568	0.655

CKD, chronic kidney disease; PMR, polymyalgia rheumatica; VTE, venous thromboembolism. Bold values indicate statistical significance $p < 0.05$.

Lastly, the observed rates of some glucocorticoid adverse effects may differ due to the fact that not every incidence of the respective glucocorticoid adverse effect may be reported by the MEDOCS system. In case of slight gastritis, arterial hypertension or asymptomatic hepatic steatosis, which can be managed by resident physicians without necessary hospitalization, those incidences were not reported in MEDOCS.

Predictors for adverse effects of glucocorticoid therapy in GCA have been rarely investigated to the best of our knowledge. In the study from Perrineau et al. (11), age > 75 years, occurrence of relapse and a past medical history of diabetes were significant predictors for glucocorticoid adverse effects. However, the predictive role of other clinical, imaging and laboratory parameters remains elusive. In our study, we observed statistically significant associations between the occurrence of any relapse and the new-onset diabetes mellitus as well as between initial glucocorticoid pulse therapy and new-onset dementia. While both associations were significant in simple regression analysis, new-onset dementia failed to be statistically significant in multiple regression analysis. This may be explained by the fact that, with the occurrence of any relapse, glucocorticoid dosages typically increase and raising thereby the risk for the development of new-onset diabetes mellitus. Regarding the new onset of dementia, a systematic review has revealed that in the majority of studies examining all-cause dementia or Alzheimer's disease in relation to glucocorticoid use, there is either no association or a negative associations suggesting even potential protective effects for glucocorticoids (29). However, vascular dementia was commonly excluded and this fact may be an explanation for these contradictory data as another study reported that the risk of vascular dementia is increased under the use of glucocorticoids and nonsteroidal anti-inflammatory drugs (13). Due to the lack of differentiation in dementia subtypes in our study, we are unable to determine which dementia subtypes have developed in GCA patients. Additionally, potential influence by other cardiovascular risk factors for the development of new-onset dementia can be assumed, especially as multiple regression analysis including cardiovascular variables did not revealed statistical significance. Prevalence of concomitant arterial hypertension, diabetes mellitus and hyperlipidemia at study inclusion was high in our GCA cohort, but similar or only slightly divergent compared to other GCA cohorts (30, 31). Thus, also the risk for cardiovascular events and ischemic complications like stroke may be increased which may lead ultimately to higher rates of new-onset dementia (32).

Interestingly, no further associations between clinical, imaging and laboratory parameters were found, especially on those parameters which may be influenced by glucocorticoid administration like inflammatory parameters or parameters of endothelial dysfunction, except for CRP and fibrinogen at GCA onset and the number of newly developed glucocorticoid adverse effects. However, due to the retrospective study design with missing systematic screening, we cannot reliably differentiate between the time from GCA onset to study inclusion if one of our defined potential glucocorticoid adverse effect was a genuine adverse effect or rather a comorbidity. Due to that insufficient

TABLE 4 Associations of potential new glucocorticoid adverse effects with imaging and laboratory parameters at study inclusion and from GCA onset with exact *p*-values of chi-square test.

	PWV > 10 m/s	IMT ≥ 0.9 mm	ESR > 30 mm/h at study inclusion	CRP > 5 mg/L at study inclusion	ESR > 30 mm/h at GCA onset	CRP > 5 mg/L at GCA onset
Arterial hypertension	0.781	0.448	0.642	0.597	0.999	>0.999
Diabetes mellitus	0.149	0.655	0.369	0.648	0.384	>0.999
Obesity	0.274	0.629	0.307	0.645	>0.999	>0.999
Hyperlipidemia	>0.999	0.144	0.348	0.270	>0.999	>0.999
Hypercholesterolemia	0.761	0.345	0.276	0.766	>0.999	>0.999
Hypertriglyceridemia	>0.999	0.184	>0.999	>0.999	>0.998	>0.999
CKD	0.216	0.405	>0.999	>0.999	>0.999	0.729
CKD stage progression	>0.999	0.562	>0.999	>0.999	0.609	0.427
Osteoporosis	0.519	0.750	0.176	0.740	>0.999	>0.999
Bone fracture	0.664	0.138	0.272	0.213	0.516	0.595
Cataract	0.350	0.649	0.403	0.653	0.626	0.517
Glaucoma	>0.999	0.194	>0.999	0.279	>0.999	>0.999
Hepatic steatosis	>0.999	0.254	>0.999	>0.999	>0.999	>0.999
Hepatic cirrhosis	–	–	–	–	–	–
VTE	0.519	0.508	0.570	0.513	0.998	0.593
Depression	>0.999	>0.999	>0.999	0.156	>0.999	>0.999
Dementia	0.563	>0.999	0.359	>0.999	>0.999	0.826
Gastritis	>0.999	>0.999	>0.999	0.381	>0.999	0.357
Peptic ulcer	0.400	>0.999	>0.999	0.393	>0.999	>0.999
Esophagitis	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999
Pancreatitis	0.649	>0.999	>0.999	0.156	>0.999	>0.999

CKD, chronic kidney disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IMT, intima-media-thickness; PWV, pulse-wave velocity; VTE, venous thromboembolism.

discrimination, the presented significant correlations of CRP and fibrinogen at GCA onset reflect only the results on the number of newly developed glucocorticoid adverse effects after study inclusion. Additionally, as the same inflammatory parameters at study inclusion did not correlated with the number of newly developed glucocorticoid adverse effects anymore, the predictive role of CRP and fibrinogen on glucocorticoid adverse effect seem to be negligible. Glucocorticoid administration typically goes along with a reduction in inflammatory parameters. In a recent cohort study from Japan, however, 30% of patients with PMR still exhibited elevated values of inflammatory parameters above the norm after 52 weeks of therapy. The cumulative incidence of glucocorticoid dosage increase associated with elevated CRP levels was 34.9% over the 52-week follow-up period. Therefore, initially, we expected an association between inflammatory markers and the emergence of glucocorticoid adverse effects (33). Similarly, other studies have demonstrated that aortic PWV decreases and aortic PWV is correlated with the percentage change in plasma CRP in patients with GCA and PMR under glucocorticoid therapy (34, 35). Hafner et al. (36) reported that glucocorticoid administration in patients with GCA had been associated with a reduction of carotid IMT. The expectation that, conversely, increased values of PWV and IMT were associated with potential new-onset of glucocorticoid adverse effects could not be therefore confirmed. Other parameters of inflammation or endothelial dysfunction, including lymphocyte subsets, ADMA, SDMA or Aix, did also not correlate with number of newly developed glucocorticoid adverse effect assuming that other pathways than inflammation and endothelial dysfunction may contribute to adverse effects of glucocorticoids.

Limitations of this study are the retrospective study design, absent control group and the missing systematic screening for all respective glucocorticoid adverse effects at study inclusion and during follow-up. Especially, a sufficient discrimination if one of our defined potential glucocorticoid adverse effect was a genuine adverse effect or an undocumented comorbidity between the time of GCA onset and study inclusion cannot be made by this sub-study design. As mentioned above, potentially developed glucocorticoid adverse effects, which have been diagnosed and treated at a resident physician, were not documented in MEDOCS and may be missed by our chart review. Additionally, glucocorticoid adverse effects which may occurred prior to study inclusion but were documented by MEDOCS at a later stage may be unintentionally attributed as newly developed adverse effects. Furthermore, many glucocorticoid adverse effects are dose-dependent while this analysis did not evaluate the exact glucocorticoid dosage (37). In addition, cumulative dose of glucocorticoids could not be reliably recorded and a reliable discrimination between an underlying comorbidity prior to GCA diagnosis and a genuine potential previously known glucocorticoid

TABLE 5 Correlations of imaging and laboratory parameters at study inclusion with number of newly developed glucocorticoid adverse effects.

	Number of newly developed glucocorticoid adverse effects	
	r	*p*-value
PWV	0.018	0.848
Aix	0.079	0.389
Carotid IMT	−0.105	0.231
Femoral IMT	−0.015	0.828
Subclavian IMT	0.112	0.093
ADMA	0.029	0.739
SDMA	−0.082	0.354
CRP	0.042	0.628
ESR	−0.014	0.879
Fibrinogen	0.076	0.556
WBC	−0.083	0.335
Neutrophils	0.032	0.711
Monocytes	−0.134	0.120
Lymphocytes	−0.090	0.294
CD subtypes		
CD3 cells	−0.063	0.464
CD3 + CD4+ cells	−0.030	0.728
CD3 + CD8+ cells	−0.072	0.405
CD4/CD8 ratio	0.077	0.373
CD3-CD16 + CD56+ cells	−0.119	0.167
CD19 cells	−0.025	0.776
CD45 cells	−0.074	0.392
CD4+/CD28-cells	0.015	0.867
CD8+/CD28-cells	0.044	0.617

ADMA, asymmetric dimethylarginine; Aix, augmentation index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IMT, intima-media-thickness; PWV, pulse-wave velocity; SDMA, symmetric dimethylarginine; WBC, white blood cells.

adverse effect cannot be made due to the retrospective sub-study design. Thus, no associations about the cumulative glucocorticoid dose could be made although glucocorticoid adverse effects seem to be dose and time dependent (9–11). Moreover, potential bias by other concomitant drugs, like osteoporosis prophylaxis or disease-modifying anti-rheumatic drugs, or by other diseases which may influence the incidence of glucocorticoid adverse effects in this study needs to be mentioned, while exact therapy durations or dosages of concomitant drugs could not reliably recorded due to the retrospective sub-study design.

In conclusion, our study demonstrated high incidence rates of glucocorticoid adverse effects over a long-term observational period and suggesting that relapse of GCA may be a clinical predictor for the development of diabetes mellitus in GCA patients. Laboratory and imaging parameters are not suitable predictors for glucocorticoid adverse effects. Prospective studies with close monitoring and dosage documentation and clinical trials investigating further alternative treatment modalities are needed for a comprehensive understanding of the risk–benefit profile of glucocorticoid therapy and to mitigate the burden of glucocorticoid adverse effects while maintaining therapeutic efficacy in patients with GCA.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by ethics committee of the medical university of Graz. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LS: Formal analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. FH: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. AM: Formal analysis, Investigation, Resources, Writing – review & editing. MB: Resources, Supervision, Writing – review & editing. CD: Formal analysis, Investigation, Writing – review & editing. PJ: Data curation, Formal analysis, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Study Protocol
PUBLISHED 03 July 2024
DOI 10.3389/fmed.2024.1415076

OPEN ACCESS

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RECEIVED 09 April 2024
ACCEPTED 11 June 2024
PUBLISHED 03 July 2024

CITATION
Nielsen BD, Kristensen S, Donskov A, Terslev L, Dreyer LW, Colic A, Hetland ML, Højgaard P, Ellingsen T, Hauge E-M, Chrysidis S and Keller KK (2024) The DANIsh VAScultitis cohort study: protocol for a national multicenter prospective study including incident and prevalent patients with giant cell arteritis and polymyalgia rheumatica.
Front. Med. 11:1415076.
doi: 10.3389/fmed.2024.1415076

The DANIsh VAScultitis cohort study: protocol for a national multicenter prospective study including incident and prevalent patients with giant cell arteritis and polymyalgia rheumatica

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The DANIsh VAScultitis cohort study, DANIVAS, is an observational national multicenter study with the overall aim to prospectively collect protocolized clinical data and biobank material from patients with polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) diagnosed and/or followed at Danish rheumatology departments. A long-term key objective is to investigate whether the use of new clinically implemented diagnostic imaging modalities facilitates disease stratification in the GCA-PMR disease spectrum. In particular, we aim to evaluate treatment requirements in GCA patients with and without large-vessel involvement, treatment needs in PMR patients with and without subclinical giant cell arteritis, and the prognostic role of imaging with respect to aneurysm development. Hence, in GCA and PMR, imaging stratification is hypothesized to be able to guide management strategies. With an established infrastructure within rheumatology for clinical studies in Denmark, the infrastructure of the Danish Rheumatologic Biobank, and the possibility to cross-link data with valid nationwide registries, the DANIVAS project holds an exceptional possibility to collect comprehensive real-world data on diagnosis, disease severity, disease duration, treatment effect, complications, and adverse events. In this paper, we present the research protocol for the DANIVAS study.

Clinical trial registration: https://clinicaltrials.gov/, identifier NCT05935709.

KEYWORDS

giant cell arteritis, polymyalgia rheumatica, imaging, prognosis, cohort study (or longitudinal study), prospective observational study

Introduction

In recent years, research advancements in giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) have improved diagnosis and treatment approaches. Imaging tests have become integral in diagnosing GCA, improving diagnostic reliability, promoting fast diagnosis, and expediting treatment initiation, thereby reducing complications (1–10). Vascular ultrasound has high diagnostic accuracy, is a cheap and non-invasive procedure, and can be performed bedside. Therefore, vascular ultrasound of temporal and axillary arteries is recommended as a first-line diagnostic tool in patients suspected of GCA. A whole-body 18F FDG PET/CT and a cranial MR have comparable diagnostic properties and can be used as alternatives or in unresolved patients (9, 10). Few studies exploring the potential value of imaging in PMR have been performed (11–15), but recent reports suggest an overall benefit of early referral and specialist care of PMR patients (16–20). Additionally, new glucocorticoid-sparing treatment options for GCA and PMR have emerged, and several clinical trials are ongoing (18, 21).

Despite these improvements in GCA and PMR management, several unmet needs call for systematic prospective observational and long-term follow-up studies in real-world settings.

GCA and PMR have different initial glucocorticoid requirements, but a long-term glucocorticoid -tapering regime over 1–2 years is the treatment target for both diseases (6, 22, 23). However, relapses are frequent, and longer treatment is often required carrying a high risk of glucocorticoid adverse events (24–29). In addition, the risk of complications and the lack of valid clinical tools to assess activity imply a high risk of over-treatment. Specific indications for initiation and optimal timing of tapering or discontinuation of IL-6 inhibitor treatment remain unresolved (30–37). To select patients who gain the most from early add-on steroid sparring therapy and to guide treatment strategy, baseline stratification tools and disease activity biomarkers are highly needed.

Despite the diagnostic value of imaging and its sensitivity to change after the institution of glucocorticoids, its prognostic value and ability to discriminate remission and relapse in clinical routine care remain less clear (7, 9, 25, 38–41). Imaging facilitates new insight into disease distribution and severity that may have prognostic potential, as, for example, discriminating large-vessel and cranial vessel involvement in GCA or by identification of subclinical GCA in phenotypic PMR (42).

Epidemiologic studies and smaller cohort studies consistently report an increased risk of vascular complications such as aortic aneurysms and dissection later in the disease course of GCA (43–46). Although the development of aortic aneurysm and dissection can be fatal, incidence rates are still low and progression rates vary (46). Current guidelines only recommend screening for aortic complications on an individual basis but do not provide any guidance for the identification of patients at risk (6, 10, 47).

In Denmark, the optimal conditions for the establishment of a national GCA and PMR research collaboration exist. The highest incidences of GCA and PMR are found in the Scandinavian countries (24), and all GCA patients and many PMR patients are evaluated and diagnosed by a rheumatologist. In addition, within the Danish Rheumatology Society, established experience and infrastructure for clinical cohort studies in GCA and PMR and the Danish Rheumatologic Biobank are present (2, 8, 48, 49). In line with Danish and European guidelines, imaging has been gradually implemented, allowing imaging-based disease characterization. Furthermore, linkage to Danish nationwide administrative registries with data on, e.g., diagnosis, prescriptions, laboratory and pathology results, time, and cause of death is available and provide important complementary data (50). Alignment with similar European cohorts has been strived for when selecting data variables for the study and developing the DANIVAS data collection instrument. Taken together, the DANIVAS cohort study will include crucial data providing new insight into GCA/PMR management and disease course, with a particular emphasis on the prognostic value of imaging-based disease stratification. Even more, DANIVAS enables data comparison across cohorts and supports future international research collaboration.

In this paper, we present the protocol for the DANIVAS study.

Study design

A national multicenter prospective observational study of incident and prevalent patients with PMR and GCA diagnosed and/or followed at Danish rheumatology departments.

Descriptive clinical data are collected in a web-based, clinician-driven database, and blood samples are collected through the infrastructure of the Danish Rheumatologic Biobank. Complementary data are obtained from national administrative registries.

Study objectives

The overall aim of the DANIVAS cohort study is to improve disease control and reduce disease- and treatment-related damage in GCA and PMR. The study objective is to investigate the use of new diagnostic imaging modalities for facilitating disease stratification that can potentially predict treatment requirements and complications and hence guide management strategies. Specific primary, key secondary, secondary, and exploratory objectives are listed in Table 1.

On top of the specific research objectives, the systematic collection of prospective clinical data and biobank blood samples provides a fundamental basis for future research projects and a scientific framework for Danish GCA/PMR researchers and for international research collaborations.

Methods and analysis

Data collection and setting

Clinical data (including imaging, blood tests, and histology), demographics, patient-reported outcomes, and biobank samples will be collected at baseline and during follow-up for as long as patients are seen in the rheumatology departments. For an angiographic sub-study, structural damage of the aorta will be assessed in a subset of GCA patients 2 years after diagnosis. Data on long-term complications, comorbidity, death and migration, and time and amount of retrieved glucocorticoid prescriptions will be collected through Danish registries.

Patients will be treated according to the Danish national treatment guideline for GCA and PMR, which adhere to current European recommendations (6, 22, 23).

The study was registered in ClinicalTrials.gov (NCT05935709) on 28 June 2023.

TABLE 1 Catalog of study objectives.

Primary objective	
1	To compare cumulative GC doses in patients with isolated c-GCA as compared to LV-GCA (with or without c-GCA).
Key secondary objectives	
1	To compare cumulative GC doses in patients with pure PMR* compared to PMR patients with subclinical LV-GCA.
2	To compare the incidence of aortic dilatation 2 years after diagnosis in patients with c-GCA as compared to LV-GCA (with or without c-GCA).
3	In the subpopulation of patients in whom a diagnostic FDG PET/CT was performed at diagnosis, to evaluate the risk of aortic complications (aneurysms and dissections) in GCA patients with aortic involvement as compared to patients without aortic involvement.
Secondary objectives	
1	To compare treatment response, risk of relapse, need for GC-sparring add-on treatment, and disease duration in patients with c-GCA as compared to LV-GCA (with or without c-GCA).
2	To compare treatment response, risk of relapse, need for GC-sparring add-on treatment, and disease duration in patients with pure PMR compared to PMR patients with subclinical LV-GCA.
3	In the subpopulation of patients in whom a diagnostic FDG PET/CT was performed, to evaluate the association between aortic FDG uptake and aortic dilatation at year 2.
Exploratory objectives	
1	To identify clinical features associated with the different disease subsets, c-GCA, LV-GCA, and PMR.
2	To assess and evaluate risk factors and biomarkers predicting GCA in patients with PMR.
3	To assess and evaluate incidence, prevalence, and predictors of ischemic events and vascular complications in GCA patients.
4	To assess and evaluate incidence, prevalence, and predictors of comorbidity in GCA and PMR patients.
5	To assess and evaluate diagnostic strategies and implementation of diagnostic imaging in GCA and PMR.
6	To evaluate adherence to clinical guidelines.
7	To evaluate and predict treatment efficacy, safety, and predictors of treatment success, treatment failure, and maintenance of remission after therapy withdrawal.
8	To assess and evaluate risk factors and biomarkers predicting vascular complications in GCA.

*Pure PMR; PMR patient without cranial GCA symptoms, new-onset claudication, or GCA. c-GCA, cranial giant cell arteritis; LV-GCA, large-vessel GCA; PMR, polymyalgia rheumatica; GC, glucocorticoid; ^{18}F-FDG PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography.

Recruitment

Patients will be recruited from Danish rheumatology departments at routine visits either at the time of diagnosis or during the disease course.

Enrollment was initiated on 1 November 2023 from two centers in order to test the feasibility of study organization and data collection. Within the next year, all rheumatology departments at Danish hospitals will be invited to participate in the study. The last patient's first visit is expected by the end of 2039.

The potential for recruitment from Danish rheumatology departments is excellent. High referral rates can be expected according to the Danish national GCA and PMR management guidelines that encourage PMR evaluation by rheumatologists and recommend that all patients suspected of GCA are referred for prompt diagnostic evaluation by a rheumatologist, the latter including diagnostic imaging performed in a hospital setting.

Study population

Sample size

In-depth disease characterization by the time of inclusion, including reporting on vessel involvement according to imaging results, allows for both incident and prevalent GCA and PMR patients to contribute to the primary and secondary outcomes. A sample size calculation was made based on the primary outcome reaching a total number of 3,000 GCA patients to be included. Assuming a pooled standard deviation of 8,500 mg (24, 51), and an equal distribution between the groups (c-GCA and LV-GCA), each group requires 1,519 samples to achieve 90% power and a 5% significance level (two-sided) for detecting a true difference in mean cumulated glucocorticoid dose of 1,000 mg between the two groups. Based on incidence rates and the proportion of referrals, we expect to be able to include the same number of PMR patients (16, 18). Expecting subclinical GCA in 20% of PMR patients and assuming a similar pooled standard deviation (52, 53), 1,370 PMR patients are needed to achieve 90% power and a 5% significance level (two-sided) for detecting a true difference in mean cumulated glucocorticoid dose of 2000 mg between the two groups (PMR with and without subclinical GCA).

Eligibility

Patients can be included at any time during the disease course. By the time of inclusion, patients will be registered as either incident (newly diagnosed within the last 3 months) or prevalent (included during routine follow-up >3 months after and ≤ 5 years after diagnosis) cases. Inclusion criteria are as follows:

- GCA and/or PMR diagnosis established or confirmed by a rheumatologist (clinical expert opinion), and
- Speak and understand Danish, and
- Are able to give signed and dated informed consent.

Patients diagnosed with other systemic autoimmune diseases that out-rule the diagnosis of GCA or PMR and patients diagnosed >5 years ago will not be included.

For participation in the angiography sub-study, patients included more than 2 years after diagnosis or with contraindications for the angiography (claustrophobia, body weight > 150 kg, pacemaker, metallic foreign body, and eGFR<30) will not be included.

Visits

The study visit schedule is adapted to standard programs for managing PMR and GCA patients in routine clinical care. In routine rheumatology care in Denmark, GCA patients are typically followed up 2–12 months after treatment discontinuation, while the follow-up schedule for PMR patients varies. The study design is illustrated in Figure 1. The following study visits will be conducted:

- Enrollment visit: First visit to obtain informed consent and collect master data regarding diagnostic subgroup classification and demography.
- Response visit: Second visit 2 months after diagnosis (only incident patients).
- Routine study visits: Six months after diagnosis (incident patients and prevalent patients included <4 months after diagnosis) and subsequently every year as long as patients are seen at the rheumatology department.
- Aortic screening visit: Two years after diagnosis, screening for aortic complications will be performed
- Withdrawal visit: Visit to complete study participation due to stable drug-free remission or dismission from rheumatology care, patients' request, or in the event of death, migration, non-compliance, or if GCA/PMR diagnosis is dismissed.

Data collection

An overview of the data collection at each study visit is presented in Table 2. All procedures, but the 2-year angiography, are performed on clinical indication according to clinical guidelines as part of routine care. As not all routine care visits are necessarily performed as study visits, the data collection at each study visit also serves the purpose of summarizing disease-related medical events in the interim period.

Diagnostic information and referral history

Diagnostic information regarding symptom onset, presentation, referral history, diagnostic work-up, time and type of clinical diagnosis (GCA and/or PMR as considered by the treating physician), and initial treatment will be recorded by the time of enrollment.

For patients with a clinical diagnosis of GCA, it will be recorded if a diagnostic test, that is temporal artery biopsy, vascular ultrasonography, 18F FDG PET/CT, MR, or CT-angiography, was conducted or not, and if so, whether the result was positive, inconclusive, or negative for GCA diagnosis.

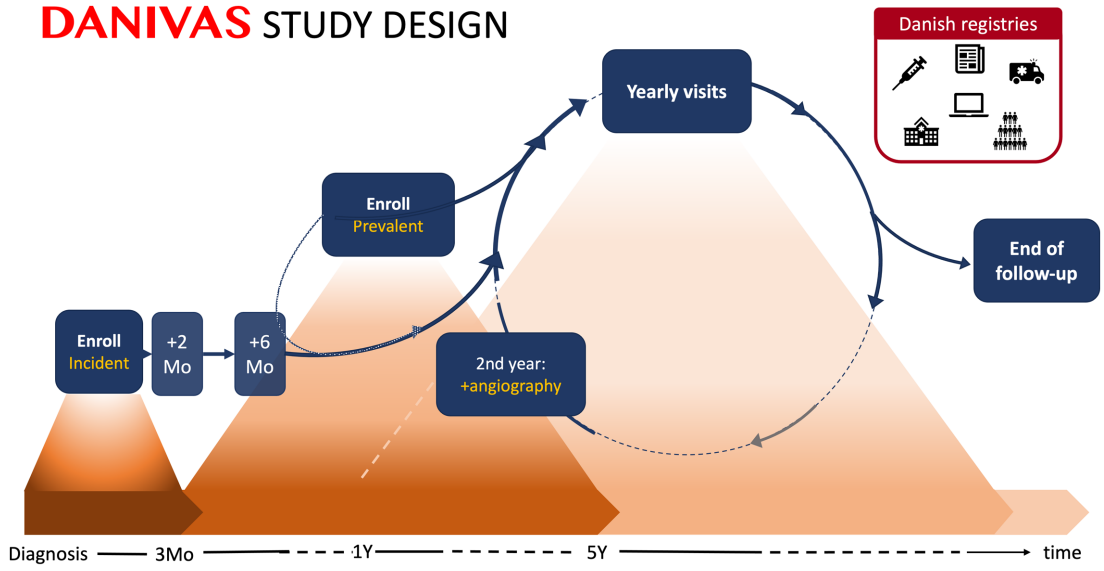

FIGURE 1
DANIVAS study design. Patients are enrolled at any time during their disease course (≤5 years disease duration) and will be registered as either incident (within 3 months of diagnosis) or prevalent. Study visits will be performed 2 (response visit) and 6 months after diagnosis (incident patients and prevalent patients included <4 months after diagnosis) and subsequently every year (all patients). At the 2-year follow-up, aortic angiography will be performed in a subset of GCA patients. Data collection for the enrollment visits and other study visits (2-month response visit, 6 months visit, and annual visits) are described in more detail in the '*Data collection*' section and Table 2. Clinical follow-up is terminated by the time of stable drug-free remission or dismission from rheumatology care, on patient's request or in the event of death, migration, non-compliance, or if the diagnosis is dismissed. Linkage of data across nationwide medical and administrative registries at the individual level will be performed to enrich outcome and covariate data. Mo, month; Y, year.

TABLE 2 Schedule of procedures and assessments at baseline, follow-up, and withdrawal.

Visit*		Enrollment visit	Response visit	Routine visit	Aortic screening visit	Withdrawal visit
Study procedures	**Time of visit (time from diagnosis)**	Diagnosis	2 Mo	6th and every 12 Mo	2 Y	
	Margin	+ 5 years	+/−1 month	+/− 2 months	+/− 6 months	
	Attendance data	X	X	X		X
	Eligibility and consent	X				
	Demography	X				
	Diagnostic characteristics, including disease stratification	X	(X)	(X)	X	X
	Clinical evaluation		X	X	X	X
	Medicine and adverse events		X	X	X	X
	Complications		X	X	X	X
	Comorbidity		X	X	X	X
	PROMs		X	X	X	X
	Laboratory tests including biobank		X	X	X	X
	Angiography of aorta				X	
	Reason for withdrawal					X
	Optional §					
	Musculoskeletal ultrasound	X	X	X		
	Vascular ultrasound	X	X	X		
	[^{18}F] FDG PET/CT	X	X	X		
	TAB	X				

*Type of visit (enrollment, response, routine study, aortic screening, and withdrawal) is described in the section 'Visits'. An enrollment visit is always performed together with a response or routine visit. Response visit is performed in incident patients after treatment initiation. Routine study visits will be performed as long as patients are followed in the rheumatology outpatient clinic. Withdrawal visit procedures will be performed in all cases where it is possible. Reason for withdrawal will always be obtained. §Imaging and/or TAB is performed at the physician's discretion and on clinical indication. The type of imaging, e.g., diagnosis may vary depending on the patient and the study site. MO, months; Y, years; PROMs, patient-reported outcome measures; [^{18}F] FDG PET/CT, ^{18}F-FDG PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography with computed; TAB, temporal artery biopsy.

For patients with a clinical diagnosis of PMR, it will be recorded if the following diagnostic tests either supporting PMR or excluding differential diagnosis was performed: musculoskeletal hip and shoulder ultrasonography, 18F FDG PET/CT, negative vascular ultrasonography, computed tomography of chest, abdomen, and pelvis, or other investigation to evaluate potential malignancy. Assessment of the variables included in the 2022 ACR/EULAR classification criteria for GCA and/or 2012 EULAR classification criteria for PMR will be registered.

Definition of imaging-based disease stratification groups

The Danish Society of Rheumatology endorses adherence to EULAR recommendations regarding the diagnostic evaluation of patients suspected of GCA and/or PMR (6, 10, 23). Consequently, we expect GCA patients to have at least one vascular imaging procedure performed, and in case of negative or inconclusive results. That additional tests to confirm diagnosis will be made. Vascular ultrasonography, including the assessment of temporal and axillary arteries as a minimum, is performed by trained rheumatologists, and recommended technical and procedural requirements are met (10, 54). Diagnostic conclusions are made according to OMERACT definitions (55). Recording of other imaging and pathology results relies on the radiology/pathology report and is interpreted according to procedural recommendations and accepted diagnostic criteria (56, 57).

GCA patients with a positive imaging test or histology will be categorized according to vessel involvement as 'c-GCA' and/or 'LV-GCA'. C-GCA is defined as the involvement of cranial arteries including, but not limited to temporal, facial, occipital, maxillary, and vertebral arteries, whereas LV-GCA is defined as the involvement of extracranial large arteries including but not limited to aorta and/or its primary branches (e.g., carotid, subclavian, axillary, and femoral arteries). If applicable, the presence or absence of aortitis will be recorded.

In patients with concomitant GCA and PMR, it will be recorded if GCA is subclinical, that is vasculitis is diagnosed by imaging or histology in the absence of cranial or claudication symptoms attributed to GCA (12).

Diagnosis and disease stratification will continuously be revised according to diagnostic test results available (at study visits and retrospectively).

Demography

Age, gender, height, weight, and history of smoking and alcohol consumption will be recorded at enrollment.

Clinical evaluation

New or persistent symptoms and findings of GCA and (58) will be recorded at each visit if present. Cranial symptoms and findings recorded include headache, scalp tenderness, jaw or tongue

claudication, visual disturbances (sight loss, amaurosis fugax, and double vision), abnormal temporal artery (tender, swollen, and pulseless), scalp necrosis, transient ischemic attack, or stroke. Large-vessel symptoms include arm or leg claudication, carotidynia, brachial blood pressure difference > 10 mmHg, pulselessness, or large-vessel bruits. PMR symptoms and findings recorded include symmetric shoulder pain and stiffness, symmetric hip pain and stiffness, mobility of upper arms, PMR activity score (58), RS3PE (remitting seronegative symmetrical synovitis with pitting edema), and peripheral arthritis. Constitutional symptoms include fever, weight loss, night sweats, and malaise. New symptoms are defined as new onset or worsening within 4 weeks, whereas symptoms lasting without worsening for >4 weeks are considered persistent. The physician's assessment of disease activity based on clinical evaluation (physician NRS and physician disease activity category; remission, potential relapse without treatment escalation, relapse (treatment escalation), and refractory disease) will be recorded. Relapses will be categorized as minor or major according to EULAR definitions (10). Any relapse that leads to treatment intensification since the last study visit will also be recorded.

Medical history and adverse events

At each visit, the current dose of glucocorticoid, tsDMARD, and/or bDMARD treatment and changes since the last visit are recorded. Date of start, change, and discontinuation of immunosuppressive therapy and reasons (start or increase: risk of disease complications, refractory disease, repeated relapses, relapse on unacceptable high glucocorticoid doses, adverse effects from other immunosuppressive therapy, and comorbidity. Discontinuation or decrease: remission, adverse events, or no effect) for these will be recorded.

Complications

At each visit, potential disease-related complications, including visual impairment and vascular complications including aortic dilatation and aortic dissection, and the time of the event will be recorded.

Comorbidity

Comorbidity including cardiovascular disease, hypertension, hypercholesterolemia, diabetes, chronic kidney disease, osteoporosis, chronic lung disease, infections, or malignancies will be recorded at the baseline visit. Routine clinical monitoring of HbA1c levels and results of DXA scans will be recorded continuously.

Patient-reported outcome measures (PROMs)

At each visit, patients will be asked to report their global disease activity [Numerical Rating Scale (NRS), 0–10] and the duration of morning stiffness (minutes) will be recorded.

Laboratory tests and biobank

Routine blood analysis, including C-reactive protein and glycated hemoglobin (HbA1c), will be performed as a standard of care. Additionally, biobank blood samples for future research purposes are collected by the infrastructure of the clinical biobank *Danish Rheumatologic Biobank* under the interregional Bio- and Genome Bank Denmark. Biobank blood samples will be collected at each study visit.

Aortic screening visit

In a subpopulation of GCA patients, an aortic angiography will be scheduled 2 years after diagnosis to screen for aortic dilatation and aneurysms. The angiography can be performed as either CT or MR angiography and will be performed according to local set-up and imaging acquisition protocols. Subsequent aortic imaging will be performed on clinical indications at an individual basis at the discretion of the treating physician.

Linkage with registries

Danish residents receive a unique 10-digit civil registration number by the time of birth or immigration that ensures the linkage of data across nationwide health and administrative registries at the individual level (Table 3). This linkage will ensure the collection of data on events, and treatment occurring after consultations in rheumatology departments has been terminated as well as the follow-up time.

The cumulated dose of glucocorticoid, time of glucocorticoid treatment, and potential treatment-free remission will be estimated based on redeemed prednisolone prescriptions obtained through the Danish National Prescription Registry (DPR).

Linkage with the Danish National Patient Registry (DNPR), the Danish Cause of Death Registry, The Registry of Laboratory Results for Research (LABKA), and the Danish Civil Registration System is performed to enrich data regarding vascular complications, treatment-related complications, potential confounding diseases, time to event, death, immigration, or censoring.

Outcomes and data analysis plan

Primary outcome

1 Cumulative glucocorticoid doses will be calculated based on redeemed prescriptions from the time of diagnosis to the end of follow-up (date of data extraction, death, or emigration). The difference between LV-GCA (with and without c-GCA) and isolated c-GCA, as characterized in the DANIVAS database will be compared by Student's t-test or Wilcoxon Mann–Whitney U-test.

Key secondary outcomes

1 Cumulative glucocorticoid doses will be calculated based on redeemed prescriptions from the time of diagnosis to the end of follow-up (date of data extraction, death, or emigration). The difference between patients with pure PMR compared to PMR patients with subclinical LV-GCA will be compared by Student's t-test or Wilcoxon Mann–Whitney U-test.

2 The incidence of aortic dilatation 2 years after diagnosis in patients with isolated c-GCA as compared to LV-GCA (with or without c-GCA) will be compared by chi-square test. Incidences will be calculated as proportions, that is events per patient at risk, and as incidence rates, that is number of events divided by the sum of the person-time of the at-risk population. Associated 95% binomial confidence intervals will be calculated.

3 The risk of aortic complications (aneurysms and dissections) in GCA patients with aortic involvement as compared to

TABLE 3 Data from national registries.

Outcomes	Type of data	Registry	Time period
Primary outcome	Redeemed prednisolone prescriptions including time of redemption, dosage, number of packages, number of tablets	Danish National Prescription Registry	From index date* to death, emigration, or end of follow-up
Secondary outcomes	Aortic aneurysm, dissections, peripheral artery disease, aortic surgery, amputation	Danish National Patient Registry (DNPR)	From 5 years before the index date to death, emigration, or end of follow-up
		The Danish Cause of Death Registry	Index date to death
Exploratory	Vascular complications: Aortic aneurysm, dissections, peripheral artery disease, aortic surgery, amputation, blindness, low vision, visual disturbances, acute myocardial infarction, ischemic stroke, percutaneous coronary intervention (PCI), and coronary artery bypass grafting	Danish National Patient Registry (DNPR)	From 5 years before the index date to death, emigration, or end of follow-up
		The Danish Cause of Death Registry	Index date to death
	Safety: Osteoporosis and osteoporotic events, infections, hypertension, myopathy, adrenal insufficiency, psychosis, gastrointestinal perforation, peptic ulcer, avascular necrosis, cataract, glaucoma	Danish National Patient Registry (DNPR)	From 5 years before index date* to death, emigration, or end of follow-up**
	Cause of death	The Danish Cause of Death Registry	Index date to death
Covariates	Diagnoses contained in the Charlson Comorbidity Index**	Danish National Patient Registry (DNPR)	From 5 years before the index date to death, emigration, or end of follow-up
	HbA1c and cholesterol (total, LDL, HDL, and triglycerides)	The Registry of Laboratory Results for Research	From 5 years before the index date to death, emigration, or end of follow-up
Follow-up time estimation	Death and emigration	Danish Civil Registration System	From index date to end of follow-up

* Index date; Date of diagnosis. **The exploratory outcomes will be evaluated after 5 years and by the end of follow-up. **Charlson comorbidity index (59): Myocardial infarction, congestive heart disease, vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes, hemiplegia, renal disease, tumor (+/−metastatic) leukemia, lymphoma, AIDS.

patients without aortic involvement (in the subpopulation of patients diagnosed by PET/CT) will be compared by chi-square test and the association between baseline aortic FDG uptake intensity and aortic diameter at year 2 will be evaluated by linear regression or Spearman correlation.

For the primary and key secondary outcome 2, subgroup analysis will be performed on patients diagnosed with PET/CT and ultrasound, respectively. In addition, an analysis comparing cumulative glucocorticoid doses in isolated LV-GCA as compared to patients with c-GCA (with or without LV-GCA) will be performed.

Study organization, collaboration, and patient involvement

DANIVAS is led by a steering committee who has the overall scientific, organizational, and economic responsibility for DANIVAS. A DANIVAS research collaboration network of researchers within the field of GCA and PMR is built and will facilitate new research projects building upon the infrastructure of, and the teamwork within, DANIVAS.

Two patient research partners will be part of the steering committee. Patient research partners will be included in the research project according to" the European League Against Rheumatism recommendations for the inclusion of patient representatives in scientific projects" (60). In the selection of potential patient partners, communication skills, motivation, and constructive assertiveness in a team will be taken into account. Patient partners will prospectively ensure patients' perspective on the relevance, feasibility, and added value of research initiatives as well as contribute to any needed adjustment of the study organization.

Through international research networks within the field of GCA and PMR, alignment of data collection with related European prospective GCA/PMR cohorts that are currently being developed was strived for in order to facilitate data comparison and future collaboration.

Data collection and management

Data collection is documented in the individual electronic Case Report Form. To ensure high data completeness, the data manager at the Department of Rheumatology, Aarhus University Hospital, monitors data completeness and a built-in notifications system automatically sends alerts to the site investigators in case of missing visits and, if unsolved, ultimately to the data manager.

Discussion

Although the implementation of diagnostic imaging has increased the awareness of the impact of disease extent and severity and led to the interpretation of GCA and PMR as overlapping diseases with a

spectrum of disease manifestations and treatment requirements, the clinical impact on management and the therapeutic consequences remains mainly unsolved (42, 47).

Higher relapse rates or longer treatment needed for LV-GCA as compared to c-GCA has been reported in some studies (61–66), but not in all (67–70). In general, many of these studies are small, retrospective, and prone to selection or misclassification bias. Therefore, data to fully support early initiation of glucocorticoid-sparring therapy based on stratification by vessel involvement are still lacking.

Subclinical GCA occurs in approximately 20% of PMR patients (52, 53). However, many of these studies were performed in selected cohorts, questioning the true incidence. Nevertheless, a recent study reported higher relapse rates for PMR patients with subclinical GCA as compared to pure PMR patients (13) and smaller studies indicated a noteworthy risk of ischemic complications in this subgroup (71, 72). Accordingly, the routine diagnostic approach for patients with suspected PMR and the standard of care needed for patients with subclinical GCA need further evaluation (13).

Prospective long-term observational data of larger cohorts that allow for the evaluation of risk factors and prognostic biomarkers to identify patients at risk of aortic aneurysms and dissection and to reduce numbers needed to screen are lacking. Screening for aortic aneurysm would allow for timely surgical intervention to prevent aortic rupture. Although the relative risk for aortic rupture in GCA is high, the overall incidence rate is still low and time to event uncertain, challenging the development of screening algorithms (22, 46). Recent studies have indicated a positive association between the presence of vessel inflammation and subsequent vessel damage and a potential prognostic role of the presence of large-vessel involvement and the risk of aortic aneurysms (39, 45, 73, 74).

With systematic disease characterization including diagnostic imaging, which is highly implemented in the clinical care of GCA and PMR in Denmark, the DANIVAS cohort study provides essential data to address these needs.

Important differences between the results of real-world observational studies and RCT or single-center expert studies in GCA and PMR have been found and call for high-quality real-life data (2, 31, 75). Moreover, the potential drawbacks of smaller single-center cohort studies such as selection bias, lack of statistic power, and limited external validity can be overcome by a protocolized prospective national cohort study including GCA and PMR patients from both secondary and tertiary hospitals. The linkage of clinical data, including comprehensive disease characteristics, and registry data on an individual level provides unique insight into GCA and PMR disease courses. Hence, the DANIVAS cohort study holds the potential to improve diagnostic strategies and identify biomarkers of disease activity and prognosis, possibly providing tools to be implemented in daily clinical practice to personalize treatment strategies and hence improve effectiveness and safety. Moreover, translation and validation of the newly developed GCA-PRO and steroid-PRO to Danish versions are currently being performed. Incorporating these into DANIVAS in the future will gain supplementary information reflecting the impact of disease and its treatment on health-related quality of life (HRQoL) from the patient's perspective (76, 77).

As a nationwide study aiming for inclusion and registration in everyday clinical care of patients with GCA and PMR in hospitality settings both with and without research experience within the field, the study comes with potential limitations. First, inclusion and data collection rely upon the clinician's effort and may compete with other clinical obligations. Consequently, we cannot ensure all GCA and PMR patients are enrolled in the study. Careful pragmatic selection of data variables to be collected has been performed in order to ensure feasibility in a clinical context. However, this may also exclude appreciated but non-essential characteristics or confounders or outcomes. For instance, we did not find it possible to prioritize the collection of detailed vascular ultrasound data including the newly developed OGUS score or the complete set of variables included in the glucocorticoid toxicity index. For the latter, selected items can be obtained through the linkage with registries. Clinical data collection feasibility is currently being tested by clinicians, and data collection instruments and variables are adjusted if needed.

Although the majority of patients diagnosed with GCA are seen in hospital settings, and current guidelines endorse rheumatologic diagnostic evaluation of PMR patients also, not all patients with PMR are seen or followed in secondary care and the PMR cohort may be prone to selection bias toward more complicated cases.

Although imaging is recommended to establish GCA diagnosis and supplementary tests should be performed in patients with negative or inconclusive results, a smaller proportion of patients with a clinical diagnosis of GCA may not have a positive diagnostic test that allows stratification into defined disease subsets. Our primary outcome will be analyzed in patients that can be categorized based on diagnostic tests as described. A sensitivity analysis including patients with negative diagnostic tests will be performed stratifying these patients according to clinical symptoms.

Routine diagnostic imaging for GCA includes both cranial and large-vessel assessment. However, only evaluation of selected cranial and large vessels is needed to establish a diagnosis, potentially misclassifying some patients. However, it is well established that including axillary artery assessment, which is currently part of routine vascular ultrasonography examination in GCA, increases overall sensitivity (9) and also that axillary ultrasound depicts the majority of LV-GCA patients when PET/CT is used as a reference diagnosis(8). Screening for subclinical GCA in PMR is a matter of debate and may not need to be assessed in all PMR patients. However, diagnostic imaging is increasingly implemented in Denmark and cranial and large-vessel diagnostic imaging is performed in the majority of GCA patients and is increasingly used to assess for vessel involvement in PMR.

The timing of aortic damage evaluation was decided to address that the risk of aortic damage appears to be present from the time of diagnosis (39, 74, 78), with the cumulative incidence rising almost linearly over time (46) and to minimize death as a competing risk. Finally, it was considered feasible, to plan a 2-year follow-up imaging visit within the time frame of routine rheumatology care, minimizing loss to follow-up. Nevertheless, the timing also implies a risk of missing damage that is not yet detectable.

In September 2023, DANIVAS held its first annual DANIVAS research symposium to officially launch the DANIVAS cohort study to a broader audience of researchers and clinicians of the Danish rheumatology community and several rheumatology departments nationwide have committed to being part of the DANIVAS study. In November 2023, the first GCA and PMR patients were enrolled in the DANIVAS study. Within the next year, more Danish centers will

be enrolled. On a longer perspective, the DANIVAS study is designed to improve the care and outcomes for patients with GCA and PMR.

Ethics statement

The study has been conducted in full conformance with the principles of the Declaration of Helsinki. The Central Denmark Region Committees on Health Research Ethics (reference number 1–10–72-174-22) have approved the DANIVAS study protocol. The DANIVAS study is registered in the Danish Central Region internal list of research projects (reference number 1–16–02-470-22). All patients included in the study gave their written informed consent.

Author contributions

BN: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. SK: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing, Validation. AD: Investigation, Methodology, Project administration, Writing – review & editing. LT: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. LD: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. AC: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. MH: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. PH: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. TE: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. E-MH: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Writing – review & editing. SC: Investigation, Methodology, Project administration, Writing – review & editing, Conceptualization. KK: Funding acquisition, Investigation, Methodology, Project administration, Writing – review & editing, Conceptualization.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The study has received grants for the establishment and implementation of the database from AbbVie (Agr-2021-731-16898) and The Danish Rheumatism Association (R214-A8127). The funders were not involved in the study design, data collection or analysis plan, the writing of this article, or the decision to submit it for publication.

Conflict of interest

BN has received speaker's fees from Novartis and AbbVie. AC has received research grants from Novartis, Janssen, GSK, Syneos, and personal fees from UCB. LT has received speaker's fees from Janssen, Pfizer, and Novartis. LD has received a research grant (paid to the institution) from BMS and AbbVie outside the present work; travel expenses from Janssen, UCB, and Boehringer Ingelheim. MH has received a research grant (paid to Institution) from AbbVie, BMS, Eli Lilly, MSD, Pfizer, Sandoz, and Novartis; speaker's fee (paid to Institution) from Medac, Pfizer, Sandoz, and speaker's fee (personal) from Novartis. E-MH has received fees for speaking and/or consulting from Novo, Novartis, and SynAct Pharma; research funding to Aarhus University Hospital from Novo Nordic Foundation, Galapagos, AbbVie; travel expenses from Pfizer, Sobi, and AbbVie. SC received speaker's fee from Pfizer, Novartis, and Roche.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 10 July 2024
DOI 10.3389/fmed.2024.1431385

OPEN ACCESS

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RECEIVED 11 May 2024
ACCEPTED 26 June 2024
PUBLISHED 10 July 2024

CITATION
Skoog J, Svensson C, Eriksson P, Sjöwall C and Zachrisson H (2024) High-frequency ultrasound with superb microvascular imaging: a potential tool for ultrasound assessment in patients with giant cell arteritis. *Front. Med.* 11:1431385. doi: 10.3389/fmed.2024.1431385

High-frequency ultrasound with superb microvascular imaging: a potential tool for ultrasound assessment in patients with giant cell arteritis

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Objective: The objective of this study was 2-fold: first, to evaluate whether superb microvascular imaging (SMI) could be used to visualize neovascularization in temporal arteries, and, second, to evaluate the diagnostic performance of high frequency ultrasound with SMI using an extended protocol in patients with suspected giant cell arteritis (GCA).

Methods: This retrospective study comprised 120 patients consecutively examined with an extended CDU protocol (temporal, facial, axillary, subclavian, brachiocephalic, and carotid arteries) between 2020 and 2022. Of all patients, 107 had no previous GCA diagnosis and 13 had a previous GCA diagnosis. SMI was used to evaluate neovascularization in the temporal arteries. Arteritis were characterized as low- or medium-echogenic, homogeneous wall thickening, with or without a positive compression sign in the temporal arteries. The Halo count, i.e., the number of temporal and axillary artery segments with signs of arteritis, was evaluated. The reference was clinically diagnosed GCA confirmed after ≥6-month follow-up.

Results: Of the eligible 107 patients with new suspected GCA, 33 (31%) received a clinical GCA diagnosis. Neovascularization was detected in 14 patients (43%). Patients with neovascularization displayed a higher halo count [median 6 (25th–75th percentile 4.75–7) vs. 3 (2-4-4), $p = 0.005$]. CDU of only the temporal arteries showed sensitivity and specificity (95% confidence intervals) of 94% (80–100%) and 100% (95–100%), respectively. The addition of extra-cranial arteries increased the sensitivity to 100%. Of the 13 patients investigated for suspected relapse, three had a clinically confirmed relapse. One of them displayed neovascularization together with other signs of inflammation.

Conclusions: We show for the first time that inflammatory neovascularization of the temporal arteries can be detected by SMI. Neovascularization is associated with a more-widespread cranial disease. The value of neovascularization should be further investigated, especially for the detection of GCA relapse.

KEYWORDS

giant cell arteritis, color duplex ultrasound, large vessel vasculitis, superb microvascular imaging, neovascularization

Introduction

Giant cell arteritis (GCA) is a systemic vasculitis that mainly targets larger arteries (1). Temporal artery biopsy (TAB) has long been regarded as the gold standard for diagnosing GCA. However, the latest recommendations from European Alliance of Associations for Rheumatology (EULAR) are to use color duplex ultrasound (CDU), if available, as the initial diagnostic modality (2). Recently, several studies have validated CDU including the temporal and axillary arteries, for the diagnosis of GCA (2–4). Data for more extended CDU protocols that include additional extra-cranial vessels are scarcer but have shown improved sensitivity with retained high specificity for GCA (5–7). During the past few years, ultrasound equipment has been refined. Modern high-frequency probes that give higher resolution are increasingly available. Furthermore, novel ultrasound imaging modalities, such as superb microvascular imaging (SMI), have been developed (8). SMI is a technology that is based on an algorithm that identifies and separates tissue movements (clutter) from low-flow components. Conventional Doppler identifies high velocity arterial blood flow, whereas SMI identifies low-velocity blood flow, enabling assessments of the micro-circulation (8). This seems interesting from the pathophysiological point-of-view because ingrowth of the vasa vasorum and extension of neovascularization into the media have been associated with inflammation in patients with GCA (9–11). SMI has been used as an inflammatory marker in Takayasu's arteritis (TAK), where neovascularization in the vessel wall has been associated with active TAK disease (12–14). Vessel wall vascularisation with SMI in cases of active TAK has also been shown to correspond to fluorodeoxyglucose (FDG) uptake in positron emission tomography (PET) (8). However, only a few case reports have evaluated SMI in patients with suspected GCA, and the temporal artery has not been investigated (15, 16). The objective of this study was 2-fold: first, to evaluate whether superb microvascular imaging (SMI) could be used to visualize neovascularization in temporal arteries, and, second, to evaluate the diagnostic performance of high frequency ultrasound with SMI using an extended protocol in patients with suspected giant cell arteritis (GCA).

Materials and methods

Study population

This retrospective study comprised 120 patients who were consecutively examined with CDU at the Department of Clinical Physiology, Linköping, Sweden, between October 2020 and April 2022. Of these 120 patients, 13 had a previous GCA diagnosis in which CDU was conducted as a follow-up examination, and 107 patients had no previous GCA diagnosis and CDU was performed due to clinically suspected GCA. The diagnosis of GCA was based on both the CDU results and clinical parameters (17). Patients were classified as having GCA if the 1990 American College of Rheumatology (ACR) criteria were satisfied (18), and/or if the patients had the typical ultrasound picture of arteritis characterized by low- or medium-echogenic, homogeneous, wall thickening combined with increased levels of CRP and/or higher erythrocyte sedimentation rate (ESR) and regression of the initial symptoms after treatment with corticosteroids. Digital medical records at least 6 months after the CDU were reviewed by an experienced rheumatologist (P.E.), not responsible for the clinical care of the patients. Final clinical diagnosis of arteritis was assessed based on the re-evaluation of all digital medical records comprising both clinical and laboratory data. However, the patients were treated by different physicians and a standardized clinical protocol was not used. The 6-month clinical follow-up used as the reference diagnosis in the present study is commonly applied in studies of GCA (19, 20). Patients with clinically suspected GCA were excluded if they (i) died or migrated within 6 months after the CDU; or (ii) were treated with high doses of steroids more than 2 months preceding the CDU.

CDU assessment

The Canon Aplio i800 (Canon Medical Systems, Tochigi, Japan) high-frequency ultrasound system with linear transducer i11LX3 and hockeystick transducer i22LH8 were used for the ultrasound measurements. The protocol has previously been described in detail, also including extra-cranial vessels (7, 21–23). Additionally, color SMI was employed to scan the temporal arteries. The SMI settings were configured with a velocity scale of 1.1 cm/s, a color frequency of 12 MHz, a color filter set to 4, and a frame rate of 56 fps. In brief, bilateral examinations of the three branches of the temporal artery (common superficial artery, parietal, and frontal branches) and the facial artery, as well as the axillary, subclavian, brachiocephalic and carotid arteries were conducted. The intima-media thickness (IMT) was measured in the common superficial temporal, axillary, subclavian and carotid arteries. Atherosclerotic plaques were evaluated and defined as focal areas in the vessel wall where IMT demonstrated an increase of either 0.5 mm or 50% compared to the IMT in the adjacent wall. One experienced vascular technologist performed the CDU examinations as part of a standardized routine examination. The same vascular technologist and one physician reviewed the CDU examinations.

Interpretation of inflammation in the CDU assessments

Increased IMT with low- or medium-echogenic, circumferential, homogeneous wall thickening in at least one vessel with or without a positive compression test were considered as typical signs of arteritis. In this study, SMI was used to visualize neovascularization, which was considered to be indicative of active inflammation (8). Furthermore, low- or medium-echogenic areas outside the vessel wall, as well as sub-intimally, were interpreted as inflammatory oedema. Increased IMT with hyper-echogenic areas was assumed to represent long-standing inactive arteritis (24). However, a mixture of hyper-echogenic and low-/medium-echogenic wall thickening may be observed in cases of relapsing arteritis. The number of affected arteries was assessed, and the halo count (between 0 and 8) was calculated for the temporal an axillary arteries in accordance with the report of van der Geest et al. (20).

TABLE 1 Patients' characteristics and comparison between patients with and without giant cell arteritis.

Patients' characteristics	Patients with GCA ($n = 33$)	Patients without GCA ($n = 74$)	p-value
Age, median (range) years	76 (63–92)	73 (44–89)	0.006
Female, n (%)	21 (64)	47 (64)	1.0
Smoking, n (%)	2 (6)	6 (8)	1.0
Clinical characteristics, n (%)			
New headache	23 (70)	38 (62)	0.093
Jaw claudication	12 (36)	3 (4)	<0.0001
Reduced or lost vision	5 (18)	11 (15)	1.0
Double vision	1 (3)	1 (1)	0.52
Temporal artery abormalities[a]	20 (61)	21 (29)	0.0024
Joint pain	8 (24)	33 (45)	0.054
Fatigue	16 (49)	20 (28)	0.045
Loss of appetite	7 (21)	12 (16)	0.59
Weight loss > 2 kg	11 (33)	11 (15)	0.15
Temp > 38.5°C	2 (6)	1 (1)	0.22
Laboratory findings[b]			
ESR, mm/h, median (range)	72 (15–119)	56 (2–106)	0.017
CRP, mg/L, median (range)	48 (4–225)	19 (4–173)	0.030
Comorbidities, n (%)			
Hypertension	21 (64)	40 (55)	0.40
Diabetes mellitus	13 (39)	14 (19)	0.031
Hyperlipidaemia	13 (39)	24 (32)	0.52
Myocardial infarction	4 (12)	7 (10)	0.74
Cerebrovascular disease	4 (12)	5 (7)	0.45
Peripheral artery disease	2 (6)	0 (0)	0.093

[a]Tenderness, pain, swelling or decreased pulsations.
[b]Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured before initiation of high-dose glucocorticoid treatment.

Statistical evaluation

Data are presented as numbers and percentages or median with min and max value or the 25th and 75th percentiles. Differences between patients with or without GCA were evaluated with the Mann-Whitney U-test. Categorical variables were tested with Fisher's exact test. The sensitivity and specificity (95% CI) of CDU were calculated using the clinical GCA diagnosis after 6 months as reference. Statistical analyses were carried out using the SPSS 27.0 for Windows software (IBM Corp., Armonk, NY, USA). Differences with p-values < 0.05 were considered statistically significant.

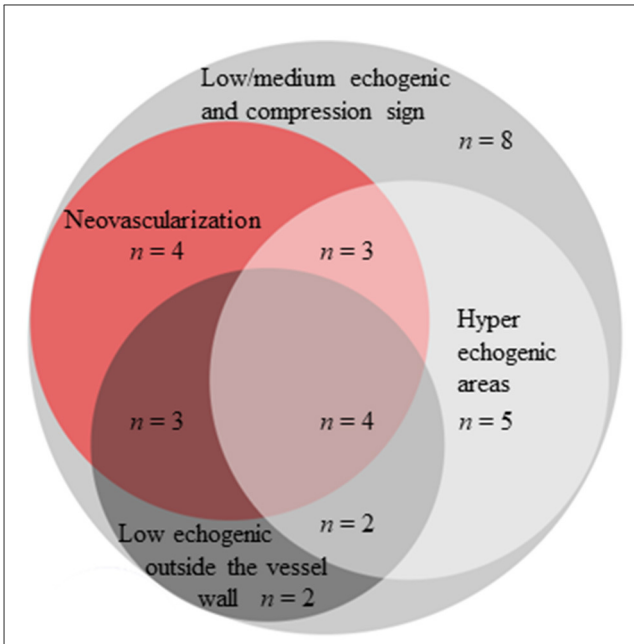

FIGURE 1
Morphological findings in the temporal arteries of patients with GCA using high-frequency ultrasound and SMI.

Ethical considerations

The study was performed according to the Declaration of Helsinki, and the study protocol was approved by the Regional Ethical Board in Linköping (Decision number, 2013/33-31). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Results

Demographic and clinical features of patients with suspected GCA

In total, 107 patients without a previous diagnosis of GCA were included and examined with an extended CDU protocol. One patient who died within 6 months of the CDU examination was excluded from the final analysis. The median age (range) of the participants was 74 (48–92) years, and 68 (64%) were females and 33 (31%) received a clinical diagnosis of GCA based on an evaluation that was conducted ≥ 6 months after the CDU. The baseline characteristics of the patients are detailed in Table 1. Temporal artery abnormalities, jaw claudication, and symptoms of fatigue were seen more frequently in patients who received a GCA diagnosis, and these patients had higher levels of CRP and ESR and were older. The 1990 ACR criteria were

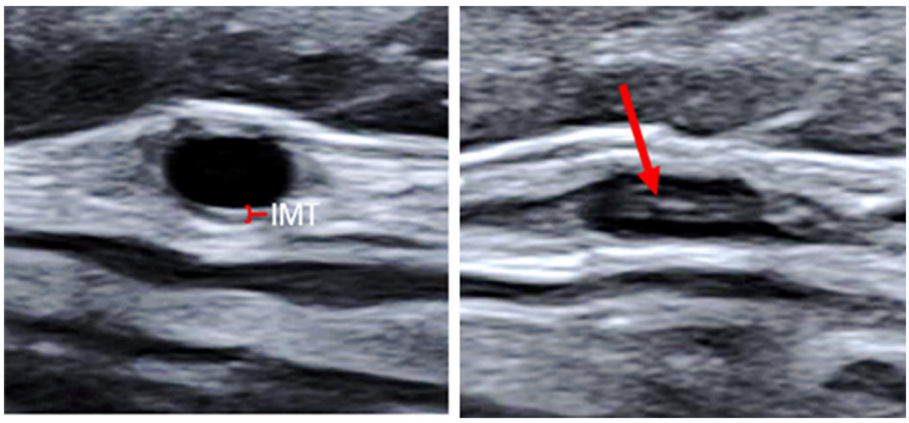

FIGURE 2
Transverse ultrasound images of the common superficial temporal artery. Non-compressed to the left (the red mark indicates the normal thin IMT), and compressed to the right. The high-echogenic part (red arrow) in the middle of the compressed vessel is the intima from the near and far wall pressed together. IMT, Intima-media thickness.

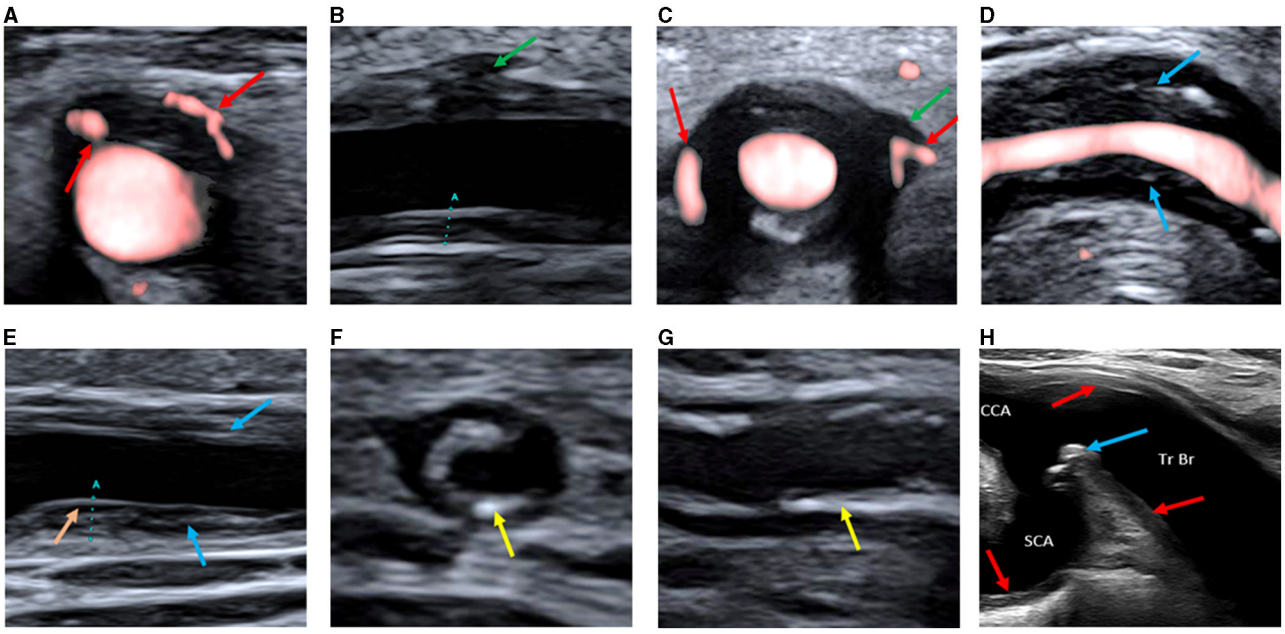

FIGURE 3
(A) Transverse ultrasound image of the common superficial temporal artery showing increased vessel wall thickness with hypoechogenicity and neovascularization in the wall (red arrows). **(B)** Longitudinal ultrasound image of the common superficial temporal artery showing a hypo-low-echogenic area outside the vessel wall (interpreted as inflammatory oedema, green arrow). The marker **(A)** is the IMT measurement. **(C)** Transverse ultrasound image of the common superficial temporal artery showing a hypo-low-echogenic area outside the vessel wall (interpreted as inflammatory oedema, green arrow) and neovascularization both in and outside the wall (red arrows). **(D)** Longitudinal ultrasound image of the facial artery showing increased vessel wall thickness with medium-echogenic areas (blue arrows), without neovascularization or hypo-echogenic areas outside the vessel wall. **(E)** Longitudinal ultrasound image of the common superficial temporal artery showing increased vessel wall thickness with medium-echogenic areas (blue arrows), without neovascularization or hypo-echogenic areas outside the vessel wall. A hypo-echogenic area interpreted as oedema below the intima layer is seen in the far wall (orange arrow). The marker **(A)** is the IMT measurement. **(F)** Transverse ultrasound image of the common superficial temporal artery showing increased vessel wall thickness with high-echogenicity areas (yellow arrows). **(G)** Longitudinal ultrasound image of the common superficial temporal artery showing increased vessel wall thickness with high-echogenicity areas (yellow arrow). **(H)** Ultrasound image of the brachiocephalic trunk and proximal parts of common carotid and subclavian artery, showing both inflammatory changes in the vessel walls (red arrows) and atherosclerotic plaque (blue arrow). SCA, subclavian artery; CCA, common carotid artery; Tr Br, brachiocephalic trunk; IMT; Intima-media thickness.

fulfilled in 25 (76%) and the 2022 ACR/EULAR criteria in 31 (94%) of the patients with GCA (18, 25). Cranial symptoms (headache, jaw claudication, and/or vision disturbances) were noted for 25 patients (76%). The median (25th–75th percentile) duration of prednisolone treatment before CDU was 0 (0–1) days.

TABLE 2 IMT and atherosclerotic plaques in patients with and without giant cell arteritis (GCA).

Variable	Patients with GCA ($n = 33$)	Patients without GCA ($n = 74$)	p-value
IMT, right			
TA superficial, median (IQR)	0.55 (0.40–0.71)	0.20 (0.16–0.24)	<0.0001
AxA, mm median (IQR)	0.70 (0.60–1.00)	0.65 (0.50–0.70)	0.007
SCA, mm median (IQR)	0.80 (0.70–1.03)	0.60 (0.50–0.80)	0.003
CCA, mm median (IQR)	0.80 (0.70–1.00)	0.80 (0.70–0.90)	0.091
IMT, left			
TA superficial, median (IQR)	0.59 (0.43–0.69)	0.20 (0.16–0.25)	<0.0001
AxA, mm median (IQR)	0.70 (0.60–0.80)	0.60 (0.50–0.70)	0.12
SCA, mm median (IQR)	0.80 (0.65–0.95)	0.60 (0.50–0.70)	<0.0001
CCA, mm median (IQR)	0.90 (0.80–1.10)	0.80 (0.70–1.00)	0.13
Atherosclerotic plaque			
Carotid area, *n* (%)	29 (88%)	61 (82%)	0.58

IQR, interquartile range; GCA, giant cell arteritis; IMT, intima-media thickness; AxA, axillary artery; SCA, subclavian artery; CCA, common carotid artery; TA, temporal artery.

High-frequency CDU and SMI for patients with suspected GCA

Of the 33 patients with GCA, CDU detected affection of the temporal artery in 31 (94%), facial artery in 17 (52%), axillary artery in 8 (24%), subclavian artery in 6 (18%), brachiocephalic artery in 1 (3%), and common carotid artery in 7 (21%). Vessel wall inflammation were restricted to the cranial vessels in 21 patients (64%), 2 (6%) had inflammation that was restricted to extra-cranial vessels, and 10 (30%) displayed a mixed phenotype, with inflammatory changes in both the cranial and extra-cranial arteries.

Based on the CDU protocol of the temporal arteries different morphological patterns could be distinguished as displayed in Figure 1. It is of note that the high resolution allows for the different layers of the vessel wall to be visualized. A consequence of this is that during compression of the temporal artery, the bright visible intima layers may be misinterpreted as a positive compression sign (Figure 2). Eighteen patients demonstrated increased IMT with low-medium echogenicity and a positive compression test together with neovascularization (Figure 3A) and/or low-medium-echogenic areas outside the vessel wall (interpreted as inflammatory oedema) (Figures 3B, C). Thirteen patients demonstrated increased IMT with low-medium echogenicity and a positive compression test without additional signs of neovascularization or low-medium echogenic areas outside the vessel wall (Figures 3D, E). Fourteen patients showed areas of high echogenicity in combination with a low- to medium-echogenic homogeneous wall thickening (Figures 3F, G). One patient also showed sub-intimal hypo-echogenic areas interpreted as oedema (Figure 3E). The IMT measurements and atherosclerotic burdens are shown in Table 2. Atherosclerotic plaques in the carotid arteries were detected in >80% of patients, with no differences between the groups. Figure 3H shows one patient who had both large vessel vasculitis and atherosclerotic plaque in the brachiocephalic artery.

Using SMI, neovascularization was detected in 14 patients (43%). Neovascularization was associated with more-extensive inflammation in terms of the numbers of affected cranial vessels, i.e., the common superficial temporal artery, its parietal and frontal branches and the facial artery, [6 (5.75–8) vs. 3 (2–6), $p < 0.001$], as well as a higher halo count [6 (4.75–7) vs. 3 (2–4), $p = 0.005$]. No significant differences were found regarding extra-cranial inflammation between patients with neovascularization and those without neovascularization [0 (0–2.25) vs. 0 (0–2), $p = 0.53$]. The CRP and ESR levels were also similar in patients with and without neovascularization [for CRP: 68 (27–89) vs. 38 (6–103), $p = 0.27$; and for ESR 73 (48–95) vs. 65 (59–90), $p = 0.69$]. Of all the patients diagnosed with GCA, 11 (33%) showed a low-medium echogenic area outside the vessel wall interpreted as oedema. No differences in the number of affected cranial vessels ($p = 0.59$), halo score ($p = 0.85$) or inflammatory markers such as CRP ($p = 0.77$) or ESR ($p = 0.62$) were detected between the GCA patients with and without oedema outside the vessel wall.

CDU and diagnostic accuracy for patients with suspected GCA

CDU evaluation of the temporal arteries yielded diagnostic sensitivity and specificity values [95% confidence intervals (CI)] of 94% (80–99%) and 100% (89–100%), respectively. The sensitivity and specificity were unchanged after adding the facial artery. When the extra-cranial vessels, i.e., axillary, subclavian and common carotid arteries, were added the sensitivity and specificity values were 100% (89–100%) and 100% (95–100%), respectively.

CDU for patients with a previous GCA diagnosis

Thirteen patients had a previous diagnosis of GCA and were admitted to CDU based on suspicion of inflammatory relapse (Table 3). Many of these patients had old lesions that were visualized with CDU. However, some of them were assessed long ago with old ultrasound equipment making it difficult to differentiate between new and old findings. Nonetheless, Case 8 in Table 3 is interesting because neovascularization together with low echogenic vessel wall swelling strongly suggests inflammatory activity (in a patient showing progression as well as regression of inflammatory wall changes in different vessels).

TABLE 3 Color duplex ultrasound (CDU) at follow-up of patients with previously established diagnosis of giant cell arteritis (GCA).

No	Year of GCA diagnosis/ follow-up	CDU at follow-up		CRP/ESR at follow-up (mg/L)	Symptoms at follow-up	Steroids before CDU follow-up	Clinical relapse at evaluation
		Morphology/IMT	Active[a]				
1	2016/2020	TA: no compression sign, high echogenicity. FA: increased IMT, medium-high echogenicity.	No	8/8	Headache	2.5 mg	No[b]
2	2020/2021	TA: compression sign, low-medium echogenicity.	Active	140/117	CSx, hip pain	12.5 mg	Yes
3	2010/2022	TA and FA: compression sign, medium-high echogenicity. AxA: fibrotic stripes.	No?	4/87	CSx (weight loss)		No[c]
4	2019/2020	TA: medium-high echogenicity, borderline increased IMT.	No	4/10	Headache, chronic pain	20 mg	No[b]
5	2015/2021	AxA and SCA: fibrotic stripes.	No	4/34	CSx, dementia	10 mg	No
6	2015/2020	Right TA: high echogenicity, borderline increased IMT. Left TA:[d]	No?	10/80	Headache	50 mg	No[b]
7	2020/2021	Normal	No	9/34	None	30–40 mg	No
8	2021/2021	TA: decreased and increased IMT, low echogenicity and neovascularization. SCA and AxA: decreased IMT. FA: increased IMT.	Active	64/73	Stiff muscles	5 mg	Yes
9	2020/2022	Normal	No	25/60	None	0	No
10	2020/2021	Normal	No	4/6	Headache	5 mg	No[b]
11	2018/2021	SCA and CCA: medium echogenicity.	No?	4/12	Temporal discomfort	0	No
12	2020/2021	Normal	No	11/26	None	0	No
13	2017/2022	AxA, SCA, CCA: medium echogenicity, increasing IMT.	Active?	25/65	None	5 mg + TCZ	Yes

[a]Active inflammation of the vessel wall.
[b]Non-specific headache.
[c]Myeloma explained high ESR.
[d]Difficult to assess due to previous TAB.
CDU, color duplex ultrasound; TA, temporal artery; FA, facial artery; AxA, axillary artery; SCA, subclavian artery; CCA, common carotid artery; TCZ, Tocilizumab; IMT, Intima-Media Thickness, Csx; constitutional symptoms. Steroids implied Prednisolone in all cases.

Discussion

The present study shows that modern ultrasound equipment, including high frequency transducers and software such as SMI, allows the detection of inflammatory neovascularization and facilitates the interpretation of morphological changes in temporal arteries. This technique, combined with our extended CDU protocol, that includes extra cranial-vessels, results in high diagnostic sensitivity for patients with suspected GCA.

Current recommendations regarding the diagnosis of GCA with ultrasound are based on the halo sign and the compression sign (2). Halo is traditionally referred to as a homogeneous, hypo- or iso-echoic wall thickening, and the compression sign is defined as a thickened arterial wall that remains visible upon transducer-imposed compression (26). However, the latest ultrasound equipment enables the detection of additional details of the vessel wall. The homogeneous halo observed with older equipment (Supplementary Figure 1) is replaced by an image that visualizes the different layers of the arterial wall. At compression of the artery, the intima layer can be distinguished from the media layer and simulate incomplete compression (a false-positive compression sign) to the unexperienced observer. The new technique also facilitates more-detailed localization of inflammatory oedemas, including sub-intimal and extra-vasal oedemas. Whether or not isolated histological oedemas outside the vessel wall can facilitate the diagnosis of active arteritis has been a matter of debate (27–29). However, we observed extra-vasal oedema together with other ultrasonographic signs of arteritis in 33% of the patients with GCA in the present cohort, but it is unclear if extra-vasal oedema in addition to other ultrasound findings indicates a higher degree of inflammation. In addition, the diagnostic relevance of sub-intimal oedema observed in one patient is unclear. This finding has, to the best of our knowledge, not been reported previously.

CDU has become an important tool in diagnosing GCA, and EULAR recommends ultrasound of the temporal and axillary arteries as the first imaging modality (2). Interestingly, a recent meta-analysis based on CDU examination that was restricted to the temporal arteries showed that the sensitivity for diagnosing GCA was higher in studies conducted after year 2010, as compared

to studies conducted before year 2010 (71 vs. 63%) (4). More-recent studies, not included in the meta-analysis, have shown even higher diagnostic sensitivities in the range of 80–86% (5, 7, 30). While the reasons for this are probably multifactorial, it is important to consider the extensive development of the ultrasound technique that has occurred in recent years. In the present study using a 22-MHz probe for cranial examinations, the sensitivity obtained for CDU that was restricted to the temporal arteries was 94% [95% CI, (80–99)]. High-frequency probes are now used more commonly, whereas previous studies often used probes with lower frequencies (4). The importance of the CDU equipment has been examined by Noumegni et al. who compared images from 18- to 22-MHz probes and reported that in some cases the pathology could only be visualized by using the 22-MHz probe (31). Besides the development of the ultrasound technique, the increased number of examined arteries may also have contributed to the increased sensitivity of GCA diagnosis. Compared to when only temporal arteries were studied, our extended protocol increased the sensitivity from 94 to 100% (95% CI, 89–100).

New ultrasound imaging modalities, such as contrast-enhanced ultrasound (CEUS) and SMI, have been developed. Both modalities are able to visualize low-velocity blood flow in the vessel wall representing inflammatory neovascularization (8, 32). CEUS has been used to detect neovascularization in larger arteries, although it has proven difficult to use in smaller arteries such as the temporal vessels (32–34). Furthermore, CEUS requires intravenous injection and is time-consuming which means that its use in the clinical routine is problematic. In contrast, SMI is less time-consuming and can be used in multiple vascular areas without the use of injected contrast agents. In the present study, SMI was used in the temporal arteries, and neovascularization was detected in 43% of the patients with ultrasonographic signs of inflammation but not in those without inflammation. Patients with neovascularization displayed a more-extended inflammation when the affected cranial vessels, i.e., temporal and facial vessels, were enumerated. Furthermore, neovascularization was also associated with higher halo counts. Neovascularization in temporal arterial biopsies has been associated with a more-prominent systemic inflammatory response based on clinical data, including fever, weight loss, anemia and ESR as well as a higher level of infiltration of mononuclear inflammatory cells in the vessel wall (9, 10). Halo counts have also been shown to correlate positively with the levels of CRP (20). However, no differences in CRP or ESR were found in our patients with GCA regardless of the presence or absence of neovascularization. Nevertheless, this is the first study to apply SMI to consecutive GCA patients, and further research on SMI in GCA is warranted in relation to its role as a diagnostic, prognostic or monitoring tool for disease activity in both cranial and extra-cranial vessels.

Follow-up of disease activity in patients with GCA using CDU is challenging. Inflammation-induced vessel wall thickening may disappear or persist despite the arteritis being in clinical remission. If earlier CDU examinations are available, there may appear contradictory results showing both an increase and decrease of IMT in different vessels, and images derived using old and modern machines are often difficult to compare. Nevertheless, as was seen in 1 of the 13 patients with previously known GCA, hypo-echogenic vessel wall swelling combined with neovascularization in the temporal artery is a as sign of relapsing disease. CDU of this patient showed both progression and regression of IMT in different vessel areas, and the visualization of neovascularization facilitated the diagnosis of relapse. Recently an Ultrasonography Score (OGUS) was developed for monitoring disease activity in patients with GCA (35, 36). OGUS is quantitative score based on IMT measurements in the temporal artery and its branches, as well as in the axillary artery. Although quantitative scores, such as OGUS, most certainly will help clinicians to evaluate disease activity over time, concurrent increases and decreases in IMT across different vascular beds can complicate the overall interpretation. In such cases, SMI, with its relatively straightforward morphological interpretation, may serve as a valuable complementary tool.

Some limitations are worth noting. Although the present study used consecutive recruitment, the design was retrospective in that the patients were cared for by different rheumatologists using different clinical protocols. Nevertheless, a strength of the study was the strictly standardized CDU protocol performed by one experienced vascular technologist. PET was only conducted in cases where it was clinically indicated, and comparison of the PET and CDU results was not planned prospectively and could not be performed retrospectively. The present study was also limited by its sample size and its relative predominance toward a cranial phenotype of the disease, which may affect the calculated distribution among the various GCA phenotypes.

Conclusions

Modern ultrasound technique has facilitated visualization of morphological changes in the arterial wall of patients with GCA. We show for the first time that SMI can be used to visualize neovascularization in the temporal arteries as a sign of inflammation in the vessel wall and that neovascularization seems to be related to a more-widespread cranial disease. Nevertheless, further prospective studies are required to evaluate whether SMI can provide prognostic information and to determine its role in the monitoring of disease activity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Regional Ethical Board in Linköping (Dnr. 2013/33-31). The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/Institutional Review Board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JS: Writing – original draft. CSv: Writing – review & editing. PE: Writing – review & editing. CSj: Writing – review & editing. HZ: Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from the Swedish Research Council for Medicine and Health (to CSj), the Swedish Rheumatism Association (to CSj), the Region Östergötland (ALF Grants: to HZ and CSj), and the Gustafsson Foundation (to CSj).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1431385/full#supplementary-material

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TYPE Original Research
PUBLISHED 02 August 2024
DOI 10.3389/fmed.2024.1440725

OPEN ACCESS

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RECEIVED 29 May 2024
ACCEPTED 22 July 2024
PUBLISHED 02 August 2024

CITATION
Milchert M, Wójcik K, Musiał J, Masiak A, Majdan M, Jeleniewicz R, Tłustochowicz W, Kur-Zalewska J, Wisłowska M, Lewandowska-Polak A, Makowska J and Brzosko M (2024) Increased interest with the introduction of fast-track diagnostic pathway is associated with the regionally increased frequency of giant cell arteritis in Poland: a study based on POLVAS registry data. *Front. Med.* 11:1440725. doi: 10.3389/fmed.2024.1440725

Increased interest with the introduction of fast-track diagnostic pathway is associated with the regionally increased frequency of giant cell arteritis in Poland: a study based on POLVAS registry data

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Slavic populations, such as those in Poland, are considered to have a low prevalence of giant cell arteritis (GCA), although epidemiological data are sparse. The study aimed to compare the reported frequency of GCA in various regions of Poland and analyze the differences between them. We conducted a multicenter, retrospective study of all GCA patients included in the POLVAS registry—the first large multicenter database of patients with vasculitis in Poland. The data from the POLVAS registry were compared with the reported prevalence provided by national insurers from the corresponding regions. A 10-fold increase in the diagnostic rates of GCA was observed in Poland between 2008 and 2019, reaching 8.38 per 100,000 population > 50 years old. It may be attributed to increased interest accompanied by improved diagnostic modalities with the introduction of ultrasound-based, fast-track diagnostic pathways in some centers. However, regional inequities are present, resulting in 10-fold differences (from 2.57 to 24.92) in reported prevalence between different regions. Corticosteroid (CS) monotherapy was the main stem of treatment. Further cooperation and education are needed to minimize regional inequities. This observational study suggests some potential for further increase of the recognizability of GCA and wider use of other than CS monotherapy treatment regimens. We hope that the Polish experience might be interesting and serve as some guidance for the populations where GCA is underdiagnosed.

KEYWORDS
giant cell arteritis, fast-track clinic, ultrasound, prevalence, registry

Introduction

GCA is the most common vasculitis affecting large- and medium-sized arteries (1). Overall GCA incidence seems not to be increasing, as demonstrated in the homogeneous population of Norway (2). However, some studies demonstrated an increase in the prevalence of GCA that their authors attribute to increased interest and raising awareness of this disease, as demonstrated by the study from northern Germany performed between 1994 and 2006 (3). In this regard, in the Lugo region of Norwest Spain, a progressive increase in the incidence was observed. With respect to this, while the incidence of biopsy-proven GCA was 6.0 per 100,000 people aged 50 years and older from 1981 to 1990, the annual incidence rate in the same region increased up to 15.90 between 1996 and 2000 (4). Therefore, there may still be potential for diagnostic improvement. Clinical phenotypes and outcomes of GCA patients may differ depending on geographic area and ethnicity. In contrast with the above-mentioned Scandinavian and German cohorts, a Slavic population such as this in Poland is not considered to have a high frequency of GCA, although epidemiological data are sparse. A low incidence of GCA may further limit its recognizability. Modern diagnostic techniques such as arterial ultrasound for large vessel vasculitis are mandatory for efficient fast-track clinics to improve the diagnosis of GCA (5). However, the introduction of arterial ultrasound into rheumatology's daily practice may be troublesome, and time and education are still needed for it to be widely used. An increase in GCA recognizability requires not only the availability of sensitive diagnostic methods (optimally reaching out to reference centers) but also diagnostic awareness, defined as an efficient system for selecting patients suspected of GCA and referring them to undergo specific examinations. Despite advances in the development of new possibilities for treatment, underdiagnosis of GCA can result in serious complications for the patient, with mostly feared but still observed irreversible vision loss (6). Therefore, prompt diagnosis of this disease and timely treatment initiation remain crucial.

This study aimed to compare the reported frequency of GCA in various regions of Poland and to analyze factors potentially influencing observed differences based on the data from the POLVAS registry as interpreted by experienced researchers and practitioners. Such an analysis may uncover potential care problems to improve them.

Methods

We conducted a multicenter, retrospective study of all GCA patients included in the POLVAS registry (7) before the COVID-19 pandemic, between 2008 and 2019. Patients' data were supplied by 11 referral centers participating in the POLVAS project from nine administrative regions (Voivodeships), encompassing 70% of the Polish population (27×10^6 inhabitants). Data were obtained cumulatively, including information on demographics, clinical, laboratory, imaging, pathology, and treatment details, that were collected according to the common protocol. Data from two centers reporting <4 cases were excluded from the analysis, but the reported prevalence of GCA in these regions was calculated. Only patients who met the American College of Rheumatology (ACR) classification criteria for GCA or fulfilled requirements for the nomenclature of GCA according to CHCC 2012 (8) were included in the study. In case of any diagnostic uncertainty as judged by the treating physician, the center was left free to note if the diagnosis was either certain or probable.

We analyzed data on GCA cases reported to the Polish National Insurance Fund (NFZ) from 2008 to 2019 based on ICD10 codes (M31.5 and M31.6). The national insurer is responsible for all of the health care participants in Poland, with the exception of the small number of non-insurance subjects. The data on reported prevalence in individual regions according to national insurer data were compared to the POLVAS registry data (if they were available) from the same regions. By exchanging information about local diagnostic capabilities and management strategies among POLVAS members, we analyzed factors potentially influencing the increase in GCA recognizability in individual regions. The pre-COVID-19 pandemic period was analyzed to avoid difficulties in interpreting data during a potential deepening of healthcare inequities.

The study described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study protocol was approved by the Bioethical Commission of Jagiellonian University, decision No 122.6120.25.2016. The ethics committee of each partner has approved the research protocol. Informed consent has been obtained from each subject (or their legally authorized representative).

Statistical analysis

Descriptive statistics were utilized to analyze trends in GCA diagnosis and management in Poland from the practitioners' perspective. Categorical data were summarized as percentages. Continuous variables were presented as mean. Calculations and principal component analysis (PCA) were performed using RStudio (version 3.6.0).

Results

Demographic data analysis of GCA patients

In 2008, there were 109 GCA cases among Polish patients reported to national insurance institutions, compared to 1,005 cases in 2019 (including both inpatient and outpatient care). The average reported prevalence in 2019 was 8.38 per 100,000 population > 50 years old, but it ranged from 24.92 to 2.57 in different Voivodships (Table 1). A total of 219 patients were included in the POLVAS registry until 2019. All

TABLE 1 Giant cell arteritis cases reported yearly to national insurance by region and factors demonstrating local interest in the disease.

	Voivodship name (name in polish)*	Population in mln (in 2015)	GCA cases reported to insurance by year												Number of cases reported per region's population in 2019**	GCA cases reported to the POLVAS registry until 2019	Active fast-track clinics (year of introduction)	Founding sites of POLVAS registry	Attendance at GCA ultrasound courses***
			2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019					
1.	West Pomeranian (zachodniopomorskie)	1,71	10	19	12	15	25	32	46	51	72	98	115	133	24,92	48	Yes (2008)	Yes	Yes
2.	Pomeranian (pomorskie)	2,31	5	7	6	31	40	45	43	51	58	56	88	110	15,28	67	Yes (2015)	Yes	Yes
3.	Masovian (mazowieckie) capital city region	5,35	44	50	55	74	87	89	106	116	124	123	153	193	11,56	43	–	Yes	–
4.	Lower Silesian (dolnośląskie)	2,90	9	15	20	18	20	24	34	44	39	45	38	94	10,37	1	–	Yes	Yes
5.	Kuyavian-Pomeranian (kujawsko-pomorskie)	2,09	6	6	3	9	14	17	21	24	29	39	53	60	9,22	4	–	–	–
6.	Lesser Poland (małopolskie)	3,37	2	2	6	16	19	22	25	25	22	24	71	94	8,93	6	Yes (2018)	Yes	–
7.	Świętokrzyskie	1,26	0	2	0	2	6	10	15	11	22	21	19	32	8,16	0	–	–	–
8.	Łódź (łódzkie)	2,49	3	3	1	5	5	6	6	3	8	21	32	51	6,56	14	–	–	–
9.	Subcarpathian (podkarpackie)	2,13	5	3	5	4	10	15	14	14	16	16	29	43	6,48	0	–	–	–
10.	Lublin (lubelskie)	2,14	4	4	2	2	9	9	16	17	19	24	30	40	5,99	35	–	Yes	Yes
11.	Podlaskie (podlaskie)	1,19	3	5	10	7	37	32	20	20	22	28	19	21	5,66	0	–	–	–
12.	Lubusz (lubuskie)	1,02	7	0	1	0	0	1	3	9	6	6	12	14	4,41	0	–	–	–
13.	Greater Poland (wielkopolskie)	3,48	2	9	7	6	12	11	11	15	24	28	33	45	4,15	0	–	–	–
14.	Warmian-Masurian (warmińsko-mazurskie)	1,44	1	1	1	2	3	5	6	5	10	9	15	18	4,01	0	–	–	–
15.	Silesian (śląskie)	4,57	7	10	5	10	14	24	16	23	29	41	44	53	3,72	1	–	Yes	–
16.	Opole (opolskie)	1,00	1	0	4	5	3	5	2	5	2	9	7	8	2,57	0	–	–	–
	All	38,44	109	136	138	206	304	347	384	433	502	469	758	1,005	8,38	219			

GCA – giant cell arteritis. *Order by number of cases reported per region's population in 2019, **per 100,000 region's population > 50 years old, ***At least 2 $\times 10^6$ of population attendees of GCA ultrasound courses organized annually in West Pomeranian from 2013 to 2017.

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patients were Caucasian. The male-to-female ratio was 1:2. Demographic data of patients are given in Table 2.

High reported prevalence in the regions engaged in the POLVAS registry

Reference hospital centers from all six Voivodeships with the highest reported prevalence according to national insurer data (West Pomeranian, Pomeranian, Masovian, Lower Silesian, Kuyavian-Pomeranian, and Lesser Poland) were participating in the POLVAS registry. Centers from three Voivodeships with the highest reported prevalence (West Pomeranian, Pomeranian, and Masovian) supplied POLVAS with the majority of patients (Table 1). Most of the top recruiting POLVAS centers showed an active interest in GCA and other vasculitides, as 5 of them belonged to founding parties of the POLVAS registry (6). All three actively running fast-track clinics for GCA were localized in centers within the six Voivodeships with the highest reported prevalence. There was a significant correlation between the funding of the fast-track clinics and the number of GCA cases reported per region's population from 2015—the date when the second center implemented the fast-track approach (Spearman's rank correlation coefficient, $R = 0.72$, $p = 0.001$). PCA was performed to analyze and detect the overall pattern in the incidence rate throughout the years 2008–2019. After the reduction of multidimensionality, two clusters differentiated institutions where the fast-track approach was implemented separately from the departments without it. Two principal components contribute to 84.9% of variability, implying a strong effect. There was also a high attendance of physicians at GCA ultrasound courses from these sites (defined as at least two attendees per 10^6 of the population) that were organized in West Pomerania from 2013 to 2017. The site in the region with the highest reported prevalence (West Pomerania) was the first to start fast-track GCA clinic in 2008 and organized annual ultrasound courses on vascular ultrasound in GCA from 2013 to 2017 educating personnel from other centers. It was also one of the founding sites of the POLVAS registry. No fast-track GCA centers were running in 10 Voivodeships with the lowest reported prevalence.

Differences within the sites engaged in the POLVAS initiative

Diagnostic procedures were analyzed based on the data collected by the centers from nine regions involved in the POLVAS registry, with six regions with the highest reported prevalence among them. There were local differences in the diagnostic procedures applied in the different sites. Imaging was generally used for the diagnosis in 74% of all cases, in contrast with temporal artery biopsy (TAB) performed in 23%. Once performed, TAB yielded 64% of positive results. The site from the region having the highest reported prevalence (West Pomeranian) used arterial visualization for the diagnoses of 90% of patients; however, the percentage of TAB in that site was also relatively high (46% - the third result among all of the centers). The three centers from the capital city region showed different diagnostic approaches: from based on clinical manifestations (88% of patients) and mixed strategy to imaging-based diagnosis (94%), with a low percentage of TAB performed (0–11%). The five POLVAS centers that reported the smallest number of patients (<15 patients per site) in the registry (Łódź, Lesser Poland, Kuyavian-Pomeranian, Lower Silesian, Silesian; all but one coming from the regions with the lowest reported prevalence) included mainly patients with confirmed diagnosis (67–100%) with high number of TAB performed in three of them (50–100%) and high TAB positivity (50–100%). In this group, after excluding sites reporting only one patient, there were two sites (Lublin, Łódź) reporting a high number of patients with certain diagnoses and a low number of patients with a probable diagnosis; however, one of them reported that most of the diagnosis was based on imaging, while the other—on clinical diagnosis (in 79% - the second highest result between all centers).

Polymyalgia rheumatica (PMR) was present in 53% of all patients, and ophthalmological manifestations were present in 45%, which was comparable between the POLVAS sites reporting a high number of cases.

Treatment

All patients received CSs. They were used in monotherapy in 76% of patients as initial treatment and in 66% during maintenance therapy. The most commonly used disease-modifying antirheumatic drug (DMARD) was methotrexate (MTX)—applied in 18% of patients as initial treatment and in 28% during follow-up. Other DMARDs applied were: cyclophosphamide (CTX), azathioprine (AZA), and mycophenolate mofetil (MMF), but their use was limited to isolated cases. Leflunomide and biologic DMARDs (bDMARDs) were not used. MTX and other DMARDs were mainly used in centers reporting the highest number of patients and in some centers from the capital city region (Table 3).

Discussion

POLVAS registry is the first large multicenter database of patients with vasculitis in Poland. For this study, especially data with a potential impact on the diagnosis were selected: the presence of ophthalmological manifestations falling within a spectrum of classical temporal arteritis, the presence of PMR, the probability of the diagnosis, and the diagnostic approach—based on biopsy, imaging, or exclusively on clinical manifestations.

In the last few years, an increase in interest in GCA in Poland has become apparent, corresponding with the implementation of fast-track diagnostic pathways and higher rates of reported prevalence, especially in regions containing POLVAS participating centers. Although 219 GCA patients that were included in the POLVAS registry are the largest group thus far described in Poland, it is meaningful that the participants of this registry enrolled as many as 625 adult AAV patients diagnosed up to December 2016 (9). It is reasonable to conclude that reference centers in Poland are still mostly engaged in AAV management and research rather than GCA.

Demographic data analysis of GCA patients

There was a 10-fold, dynamic, and steady increase in the number of GCA cases reported in Poland between 2008 and 2019. This is a

TABLE 2 Demographic and clinical characteristics of giant cell arteritis patients in the POLVAS registry by different centers.

	Voivodship name (location of its reference center)	*N*	Female *N* (%)	Age at diagnosis (mean ± SD)	Ophthalmological manifestations N (%)	PMR manifestations *N* (%)	Certain diagnosis* *N* (%)	Probable diagnosis* *N* (%)	TAB performed *N* (%)	TAB positive *N* (%)	Diagnosis based on imaging N (%)	Clinical diagnosis** *N* (%)
1.	Pomeranian (Gdańsk)	67	43 (64)	70 ± 9	24 (36)	24 (36)	35 (52)	32 (48)	6 (9)	3 (50)	34 (51)	27 (45)
2.	West Pomeranian (Szczecin)	48	31 (65)	74 ± 9	22 (46)	23 (48)	39 (81)	9 (19)	21 (46)	15 (71)	43 (90)	0
3.	Masovian (Warszawa) capital city region	43	35 (81)	70 ± 13	25 (58)	21 (49)	30 (70)	13 (30)	2 (5)	1 (50)	24 (56)	17 (42)
	Masovian (Warszawa) site 1	16	14 (88)	71 ± 16	10 (63)	8 (50)	16 (100)	0	0	0	2 (13)	14 (88)
	Masovian (Warszawa) site 2	17	12 (71)	70 ± 13	9 (53)	6 (35)	14 (82)	3 (18)	1 (6)	1 (100)	16 (94)	0
	Masovian (Warszawa) site 3	10	9 (90)	67 ± 10	6 (60)	7 (70)	0	10 (100)	1 (10)	0	7 (70)	2 (30)
4.	Lublin (Lublin)	35	23 (66)	65 ± 14	14 (40)	18 (51)	32 (91)	3 (9)	7 (24)	3 (43)	25 (71)	3 (20)
5.	Łódź (Łódź)	14	12 (86)	73 ± 6	7 (50)	2 (14)	14 (100)	0	2 (17)	2 (100)	1 (7)	11 (79)
6.	Lesser Poland (Kraków)	6	2 (33)	58 ± 9	2 (33)	3 (50)	4 (67)	2 (33)	4 (67)	2 (50)	6 (100)	0
7.	Kuyavian-Pomeranian (Bydgoszcz)	4	3 (75)	71 ± 11	4 (100)	3 (75)	3 (75)	1 (25)	2 (50)	2 (100)	3 (75)	0
8.	Lower Silesian (Wrocław)	1	1 (100)	57	0	1 (100)	1 (100)	0	1 (100)	1 (100)	0	0
9.	Silesian (Katowice)	1	1 (100)	74	0	1 (100)	1 (100)	0	0	0	1 (100)	0
	All	219	151 (69)	70 ± 11	98 (45)	117 (53)	146 (67)	73 (33)	47 (23)	30 (64)	162 (74)	10 (12)

PMR, polymyalgia rheumatica and TAB, temporal artery biopsy. *As per handling clinician's judgment, **without TAB or imaging.

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TABLE 3 Treatment of GCA patients in the POLVAS registry by different centers.

	Voivodship name (location of its reference center)	MTX as initial treatment *N* (%)	DMARD other than MTX as initial treatment *N* (%)	MTX during follow-up treatment* *N* (%)	DMARD other than MTX during follow-up treatment** *N* (%)	CTX any time *N* (%)	AZA any time *N* (%)	MMF any time *N* (%)	LEF and bDMARDs any time
1.	Pomeranian (Gdańsk)	12 (18)	0	23 (34)	0	0	0	1 (1)	0
2.	West Pomeranian (Szczecin)	1 (2)	4 (8)	3 (6)	4 (8)	4 (8)	3 (6)	0	0
3.	Masovian (Warszawa) capital city region	13 (30)	5 (12)	15 (35)	4 (9)	3 (7)	3 (7)	2 (5)	0
	Masovian (Warszawa) site 1	0	0	1 (6)	0	0	0	0	0
	Masovian (Warszawa) site 2	12 (71)	5 (29)	8 (47)	4 (24)	3 (18)	3 (18)	2 (12)	0
	Masovian (Warszawa) site 3	1 (10)	0	6 (60)	0	0	0	0	0
4.	Lublin (Lublin)	15 (43)	0	16 (46)	3 (9)	0	2 (6)	0	0
5.	Łódź (Łódź)	0	0	2 (14)	0	0	0	0	0
6.	Lesser Poland (Kraków)	1 (17)	1 (17)	2 (33)	2 (33)	2 (33)	1 (17)	0	0
7.	Kuyavian-Pomeranian (Bydgoszcz)	0	0	0	0	0	1 (25)	0	0
8.	Lower Silesian (Wrocław)	0	0	0	0	0	0	0	0
9.	Silesian (Katowice)	0	0	0	0	0	0	0	0
	All	42 (19)	10 (5)	61 (28)	13 (6)	9 (4)	10 (5)	3 (1)	0

AZA, azathioprine; bDMARDs, biological disease-modifying antirheumatic drugs; CTX, cyclophosphamide; DMARDs, disease-modifying antirheumatic drugs; LEF, leflunomide; MMF, mycophenolate mofetil; and MTX, methotrexate. *After achieving remission or longer than 6 months.

surprisingly high increase, and to our knowledge, a phenomenon not reported previously in vasculitis (3). However, high underdiagnosis of GCA before 2008, demonstrated by very low reported prevalence, may play a role, as there was a start from a very low level. The underdiagnosis was possibly attributable to low awareness of the disease, which was considered an ultra-rare entity in Poland, a lack of local epidemiological analysis on GCA, insufficient education, and a lack of interdisciplinary cooperation, resulting in a lack of referrals to rheumatologists from other specialists. Such a high recent increase in GCA reports is hard to explain exclusively with improvements in the standard of care and healthcare access or changes in population demographics. There were no central campaigns or programs organized in Poland to increase awareness of GCA. Instead, there were regional initiatives of local rheumatology centers with cooperation, bringing improvements in the recognizability that we try to describe in this article. GCA became a frequently discussed topic within rheumatic society, e.g., at local meetings and national conferences (an increase in the number of abstracts on GCA – result not presented) with some spirit of national competition. However, current differences in the reported prevalence of GCA between various regions of Poland are still 10-fold. These differences are unexplained with potential ethnic differences (that are negligible in the uniformly Caucasian Slavic population of Poland) or with local differences in patients' ancestry that were reported in previous studies (10). These differences are only partially explained by the existence of vasculitis reference centers, which are not formally organized in Poland. Instead, some informal rheumatology reference centers that are localized in the regions' capitals are well known for their expertise and may recruit more GCA patients.

High reported prevalence in the regions engaged in the POLVAS registry

Although we analyzed 219 patients included in the POLVAS registry as only a sample of Polish GCA patients, they were mostly reported in the regions with the highest reported prevalence: centers from three Voivodeships with the highest reported prevalence supplied to POLVAS the most of all recruited patients (Table 1). Regions with high rates of reported prevalence had centers that were founding parties of the POLVAS registry or actively recruiting patients in the POLVAS registry and had a running fast-track diagnostic clinic

for GCA that significantly corresponded to GCA diagnostic rates. There was also high attendance at GCA ultrasound courses from these sites organized in West Pomerania from 2013 to 2017. Although no formal reference centers devoted to vasculitis exist in Poland, some sites seem to have more interest in GCA, which corresponds to an increase in reported prevalence. The site in the region with the highest reported prevalence (West Pomerania) was the first to start a fast-track clinic in 2008 and organized ultrasound courses on vascular ultrasound in GCA from 2013 to 2017, educating personnel from other centers. It was also among the founding sites of the POLVAS registry and is publishing in the field of GCA (10–12). Establishing and running a fast-track clinic—being a part of the active strategy for GCA diagnosis—corresponds to an increase in diagnostic rates. This process in Poland illustrates the mutual benefit of cooperation by different vasculitis centers in the formal national registry initiatives such as POLVAS in increasing awareness of rare diseases such as GCA and its modern diagnosis and management.

Differences in sites engaged in the POLVAS initiative

Diagnostic procedures utilized for the diagnosis of GCA were analyzed based on the data collected by the nine centers involved in the POLVAS registry, and there were six regions with the highest reported prevalence among them. From this observation, no causality can be referred to, as both the high reported prevalence and scientific activity can suggest increased interest in GCA. This analysis is limited by sparse data from the regions reporting no patients to the POLVAS registry which corresponded with the lowest reported prevalence. Still, there were local differences in the diagnostic approach between the different sites reflecting different diagnostic strategies. Traditional TAB was performed in only 23% of all the cases while imaging was used for the GCA diagnosis in 74%, implying a modern, imaging-based approach to GCA diagnosis (13) or relatively low popularity or availability of the biopsy. The utilization of imaging for the diagnosis of GCA according to other recent registries' analysis was even higher, reaching 96% (14). Once performed the general TAB yielded 64% positive results suggesting that the remaining 36% of cases were diagnosed despite negative TAB results. Although 64% positivity seems quite high while there is a general trend to limit TAB for ambiguous cases only, it is still lower than noted in other similar studies (14). The site from the region with the highest reported prevalence (West Pomeranian) utilized artery visualization for 90% of the diagnoses of GCA; however, the percentage of TAB was also high (46% - the third result among all of the centers) implying complementary use of TAB in biopsy positive GCA in this center.

Overall, the diagnostic approaches were quite variable: the differences were obvious even in the three centers from the capital city region: from strongly clinically based diagnosis (88%) and mixed strategy to imaging-based diagnosis (94%), but with a low percent of TAB performed in all of them (0–11%). The low recruiting POLVAS centers from the regions with low reported prevalence included mainly patients with certain but not probable diagnoses (67–100%) with a high number of TAB performed and high TAB positivity, which may imply some potential for future increases in diagnostic rates. Furthermore, in this group, there were large differences according to imaging or clinically based diagnostic strategy.

A comparable number of all patients presented musculoskeletal and ophthalmological manifestations (similarly in the POLVAS sites reporting a high number of cases). PMR was present in 53% of all patients, which is comparable to or slightly higher than reported in previous studies, implying an important role of rheumatologists in diagnosing GCA in patients referred with PMR manifestations (15). It is important in regard to the progressive increase in the annual incidence of PMR associated with GCA that was observed in some studies, e.g., from the northwest of Spain (16). Ophthalmological manifestations were present in 45% of all patients, which is comparable to the previous studies (17) that may suggest well-established cooperation with ophthalmologists.

Treatment

CSs were widely used in monotherapy both as initial treatment (76% of patients) and during follow-up (66%), which remains a major concern to be improved in the future. Leflunomide and biologic bDMARDs were not reported to be used in GCA in patients from the POLVAS registry. Reported treatment modalities illustrate current limitations in refunding GCA treatment in Poland. However, the limited availability of some drugs seems to be compensated by the use of MTX, which is currently refunded in Poland. MTX was also applied in the induction of remission, although in only 19% of patients. Early MTX induction is a modern approach in accordance with 2021 ACR guidelines (18), although our study was performed between 2008 and 2019—that is before these guidelines were formulated. Early use of MTX might also be also attributed to devotion to MTX being the only refunded DMARD in Poland for this indication and, therefore, the most affordable treatment option for the patient. MTX and other DMARDs were mainly used in the leading centers reporting the highest number of patients and in some centers in the capital city. The use of CTX, AZA, and MMF was reported in only a single case, which is in line with the lack of guidelines or data on their use that may raise concerns about their benefit-to-risk ratio in GCA.

Limitations

Analyzing diagnostic and therapeutic trends based on registry data is limited by inclusion bias. Our registry data have not been collected in a controlled, subsequent way. This analysis of the data reported to national insurance may not be considered a study to describe actual GCA epidemiology due to the clear underdiagnosis that was illustrated by large regional inequities. GCA is still a rare disease in Poland and is primarily diagnosed in large centers considered reference centers that are responsible for most of the new diagnoses of GCA. This would be a strength of our observation as experienced centers provide trustworthy diagnoses. On the other side, increased interest in GCA might also result in overdiagnosis in the most active sites, although we do not think it would significantly influence the data being the subject of this analysis. We cannot rule out the role of some changes in population demographics and healthcare access on GCA prevalence; however, no such major processes were present in Poland during the study observation period to explain such a high increase in GCA prevalence. GCA cases have been primarily reported to insurance institutions based on the place of diagnosis or performance of further medical procedures and not by

the place where patients live; therefore, some large sites considered reference centers, such as the capital city region, may have increased ratios of diagnosis. Conversely, some sparsely populated areas without well-organized reference centers might have decreased ratios of diagnosis. However, after the first diagnosis, the patient should normally return to his place of living to be further reported to insurance locally.

In summary, this is the first multicenter retrospective study of Polish GCA patients, describing the current reported prevalence and underlining regional inequities and diagnostic differences. A substantial increase has been observed in recent years in the diagnostic rates of GCA in Poland. It may be attributed to increased interest accompanied by improved diagnostic modalities with the introduction of fast-track diagnostic pathways in some centers that significantly increased GCA diagnostic rates. However, regional inequities are present. Further cooperation and education (such as implementing targeted educational programs and workshops) are needed to minimize them and unify local diagnostic and therapeutic traditions. This observational study suggests some potential for further increases in the recognizability of GCA and wider use of DMARDs and bDMARDs instead of CS monotherapy. We hope that the Polish experience might be interesting and serve as some guidance for the populations with the problem of underdiagnosis of GCA. Future research should consider prospective data collection to provide more accurate and reliable insights into GCA prevalence and diagnostic practices.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Bioethical Commission of Jagiellonian University, decision No. 122.6120.25.2016. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MMi: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. KW: Writing – review & editing. JMu: Writing – review & editing. AM: Writing – review & editing. MMa: Writing – review & editing. RJ: Writing – review & editing. WT: Writing – review & editing. JK-Z: Writing – review & editing. MW: Writing – review & editing. AL-P: Writing – review & editing. JMa: Writing – review & editing. MB: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We thank Piotr Kulig for the statistical analysis.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Mini Review
PUBLISHED 07 August 2024
DOI 10.3389/fmed.2024.1432865

OPEN ACCESS

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RECEIVED 14 May 2024
ACCEPTED 23 July 2024
PUBLISHED 07 August 2024

CITATION
Collada-Carrasco J, Gómez-León N, Castillo-Morales V, Lumbreras-Fernández B, Castañeda S and Rodríguez-Laval V (2024) Role and potential of ^{18}F-fluorodeoxyglucose-positron emission tomography-computed tomography in large-vessel vasculitis: a comprehensive review. *Front. Med.* 11:1432865. doi: 10.3389/fmed.2024.1432865

Role and potential of ^{18}F-fluorodeoxyglucose-positron emission tomography-computed tomography in large-vessel vasculitis: a comprehensive review

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Large-vessel vasculitis (LVV) is a group of diseases characterized by inflammation of the aorta and its main branches, which includes giant cell arteritis (GCA), polymyalgia rheumatica (PMR), and Takayasu's arteritis (TAK). These conditions pose significant diagnostic and management challenges due to their diverse clinical presentations and potential for serious complications. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG-PET-CT) has emerged as a valuable imaging modality for the diagnosis and monitoring of LVV, offering insights into disease activity, extent, and response to treatment. ^{18}F-FDG-PET-CT plays a crucial role in the diagnosis and management of LVV by allowing to visualize vessel involvement, assess disease activity, and guide treatment decisions. Studies have demonstrated the utility of ^{18}F-FDG-PET-CT in distinguishing between LVV subtypes, evaluating disease distribution, and detecting extracranial involvement in patients with cranial GCA or PMR phenotypes. Additionally, ^{18}F-FDG-PET-CT has shown promising utility in predicting clinical outcomes and assessing treatment response, based on the correlation between reductions in FDG uptake and improved disease control. Future research should focus on further refining PET-CT techniques, exploring their utility in monitoring treatment response, and investigating novel imaging modalities such as PET-MRI for enhanced diagnostic accuracy in LVV. Overall, ^{18}F-FDG-PET-CT represents a valuable tool in the multidisciplinary management of LVV, facilitating timely diagnosis and personalized treatment strategies to improve patient outcomes.

KEYWORDS

PET-CT, large-vessel vasculitis, giant cell arteritis, polymyalgia rheumatica, Takayasu's arteritis

1 Introduction

Large-vessel vasculitis (LVV) encompasses a group of diseases characterized by inflammation of the vessel wall of the median and great arteries (aorta and main branches), giving rise to systemic inflammation and territorial ischemia. The most characteristic entities are giant cell arteritis (GCA), polymyalgia rheumatica (PMR) and Takayasu's arteritis (TAK). Nevertheless, inflammation of the wall of median and large blood vessels can be detected in other systemic inflammatory and autoimmune diseases, such as spondyloarthritis, relapsing polychondritis, Behçet's disease or IgG_4-related disease.

In this review, we will focus on the role of ^{18}F-fluorodeoxyglucose-positron emission tomography-computed tomography (^{18}F-FDG-PET-CT) in the diagnosis and follow-up of GCA, PMR and TAK.

2 Discussion

2.1 Large-vessel vasculitis

Giant cell arteritis (GCA) is the most common vasculitis in individuals over the age of 50 years in Northern Europe (1); the number of GCA patients in Europe, North America and Oceania is expected to be greater than three million by 2050 (2). A recent study carried out in Spain estimated an annual incidence of 7.42 cases per 100,000 people with age $\geq$ 50 years, with a peak for patients aged 80–84 years. Furthermore, the incidence was greater in women (10.06) than in men (4.83) (3).

GCA includes two main and opposed phenotypes: cranial GCA (C-GCA) and large-vessel GCA (LV-GCA). PMR is considered a part of the GCA disease spectrum by some authors (4, 5). C-GCA patients exhibit headaches, changes in vision or jaw claudication; whereas, at the other end of the spectrum, PMR causes inflammatory musculoskeletal manifestations such as arthritis, bursitis, and tenosynovitis (6). Both typically affect people over 70 years, while LV-GCA tends to appear earlier (4).

These phenotypes frequently overlap, as a third of C-GCA patients show extra-cranial involvement and 10–40% of PMR patients also experience C-GCA or LV-GCA (7). In addition, more than a quarter of PMR patients may have subclinical GCA (8), although meta-analyses have failed to identify a specific marker for their early identification. Therefore, we consider necessary a paradigm shift in the assessment of PMR patients that favors the early implementation of imaging studies.

Takayasu's arteritis (TAK) is a rare autoimmune granulomatous condition of the aorta and primary branches, including the carotid, subclavian, renal, ilio-femoral and splanchnic arteries. Coronary involvement occurs in 15 to 25% of cases. Its incidence is approximately 1 case/million people/year, with a higher prevalence among Asian population and younger women. TAK presents two clinical phases that may overlap: an acute/systemic phase with constitutional symptoms caused by active inflammation, which can last for years before the definitive diagnosis (9); and a chronic/occlusive phase characterized by structural vascular abnormalities. Intimal hyperplasia, observed in over 90% of the cases, leads to stenosis or occlusion, while aneurysms occur in approximately 25% of the cases. Symptoms of the occlusive phase include weakened peripheral pulses, claudication, and differences in blood pressure between arms. As previously stated, diagnosis often occurs late in the disease course.

^{18}F-FDG-PET-CT plays a vital role in visualizing blood vessel involvement, disease extension and activity in patients with established or suspected LVV (10, 11). It is useful to confirm the diagnosis when LV-GCA or TAK is suspected based on clinical and paraclinical findings. In cases of suspected C-GCA, ^{18}F-FDG-PET-CT allows assessing large artery involvement, particularly with digital PET scanners (12). The addition of ^{18}F-FDG-PET-CT to diagnosis assessment in suspected GCA cases improves diagnostic accuracy and prompts therapy changes in approximately a quarter of patients (11). This technique is also useful to confirm or rule out large-vessel inflammation and assess musculoskeletal involvement in established or suspected PMR. Additionally, ^{18}F-FDG-PET-CT aids in differentiating PMR from other musculoskeletal diseases in the elderly, such as rheumatoid arthritis or late-onset spondyloarthritis (6, 13). Furthermore, LVV or PMR may be identified in ^{18}F-FDG-PET-CT studies conducted for fever or inflammation of unknown origin.

2.2 Scanning protocol

For optimal performance standardizing ^{18}F-FDG-PET-CT scans is imperative, including the entire procedure, patient preparation, acquisition, reconstruction, and analysis.

Patients are advised to fast for a minimum of 6 h and abstain from strenuous activity for 24 h before ^{18}F-FDG injection. To minimize physiological uptake in muscles and brown fat, the radioisotope is administered in a quiet room with controlled temperature (20–22°C), and beta-blockers (20 mg oral propranolol 1 h before) may be employed in specific situations. In scenarios involving fever of unknown origin or suspected cardiac involvement, a high-fat, carbohydrate-free diet for 48 h, fasting for 12–18 h, or intravenous unfractionated heparin 15 min before ^{18}F-FDG injection should be considered (14).

Blood glucose levels below 160 mg/dl before injection are preferable. Although hyperglycemia might not be decisive on the false-negative rate of ^{18}F-FDG-PET-CT in the inflammatory context, in contrast to its impact on oncologic indications, a negative correlation exists between glycemia and ^{18}F-FDG uptake in blood vessels.

^{18}F-FDG-PET-CT acquisition involves low-dose, non-contrast CT for attenuation correction and anatomic reference, performed 90–120 min post-injection (even up to 180 min). Late acquisition is optimal for PET activity detection in GCA, especially in patients already treated with glucocorticoids, as it enhances the vascular wall-to-blood pool activity ratio, improving precision and spatial resolution (15–17).

Depending on local resources and practices, contrast-enhanced CT may be used as modern PET/CT systems allow for CT angiography immediately post-PET acquisition, offering an excellent anatomic assessment in a single modality. This procedure is optional but beneficial for detecting stenosis and characterizing aneurysms; its validity for detecting arterial abnormalities has been proved in one study focused on the evaluation of the

superficial temporal artery in GCA (18). Contrast-enhanced CT for attenuation correction can be employed in the venous or equilibrium phase (e.g., delayed acquisition).

Duration of the examination process is 2–3 min per bed, even shorter with digital scanners. A whole-body study covering the vertex to the knees, with the patient in a supine position and arms alongside the body, is recommended. Optionally, the acquisition may be extended to the feet, although the low spatial resolution of ^{18}F-FDG-PET-CT for vessels lesser than femoral arteries should be taken into account (19).

The recommended intravenous dose is 2–3 MBq/kg. Corticosteroid treatment may decrease ^{18}F-FDG uptake; thus, it is recommended to start treatment after performing ^{18}F-FDG-PET-CT, unless ischemic complications are imminent (especially in suspected ocular or temporal arteritis). Performing ^{18}F-FDG-PET-CT within 3 days of initiating corticosteroids is an alternative, as sensitivity was proven to be unaffected after administration of a daily dose of methylprednisolone 60 mg (20). As observed by Nielsen et al. (20), after a 10-day course of treatment there is almost a 30–40% reduction in vessel FDG uptake and a 60% decrease in the sensitivity of 18F-FDG-PET-CT for diagnosing LVV. Limited data exist for the 3- to 10-day window, and adherence to the 3-day timeframe is currently recommended (21).

However, a late ^{18}F-FDG-PET-CT (beyond the first 10 days of treatment) can often be informative. Narvaez el al. observed that ^{18}F-FDG-PET-CT positivity in new-onset GCA patients treated with high-dose oral glucocorticoids was 54.5% in the first two weeks, 38.5% in those treated for 2 to 4 weeks, and 25% in those treated for 4 to 6 weeks. Boluses of intravenous glucocorticoids can distort PET-CT results since the first endovenous bolus of 125 mg (22). Corticosteroids increase hepatic ^{18}F-FDG uptake, impacting liver assessment and visual uptake scoring; and may also distort the results of the diagnostic biopsy (23).

There might be a dose-related and duration-related effect of corticosteroid treatment on ^{18}F-FDG-PET-CT diagnostic performance. A study comparing different treatment courses found that patients with a positive ^{18}F-FDG-PET-CT result for vasculitis were treated with significantly lower doses and lengths of corticosteroid treatment (24).

Long acquisition time, combined with the use of diagnostic scales (see section "2.5 Diagnostic scales") may decrease the number of false-positive assessments of ^{18}F-FDG-PET-CT, also increasing inter and intra-observer agreement.

2.3 Diagnostic performance

It is important to emphasize the growing significance of ^{18}F-FDG-PET-CT in the diagnosis of LVV.

Previous recommendations (25) discouraged the use of ^{18}F-FDG-PET-CT for the assessment of cranial arteries, as evidence regarding the visibility of these vessels with this technique was limited. However, since several studies now support its use for the diagnosis of temporal arteritis, ^{18}F-FDG-PET-CT has been included in the new diagnostic criteria for LVV, to the extent that, in many cases, biopsy is no longer necessary (11, 12, 26–28). This modification of diagnostic criteria aims to promote early detection of vasculitis in order to prevent structural damage or long-term sequelae, such as visual loss in GCA or severe focal arterial stenosis in TAK (29).

In their meta-analysis of 400 patients with LVV, Lee et al. (30) observed an overall pooled sensitivity of ^{18}F-FDG-PET-CT for diagnosis of 76% and a specificity of 93%. Notably, the sensitivity was higher for GCA compared to TAK, with values of 83% for sensitivity and 90% for specificity (30).

Altered uptake in atherosclerotic blood vessels, particularly in the elderly and at the ilio-femoral arteries, may diminish the specificity of ^{18}F-FDG-PET-CT for LVV. While there may be some overlap between LVV and atherosclerosis, distinct patterns of ^{18}F-FDG uptake and the presence of calcifications on CT can ease the differential diagnosis: LVV manifests as a linear, diffuse, circumferential uptake, different from the typical mild, patchy uptake pattern of atherosclerosis (14).

Concerns also arise in the diagnosis or assessment of disease activity in LVV patients with arterial grafts. However, it should be noted that ^{18}F-FDG uptake restricted to the graft does not imply active vasculitis, but rather indicates a chronic, low-grade, nonspecific reaction to the graft material (11).

2.4 Uptake values and distribution

^{18}F-FDG-PET-CT imaging reveals vascular uptake in 83% of GCA patients, especially at the subclavian arteries (74%), the aorta (> 50%) and the femoral arteries (37%) (31). A meta-analysis of 6 studies on ^{18}F-FDG-PET-CT's diagnostic utility for GCA found an overall sensitivity of 80% and a specificity of 89%, with an excellent negative predictive value (88%) (32). Some heterogeneity in the evaluation of a positive result was observed depending on the study and the territory examined; in general, a semi-quantitative analysis of ^{18}F-FDG uptakes was performed comparing them with those of other anatomical areas; vessel uptake superior to that of liver was considered an efficient marker for vasculitis. Some studies considered positivity for GCA when aortic uptake was greater than that of the liver, or any uptake was detected in the rest of arteries. Other studies used the semi-quantitative score PETVAS, in which a mean value of 6 was found at the time of diagnosis (see section "2.5 Diagnostic scales" for further information about diagnostic scores).

When comparing both GCA phenotypes, LV-GCA patients, compared to those with C-GCA, exhibit a younger age (68 vs. 75 years; $p = 0.02$) and a longer diagnostic delay (12 vs. 4 months; $p = 0.006$). Despite non-statistically significant, they manifest PMR symptoms and lower-extremity involvement more often (33, 34).

Among patients with PMR, those with subclinical GCA exhibit advanced age, prolonged morning stiffness and a higher prevalence of hip pain. They predominantly display a LV-GCA phenotype. However, patients with PMR in the classic GCA group stick to the C-GCA pattern of involvement (35).

The most prevalent ^{18}F-FDG-PET-CT imaging pattern observed in PMR patients is a periarticular uptake, notably in the shoulders (80–100%), hips (70–100%), and sternoclavicular joints (43–93%). A recent meta-analysis identified the uptake in the ischial tuberosities as the most sensitive finding for PMR (sensitivity 85.4%; specificity 70.1%), while the uptake in interspinous processes was the most specific (sensitivity 75.4%; specificity 81.4%) (36).

TABLE 1 Overview of large-vessel vasculitis spectrum [refs.: (3, 4, 6, 32, 33, 36, 37, 41, 48)].

	C-GCA	LV-GCA	TAK	PMR
Distribution	Europe	Europe	Asia	Europe
Patients	♀≈ 75 year	♀ > 50 year	♀ < 40 year	♀ > 50 year
Symptoms	• Headache, scalp tenderness, jaw claudication, visual loss. • Fever, anemia, constitutional symptoms	• Fever, anemia, constitutional symptoms • Arm/leg claudication, carotidynia • Vascular bruits, pulse discrepancy	• Fever, anemia, constitutional symptoms • Arm/leg claudication, carotidynia • Vascular bruits, pulse discrepancy	• Shoulder and pelvic girdle pain. • Morning stiffness • Arthritis, bursitis, tenosynovitis • Constitutional symptoms
Structures involved	• Aorta and major branches (aneurysms) • Subclavian arteries • Temporal, ocular arteries	• Aorta and major branches (aneurysms) • Femoral arteries	• Aorta and major branches (stenosis) • Renal, mesenteric, carotid, left subclavian arteries • Coronary arteries	Periarticular involvement of: • Shoulders and hips • Sternoclavicular joints • Ischial tuberosities • Interspinous cervical- lumbar bursae • Symphysis pubis • Anterior inferior iliac spines
Overlapping	• PMR (53%) • LV-GCA (30%)	• PMR (35%)		• GCA (10–40%). Suspected if refractory-atypical PMR. • Subclinical GCA (> 25%), more often LV-GCA.
Preferred imaging diagnosis (EULAR)	1. Doppler-US (temporal and axillary arteries) 2. PET-CT or MRI	1. PET-CT 2. MRI or CT	1. MRI 2. PET-CT	Clinical diagnosis, optional US evaluation of shoulder/hip
^{18}F-FDG-PET-CT diagnostic performance	Initial diagnosis: • Sensitivity 80% • Specificity 89% Treatment response: • Sensitivity 78% • Specificity 71%	Initial diagnosis: • Sensitivity 80% • Specificity 89% Treatment response: • Sensitivity 78% • Specificity 71%	Sensitivity 81% Specificity 74%	• Most sensitive: Ischial tuberosities 85% • Most specific: Interspinous processes 81% • Leuven Score ≥ 16: Sensitivity 91% Specificity 98%

C-GCA, cranial giant cell arteritis; EULAR, European Alliance of Associations for Rheumatology; LV-GCA, large-vessel giant cell arteritis; LVV, large-vessel vasculitis; PMR, polymyalgia rheumatica.

Taking the ischial tuberosities, interspinous bursae, periarticular hips and symphysis pubis enthesis as the characteristic sites for PMR, one study evaluated the characteristic-site standardized uptake values (SUV) index (that is, the mean SUV index of these sites; SUV index being the ratio between lesional maximum SUV [SUVmax] and liver mean SUV) and yielded an area under the ROC curve (AUC) of 0.93, establishing the optimal SUV index threshold at 1.685 for a sensitivity of 84.6% and a specificity of 92.6%. The probability of PMR surpassed 90% when the characteristic-site SUV index exceeded 2.56 (37).

Extraarticular uptake is also described in PMR patients as iliopectineal (8–100%), subtrochanteric (71–93%), or ischiogluteal (52–96%) bursitis as well as uptake in the cervical (7–56%) and lumbar (38–87%) spinal processes. Further involvement includes enthesitis and tenosynovitis of the pectineus and long adductor muscles, rectus femoris and biceps femoris, resulting in prepubic, anteroinferior iliac spine, and adjacent ischial tuberosity uptake, respectively (38, 39). Individual uptake assessments lack sufficient diagnostic precision, prompting the development of various scales and algorithms; the Leuven score stands out as the most useful for diagnosis (section "2.5 Diagnostic scales", Figure 1) (40).

A meta-analysis including TAK patients disclosed a sensitivity of 81% and specificity of 74% for ^{18}F-FDG-PET-CT (41, 42). Some features were able to distinguish between GCA and TAK; TAK patients exhibited a higher likelihood of abdominal, carotid and subclavian artery disease, the latter sometimes being focal and restricted to the left subclavian artery ($p < 0.01$). Conversely, GCA patients were more prone to diffuse disease, bilateral axillary/subclavian artery involvement, or minimal disease lacking a discernible pattern ($p < 0.01$). Finally, TAK patients were more likely to have angiographically detectable structural damage, while GCA patients tended to show arterial FDG uptake without associated vascular damage (43).

A comparative overview of LVV and PMR can be found in Table 1.

2.5 Diagnostic scales

Various interpretation criteria for ^{18}F-FDG-PET-CT have been proposed. Existing evidence suggests that semi-quantitative parameters may not be superior to a visual grading scale in the routine clinical diagnosis of LVV (44).

A standardized 4-point visual grading scale, based on the comparison between arterial and liver uptake, is recommended as follows: grade 0 for no uptake, grade 1 for lower arterial than liver uptake, grade 2 for similar arterial and liver uptake, and grade 3 for higher arterial than liver uptake. Grade 3 is considered positive for LVV, while grade 2 indicates possible LVV (14, 45). The cranial arteries are evaluated with a 3-point visual grading scale based

on the comparison between the arterial uptake and that of the surrounding tissue: grade 0 indicates arterial uptake not above that of the surrounding tissue, grade 1 indicates arterial uptake just above that of the surrounding tissue, and grade 2 indicates arterial uptake significantly above that of the surrounding tissue (14, 46). In cases of active liver disease when hepatic uptake is increased, the uptake of the arterial vessels is compared with that of the vena cava to avoid comparison mistakes.

Additionally, a quantitative composite score, known as the PET vascular activity score or total vascular score (PETVAS or TVAS) is based on a visual grading scale of 7 to 15 arterial segments. This score offers an overall assessment of disease burden with proven robustness and minimal interobserver variability. The PETVAS score may be preferred for evaluating treatment response. In one study, a ROC curve analysis showed that a PETVAS $\geq$ 10 yielded 60.8% sensitivity and 80.6% specificity to distinguish clinically active from inactive LVV, with an AUC of 0.73 (47).

Regarding PMR, the Leuven Score, developed by Henckaerts et al. in a prospective study, is a semiquantitative evaluation of 12 anatomical landmarks (shoulders, sternoclavicular joints, hips, greater trochanters, ischial tuberosities and cervical and lumbar interspinous bursae). Each one is assigned a value of 0 to 2 depending on the uptake intensity. It has demonstrated optimal sensitivity (91.4%) and specificity (97.6%) at a cut-off point of 16 for clinical diagnosis of PMR (Figure 1). A concise Leuven/Groningen Score, focused on the evaluation of 7 anatomical sites, might perform equally well, although further validation is required (39, 48, 49).

A summary of the most relevant diagnostic scales can be found in Table 2.

2.6 Prognostic value

In patients with LVV, assessing both the intensity and extent of vascular FDG uptake at diagnosis can predict their clinical outcome (50). Prior research has hinted at the correlation between aortic ^{18}F-FDG uptake at the time of diagnosis and an elevated long-term risk of aortic aneurysm development (51). Other studies have identified an association between FDG uptake at the thoracic aorta and late thoracic aorta volume ($p = 0.039$); and between a positive ^{18}F-FDG-PET-CT scan and an increased likelihood of aortic complications ($p = 0.004$) over a 5-year timeframe (52). Specific guidelines on aortic sequelae monitoring in LVV are required.

Future investigations are imperative to explore the utility as a prognostic indicator for PMR.

2.7 Assessment of treatment response

The value of imaging techniques for disease monitoring is becoming increasingly important, moreover when several of the recent treatments for LVV directly influence acute phase reactants, rendering them unreliable for the assessment of disease activity (53). ^{18}F-FDG-PET-CT shows promising results in evaluating treatment response in GCA and PMR, through assessment of metabolic activity and vascular structural changes (54). Some studies also suggest that late-acquisition PET-CT may be useful in detecting activity, even in completely treated patients (15–17).

Despite ^{18}F-FDG-PET-CT is not being routinely recommended for treatment monitoring in GCA (55), most studies demonstrate a decline in both the extent and intensity of ^{18}F-FDG uptake during treatment. A meta-analysis has shown that ^{18}F-FDG-PET-CT provides a moderate sensitivity of 78% and a specificity of 71% in discerning active from quiescent LV-GCA during treatment (56). The impact of treatment on arterial wall uptake is not exclusive to glucocorticoid therapy; analogous reductions have been observed in GCA patients treated with methotrexate and anti–interleukin (IL)-6 therapy such as tocilizumab and sarilumab (57, 58).

The prevailing consensus states that a reduction in uptake intensity exceeding 20% and/or a decline in the extent of FDG uptake can be considered indicative of a therapeutic response (59). Nonetheless, the use of ^{18}F-FDG-PET-CT is controversial as residual activity is often observed despite complete clinical and biological response; although high-dose glucocorticoid treatment exerts substantial effects on ^{18}F-FDG uptake after 10 days, persistent arterial wall uptake may last throughout treatment-induced remission, extending up to 6 months post-initiation (14, 56, 60). Multiple potential explanations have been proposed for this phenomenon, such as low inflammatory vascular remodeling, the chronic vasculitis phase, angiogenesis, chronic hyperglycemia and atherosclerosis plaques.

As a result, there is currently no consensus on the optimal timing for performing post-treatment ^{18}F-FDG-PET-CT. Blockmans et al. (61) conducted baseline ^{18}F-FDG-PET-CT imaging at 3 and 6 months following corticosteroid treatment: the total vascular score decreased from 7.9 ± 5.5 at baseline to 2.4 ± 3.5 at 3 months ($p < 0.0005$), with no further reduction at 6 months.

A recent meta-analysis of cross-sectional studies suggested that ^{18}F-FDG-PET-CT could detect relapsing/refractory disease with a sensitivity of 77% and a specificity of 71% (62).

Experience regarding the role of ^{18}F-FDG-PET-CT in monitoring PMR treatment is limited, as clinical evaluation typically guides treatment response assessment. Analogous to arterial wall ^{18}F-FDG uptake in LVV, studies in PMR patients demonstrate a reduction, though not necessarily normalization, of ^{18}F-FDG uptake at the shoulder, pelvic girdle, and interspinous bursae during treatment-induced remission (63). No study has yet investigated whether disease activity can be monitored with ^{18}F-FDG-PET-CT in PMR patients treated with glucocorticoid-sparing agents.

2.8 Other imaging techniques and future directions

Prior research has revealed comparable effectiveness of ^{18}F-FDG-PET-CT and extended vascular ultrasound for GCA diagnosis; the former excels in detecting aortic or vertebral vasculitis while ruling out alternative diagnoses, whereas the latter, more widely accessible, adds value to the identification of temporal and popliteal vasculitis, and to the measurement of the severity of stenosis and flow direction (64, 65). Likewise, similar findings have been reported regarding the diagnostic accuracy of CT angiography (CTA) compared to ^{18}F-FDG-PET-CT, even when slice thickness tends to be greater in ^{18}F-FDG-PET-CT scans.

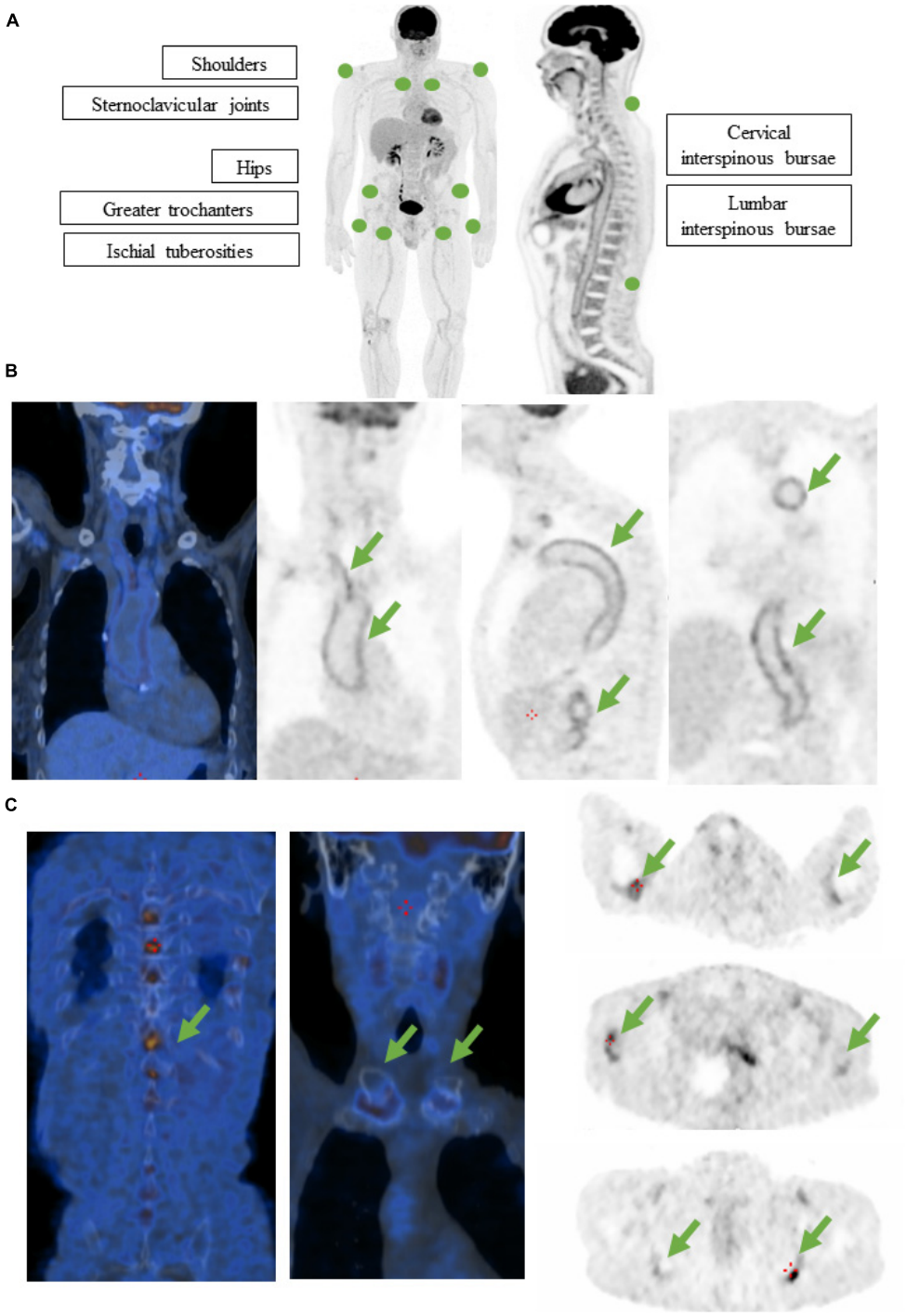

FIGURE 1
(A) Diagram representing the Leuven score for the assessment of PMR probability. A value on a 3-grade visual scale is assigned to each one of the 12 spots depicted, as follows: 0 means no uptake; 1 means less uptake than that of the liver, 2 means equal or more uptake than that of the liver. PMR is considered likely if the total score is equal or above 16 out of 24. **(B)** ^{18}F-FDG-PET-CT of an 84-year old female with GCA at diagnosis. Symptoms were asthenia, weight loss, raised inflammatory markers and diffuse bone pain. Notice the intense metabolic activity in aorta and supra-aortic vessels (arrows). Visual score: 3. **(C)** ^{18}F-FDG-PET-CT of the same patient. Notice the associated metabolic activity in shoulders, sternoclavicular joints, greater trochanters, ischial tuberosities and lumbar interspinous bursae (arrows). Leuven score: 18. Probable PMR was reported.

^{18}F-fluorodeoxyglucose positron emission tomography-magnetic resonance imaging (^{18}F-FDG-PET-MRI) is a good candidate for the evaluation of LVV and PMR. Its outstanding contrast resolution allows precise anatomical localization of PET tracer uptake while avoiding radiation exposure (this is especially applicable to younger TAK patients); possibly improving evaluation of narrow cranial arteries, characterization of vessel wall inflammation and organ assessment, including cerebral parenchyma and bone marrow. One study evaluating target-to-background ratios

TABLE 2 Summary of the most relevant diagnostic scales for LVV and PMR [refs.: (39, 45, 47–49)].

	Meller score	Leuven score	Leuven-Groningen score	PETVAS or TVAS	SUVmax aorta	SUVmax most active cranial artery	SUVmax aorta to liver ratio*
Disease	LVV	PMR	PMR	LVV	LVV	C-GCA	LVV
Type	Visual	Visual	Visual	Visual	Semi-quantitative	Semi-quantitative	Semi-quantitative
Preferred application	Diagnosis and activity	Diagnosis and activity	Diagnosis and activity	Activity and Treatment monitoring	Diagnosis and activity; Patients under GCs	Diagnosis and activity	Diagnosis and activity
Cut-off value	2–3	16	7–8	10	3.12	5	1.03
Diagnostic performance	Grade 2: Sensitivity 100% Specificity 51% Grade 3: Sensitivity 83% Specificity 91%	Sensitivity 91% Specificity 98%	Value 7: Sensitivity 97% Specificity 93% Value 8: Sensitivity 93% Specificity 95%	Sensitivity 61% Specificity 81%	Sensitivity 83% Specificity 73%	Sensitivity 79% Specificity 92%	Sensitivity 72% Specificity 92%
Pros	Easy to apply. Great diagnostic values in grade 3	Standardization of PMR findings	Easier than Leuven Score	Objective and reproducible. Overall assessment of LVV	Objective and reproducible	Objective and reproducible	Objective and reproducible
Cons	Subjective	Time-consuming	Needs further validation	Time-consuming	Absolute, non-relative values	Absolute, non-relative values	Time-consuming. Added value to Meller score is doubtful

*Other semi-quantitative, target-to-background ratio (TBR) approaches are vascular/liver ratio, vascular/lung ratio, vascular/blood pool ratio and arterial/venous ratio. C-GCA, cranial giant cell arteritis; GC, glucocorticoid; LVV, large-vessel vasculitis; PETVAS, positron-emission-tomography vascular assessment score; PMR, polymyalgia rheumatica; SUV, standardized uptake value; TVAS, total vascular assessment score.

(TBRs), maximum standardized uptake values (SUVmax), and visual scores found robust correlations between ^{18}F-FDG-PET-MRI and ^{18}F-FDG-PET-CT (r = 0.92, r = 0.91, r = 0.84; $p < 0.05$) (66). However, further studies are imperative to assess the utility of ^{18}F-FDG-PET-MRI in the evaluation of LV and PMR.

Another interesting topic is the utility of delayed-acquisition ^{18}F-FDG-PET-CT (at 150–180 min post-injection) in patients with LVV under treatment with corticosteroids, and even more so with biologic agents. Late acquisition could be useful to identify false negative cases, thus potentially rescuing patients who might otherwise be overlooked (17, 67).

Finally, as controversy exists regarding persistent ^{18}F-FDG uptake after treatment, the use of novel targeted PET-CT tracers could serve as an alternative for doubtful cases; further studies are needed to assess value of T-cell, macrophage or fibroblast specific radiotracers, such as the fibroblast activation protein inhibitor (FAPI) (68).

Author contributions

JC-C: Writing – original draft. NG-L: Writing – original draft. VC-M: Writing – review & editing. BL-F: Writing – review & editing. SC: Writing – review & editing. VR-L: Writing – review & editing.

Funding

The authors declare that financial support was received for the research, authorship, and/or publication of this article. Funding was provided by the Instituto de Investigación Sanitaria la Princesa. This study was funded by Ministerio de Economía y Competitividad (Instituto de Salud Carlos III) (Grant no. PI21/0147 to SC) and cofunded by European regional development fund (ERDF) "A way to make Europe".

Acknowledgments

We would like to thank Manuel Gómez Gutiérrez, Ph.D. member of the Methodology Unit of IIS Princesa, for his contribution to the final writing and style of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 14 August 2024
DOI 10.3389/fmed.2024.1448157

OPEN ACCESS

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RECEIVED 12 June 2024
ACCEPTED 05 August 2024
PUBLISHED 14 August 2024

CITATION
Petzinna SM, Bauer C-J and Schäfer VS (2024) Vascular-adhesion protein 1 in giant cell arteritis and polymyalgia rheumatica. *Front. Med.* 11:1448157. doi: 10.3389/fmed.2024.1448157

Vascular-adhesion protein 1 in giant cell arteritis and polymyalgia rheumatica

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Vascular adhesion protein-1 (VAP-1) is a type 2 transmembrane sialoglycoprotein with oxidative deamination functionality, encoded by the amine oxidase copper-containing 3 (AOC3) gene. VAP-1 is widely expressed across various tissues, particularly in highly vascularized tissues and organs essential for lymphocyte circulation. In the vascular system, VAP-1 is predominantly found in vascular smooth muscle cells and endothelial cells, with higher expression levels in vascular smooth muscle cells. Under inflammatory conditions, VAP-1 rapidly translocates to the endothelial cell surface, facilitating leukocyte adhesion and migration through interactions with specific ligands, such as sialic acid-binding immunoglobulin-type lectins (Siglec)-9 on neutrophils and monocytes, and Siglec-10 on B cells, monocytes, and eosinophils. This interaction is crucial for leukocyte transmigration into inflamed tissues. Furthermore, VAP-1's enzymatic activity generates hydrogen peroxide and advanced glycation end-products, contributing to cytotoxic damage and vascular inflammation. In this context, the soluble form of VAP-1 (sVAP-1), produced by matrix metalloproteinase cleavage from its membrane-bound counterpart, also significantly influences leukocyte migration. This review aims to elucidate the multifaceted pathophysiological roles of VAP-1 in vascular inflammation, particularly in giant cell arteritis (GCA) and associated polymyalgia rheumatica (PMR). By exploring its involvement in immune cell adhesion, migration, and its enzymatic contributions to oxidative stress and tissue damage, we investigate the importance of VAP-1 in GCA. Additionally, we discuss recent advancements in imaging techniques targeting VAP-1, such as [^{68}Ga]Ga-DOTA-Siglec-9 PET/CT, which have provided new insights into VAP-1's role in GCA and PMR. Overall, understanding VAP-1's comprehensive roles could pave the way for improved strategies in managing these conditions.

KEYWORDS

giant cell arteritis (GCA), polymyalgia rheumatica (PMR), large vessel vasculitides (LVV), immunology & inflammation, vasculitis

Introduction

Giant cell arteritis (GCA) is an immune-mediated vasculitis that affects large and medium-sized vessels, predominantly in individuals over 50 years of age. It is the most prevalent form of vasculitis in Western populations. GCA can lead to vascular changes and occlusion due to severe vascular inflammation, neoangiogenesis, and remodeling. Additionally, GCA is closely associated with polymyalgia rheumatica (PMR), which is characterized by inflammation in

periarticular structures. PMR may precede, coincide with, or follow the onset of GCA. Thus, subclinical GCA can be detected in 22–23% of PMR patients (1, 2). However, in some studies, the incidence of large vessel vasculitis detected by positron emission tomography–computed tomography (PET/CT) in patients with PMR can reach up to 60%, particularly in those presenting with inflammatory low back pain, pelvic girdle pain, and diffuse lower limb pain (3, 4).

Despite advances in understanding the pathophysiology of GCA, the innate and adaptive immune mechanisms involved remain only partially understood. Initial hypotheses primarily attributed the immune response in GCA to TH1 cells, driven by the activation of the Janus kinase (JAK) and Signal Transducers and Activators of Transcription (STAT) signaling pathways (5). It has been demonstrated that IFN-γ plays a significant role in mediating chemotaxis through CXCL9, CXCL10, and CXCL11 in the arterial wall of GCA patients via the JAK-STAT1 pathway (6, 7). Moreover, functional polymorphisms of IFN-γ were associated with the development of severe ischemic complications of the disease (8). Recent findings, however, suggest that cytokines beyond the STAT signaling pathway may also significantly influence inflammation in GCA (5). Various mechanisms involving both TH1 and TH17 cells have been recognized, including the recruitment of T-cells within the vascular wall facilitated by vascular dendritic cells (9). These cells are responsible not only for chemotaxis and cytokine release but also for the differentiation of TH1/TH17 cells via vasculitogenic T-effector cells (9). A chemokine-mediated link involving IFN-γ, Interleukin (IL)-17, and IL-21 fosters an inflammatory environment (10, 11). Monocytes also significantly contribute to the differentiation of TH1 and TH17 cells via the production of cytokines such as IL-12p35 (promoting TH1) and IL-1β, IL-6, and IL-23p19 (promoting TH17) (12). Activated TH1/TH17 cells not only sustain the initial immune response by producing key cytokines (IFN-γ/IL-17) but also exacerbate inflammation by recruiting cytotoxic CD8 cells and monocytic precursor cells, which evolve into macrophages leading to vascular damage and remodeling (9).

The close connection between PMR and GCA has led to joint investigations into their disease mechanisms. In PMR, similar to GCA, Treg, TH1, and TH17-associated inflammatory processes, along with their key cytokines, are crucial (13–15). Moreover, IL-6, along with IL-1 and ICAM-1, is significantly implicated in the pathophysiology of PMR, influencing the likelihood of future relapses in patients (14–17). While ICAM-1 polymorphisms alone do not appear to be associated with disease severity in isolated PMR, the presence of homozygosity for both the HLA-DRB1*0401 allele and the 241 GG codon of ICAM-1 is significantly correlated with an increased risk of relapses in these patients (18). A major distinction in the immune response between PMR and GCA is the absence of a strong IFN-γ response in PMR (19).

While the understanding of immunological and pathophysiological aspects of GCA and PMR is evolving, significant gaps remain, particularly in linking immunological processes with disease manifestations. This emphasizes the need for a better understanding of these diseases.

Structure and function of vascular-adhesion protein 1

Vascular adhesion protein-1 (VAP-1) is a type 2 transmembrane sialoglycoprotein, encoded by the amine oxidase copper-containing 3 (AOC3) gene. It forms a 180 kDa homodimer consisting of three distinct domains (D2-D4), capable of catalyzing oxidative deamination reactions (20–24). This enzymatic activity can be inhibited by semicarbazide, classifying VAP-1 within the semicarbazide-sensitive amine oxidase (SSAO) family (25). To clearly differentiate VAP-1-like SSAOs (topaquinone-containing amine oxidases) from other members of the SSAO family, they have been renamed as primary amine oxidases (26). Other SSAOs belong to the lysyl oxidase family, characterized by the presence of lysine tyrosyl quinone, rather than topaquinone, at their catalytic sites (26).

VAP-1 is expressed by various cell types, including vascular cells, pericytes on the outer surfaces of blood vessels, adipocytes, chondrocytes, follicular dendritic cells, and liver cells (26–30). Its expression is particularly prominent in tissues with high vascularization, such as blood vessels, muscle, cerebrovascular tissue, heart, liver, kidney, retina, intestine, lung, and adipose tissue. Moreover, VAP-1 is significantly expressed in organs involved in lymphocyte recirculation and homing, including the vessels of the spleen, thymic cortex, and lymph nodes (31–34).

In the vascular system, the expression of VAP-1 is predominantly observed in vascular smooth muscle cells (VSMC) and endothelial cells. VSMC, located in the medial layer of the vascular wall, exhibit higher expression and activity levels of VAP-1 compared to endothelial cells (26, 35, 36). VSMC are pivotal in producing the extracellular matrix, which is essential for the arterial wall's resilience against blood circulation pressure and exhibit significant plasticity (37, 38). Under external stimuli, VSMC can migrate and proliferate from the medial to the intimal layer, contributing to intimal hyperplasia (38). VAP-1 in VSMC is specifically localized within the caveolae of the plasma membrane (39), yet the regulation of VAP-1 in these cells, as well as its physiological functions within them, remains less understood (26). Although VAP-1 in VSMC does not facilitate lymphocyte binding *in vitro* (39), it is implicated in critical processes such as vascular tone regulation, cell differentiation, and extracellular matrix organization (22, 40, 41). An increase in VAP-1 activity can generate reactive oxygen species, leading to VSMC death and potentially contributing to atherosclerosis (37, 38, 42).

Conversely, VAP-1 is present in all three types of endothelial cells, continuous, fenestrated, and sinusoidal (34). Its role varies across different tissue types and (patho-)physiological conditions. In specific endothelial cells, like liver sinusoidal endothelium and the specialized high endothelial venules in peripheral lymph nodes, VAP-1 is constitutively expressed on the cell surface (43, 44). In all other endothelial cells, VAP-1 resides within intracellular vesicles, absent from the cell surface. However, during inflammatory conditions, stimuli such as tumor necrosis factor-alpha, interferon-gamma, lipopolysaccharide, and interleukin-1ß trigger its rapid relocation to the surface of endothelial cells (26, 45–47) (Figure 1).

Pathophysiological role of vascular-adhesion protein 1

VAP-1 plays a critical role in immune cell adhesion and migration, particularly facilitating the transmigration of leukocytes from the bloodstream into inflamed tissues. This process involves VAP-1's dual function: its enzymatic activity catalyzes the oxidative deamination of primary amines (48), a key mechanism behind most of VAP-1's

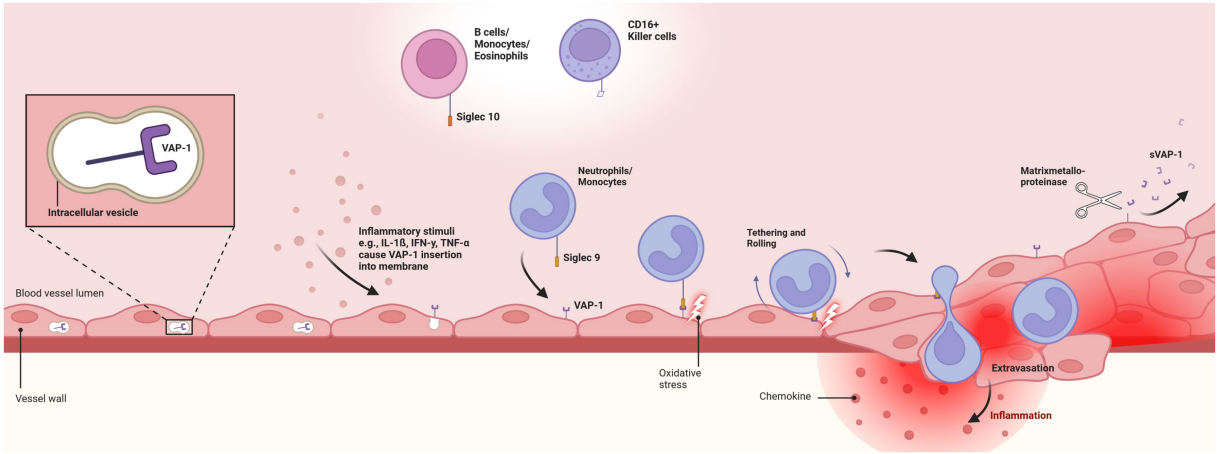

FIGURE 1
Pathophysiologal role of Vascular-adhesion protein 1. Depicts the endothelial translocation of membrane-bound vascular-adhesion protein 1 (VAP-1) from intracellular vesicles to the cell surface in response to inflammatory stimuli. Translocation facilitates the interaction of VAP-1 with circulating neutrophils and monocytes through the Siglec-9 ligand. This initiates oxidative deamination, leading to cytotoxic damage to endothelial cells and promoting an inflammatory response. Secretion of chemokines, activation of transcription factors, and expression of matrix metalloproteinases enhance leukocyte rolling, tethering, and migration. Finally, soluble VAP-1 (sVAP-1) is generated through the cleavage of membrane-bound VAP-1 by matrix metalloproteinases, releasing it into the circulation and significantly contributing to the monoamine oxidase activity in human blood. VAP-1, vascular-adhesion protein 1; sVAP-1, soluble vascular-adhesion protein 1. Created with BioRender.com.

pathophysiological effects, and its role as a membrane-bound endothelial adhesion molecule that supports enzyme-independent leukocyte binding (31). Under inflammatory conditions, VAP-1 therefore acts as an ectoenzyme with a catalytically active domain external to the cell membrane, amplifying its role in immune responses (38).

On endothelial cells, VAP-1 engages with leukocytes via specific ligands, including sialic acid-binding immunoglobulin-type lectins (Siglec)-9, predominantly found on neutrophils and monocytes, and Siglec-10, identified on B cells, monocytes, and eosinophils (48–51). Siglec-10 further acts as a substrate for VAP-1, a function not demonstrated for Siglec-9. Additionally, VAP-1 engages with CD16+ natural killer cells, although the precise mechanism of this interaction is not well understood (26, 45, 50–53).

Inflammatory stimuli lead to the rapid up-regulation of Siglec-9 and Siglec-10 on leukocytes, enhancing their interaction with endothelial VAP-1 (54, 55). This interaction fosters a transient adhesive bond, where primary amines on leukocytes serve as substrates for oxidative deamination by VAP-1's catalytic site (50, 56). This two-step oxidative deamination process, converting methylamine to formaldehyde and aminoacetone to methylglyoxal, with subsequent production of hydrogen peroxide and ammonia contributing to advanced glycation end-products (AGE) formation and increased oxidative stress, inflicts cytotoxic damage on endothelial cells (56–58). This can result in vascular damage and potential vascular complications like atherosclerosis (26, 29, 31, 57, 59–61).

The generation of VAP-1-derived hydrogen peroxide, a powerful signaling molecule at low concentrations, plays an essential role in local inflammatory responses (26). The catalytic activity of VAP-1 induces the expression of various endothelial adhesion molecules, such as ICAM-1, MadCAM-1, E-selectin, and P-selectin, and promotes the secretion of the chemokine CXCL8 (44, 62–65). It also activates key transcription factors, facilitating the engagement of multiple signaling pathways, including PI3K, MAPK, and NF-κB, thereby fostering an inflammatory milieu beneficial to leukocyte extravasation (24, 56). This complex process encompasses leukocyte tethering and rolling along the endothelium, culminating in the extravasation cascade, essential for immune cell migration to sites of inflammation (24, 26, 27, 56, 66–68). Real-time imaging studies have underscored VAP-1's facilitation of leukocyte slow rolling, firm adhesion, and subsequent migration within blood vessels, particularly at lymphoid tissues and inflamed sites (69). Notably, the interaction of various immune cells, including CD4+ helper T cells, T-regulatory cells, Th17 cells, CD8+ cytotoxic T cells, B lymphocytes, CD16+ monocytes, and granulocytes with high endothelial venules and flat-walled vessels, has been shown to be modulated, at least in part, by VAP-1 expression levels (34, 43, 52, 68, 70–76). This underscores VAP-1's vital role in mediating immune surveillance and response, highlighting its importance in the immune system's functionality.

While membrane-bound VAP-1 serves as a transmembrane glycoprotein within the vascular wall, soluble VAP-1 (sVAP-1) arises from the proteolytic cleavage of its membrane-bound form by matrix metalloproteinases, releasing it into circulation (26, 27, 59, 69). This allows VAP-1 to influence leukocyte migration in both transmembrane and soluble form, with sVAP-1 contributing significantly to the circulating monoamine oxidase activity in human blood (77). High concentrations of sVAP-1, often originating from high endothelial venules in lymphatic organs, play a crucial role in facilitating transendothelial migration of lymphocytes (78–80). In healthy individuals, sVAP-1 levels in the serum are typically low and stable, modulating the adhesive activity of its membrane-bound counterpart and enhancing leukocyte adhesion (26, 31, 79, 80).

Increased sVAP-1 expression is prevalent in various chronic inflammatory conditions (26, 81) with notable elevations in patients with type 1 diabetes and chronic liver diseases (80), as well as those suffering from skin inflammation (psoriasis), synovitis, active relapsing–remitting multiple sclerosis (RR-MS), and systemic lupus erythematosus (47, 79, 82–85). Furthermore, elevated serum VAP-1

activity is linked to vascular disorders including diabetes mellitus complications (86, 87), hypertension (56), congestive heart failure (88), multiple cerebral infarctions (89), Alzheimer's disease (90), and atherosclerosis (91), where sVAP-1 levels correlate with intima-media thickness and the presence of carotid plaques (92, 93). Additionally, s VAP-1 concentrations can predict major adverse cardiovascular events and mortality (93, 94). These sVAP-1 increases are often associated with tissue-bound VAP-1 overexpression (60, 95). However, despite these associations, sVAP-1 can not be considered as a general inflammation marker due to the lack of consistent correlation with C-reactive protein levels (93).

The increasing recognition of VAP-1's role in inflammation and its involvement in exacerbating local lesion formation has led to a growing body of research exploring its role across a spectrum of inflammatory conditions.

Vascular-adhesion protein 1 in large vessel vasculitis and polymyalgia rheumatica

VAP-1's pathophysiological role, along with the potential inflammatory and oxidative stress-inducing effects of its catalytic products, indicate its involvement in the pathogenesis of vascular inflammatory disorders. The specific localization of VAP-1 on the surface of blood vessel cells further corroborates its involvement in these diseases. This has prompted further investigations using imaging techniques targeting VAP-1 or its ligands. Recent advancements include the introduction of a novel inflammation-specific radiotracer, [^{68}Ga]Ga-DOTA-Siglec-9, for evaluating inflammatory vascular diseases (50).

A recently presented studies demonstrated that [^{68}Ga]Ga-DOTA-Siglec-9 PET/CT can detect vascular inflammation during relapses in GCA, revealing increased localized tracer uptake in regions such as the aorta and subclavian arteries (96, 97). Additionally, prednisolone treatment significantly influenced endothelial VAP-1 expression, suggesting a rapid, therapy-induced reduction of VAP-1. No significant association was found between C-reactive protein levels and tracer uptake, aligning with previous research in other diseases where no correlation could be found (93). Beyond its role as an endothelial adhesion molecule, elevated sVAP-1 has emerged as a potential biomarker for disease activity in GCA, with levels exceeding those in healthy controls (96). However, further studies are needed to confirm this finding. Comparably, in PMR, which is frequently associated with GCA, [^{68}Ga]Ga-DOTA-Siglec-9 PET/CT has indicated involvement of VAP-1 (98). In a cohort of PMR patients, increased tracer uptake was observed in the shoulder and pelvic girdle regions, with a significant negative correlation between prednisolone intake and tracer uptake in the shoulder, further supporting the hypothesis that VAP-1 is rapidly eliminated following prednisolone exposure.

Currently, the precise mechanism of VAP-1 involvement in the pathogenesis and pathophysiology of GCA and PMR remains at least partly speculative. However, its role has been elucidated in other (autoimmune) diseases with vascular inflammation, suggesting potential parallels with the pathophysiology of GCA and PMR.

In granulomatosis with polyangiitis, VAP-1 is strongly expressed in the renal endothelium during active disease, indicating its potential role in glomerular endothelial cell injury and altered barrier function, thereby contributing to disease pathogenesis (99, 100).

Similarly, in neuronal *in vitro* endothelial cell models of the blood–brain barrier, a link has been identified between VAP-1 expression and endothelial cell activation. This relationship involves the altered release of pro-inflammatory and pro-angiogenic cytokines, along with subsequent activation of signaling cascades, that also have been shown to significantly contribute to pathogenesis of GCA. Thus, it has been shown that cells expressing human VAP-1 overproduce various cytokines related to inflammation in GCA [e.g., IL-6 (101, 102), IL-8 (103, 104), ICAM (102), VCAM (105, 106)] and trophic factors [e.g. VEGF (10, 107), NGF (108)] (109). The signaling pathways of VEGF and IL-8 are particularly implicated in activating the VEGFR2 molecular pathway, leading to increased endothelial permeability (109). Moreover, VEGF and VAP-1 (110) can be upregulated in response to hypoxia, suggesting that polymorphisms affecting VEGF may also impact processes involving VAP-1. These polymorphisms could potentially affect VAP-1 levels or activity, thereby modulating the extent and nature of inflammatory responses and the development of severe ischemic complications in GCA. In this context, VEGF-induced angiogenesis may contribute to GCA associated inflammation (111).

IL-6 signaling has also been explored as a potential driver of VAP-1-associated endothelial alterations in the blood–brain barrier model, with the STAT3 pathway, which is known to significantly contribute to the pathogenesis of GCA (5, 102), being notably more activated in endothelial cells expressing VAP-1. The significance of the IL-6-activated STAT3 pathway in these alterations was further demonstrated by the application of an IL-6 blocking antibody, which negated the permeability changes induced by VAP-1 conditioned media in wild-type cells (109). This may help explain the successful application of the Interleukin 6 receptor inhibitor Tocilizumab (112).

VAP-1 may also be a potential explanation for the successful treatment of GCA with methotrexate, which has shown efficacy in GCA (113) and PMR (114) and is currently under investigation for remission maintenance therapy in GCA (115). Studies in tumor necrosis factor-α-treated human umbilical vein endothelial cell lines have shown that methotrexate can downregulate pro-inflammatory genes, including VAP-1, highlighting endothelium-protective and anti-inflammatory effects of methotrexat (116).

Furthermore, VAP-1 has been recognized as significant in cerebral ischemic processes, offering a potential explanation for GCA-associated ischemic complications. In animal models with intracerebral hemorrhage-induced brain damage, VAP-1 inhibition downregulated the adhesion molecule ICAM-1 and diminished the infiltration of systemic immune cells, particularly neutrophils, to the injury site (117). This reduction in immune cell accumulation was accompanied by decreased pro-inflammatory cytokines, including TNF-α and MCP-1, and reduced activation of microglia/macrophages. Consequently, inhibiting VAP-1 curtailed the local inflammatory process, potentially reducing cerebral edema and enhancing neurobehavioral functions (117). Finally, in diabetic vascular complications, enhanced interactions between endothelial cells and lymphocytes mediated by VAP-1 (118) and the subsequent

transmigration and recruitment of endothelial inflammatory mediators, are central to the activation and progression of various inflammatory pathways (31). Formaldehyde, methylglyoxal, and advanced glycation end-products may contribute to these complications in diabetes (63, 119).

In conclusion, VAP-1 has emerged as a pivotal factor in the pathogenesis and pathophysiology of various vascular inflammatory disorders, including GCA and PMR. The introduction of [68Ga] Ga-DOTA-Siglec-9 PET/CT has provided valuable insights, demonstrating VAP-1's role in detecting vascular inflammation during GCA relapses and PMR diagnosis, while also highlighting the significant influence of prednisolone treatment on VAP-1 expression. Elevated VAP-1 levels further underscore its potential as a biomarker for disease activity in GCA, although additional studies are necessary to confirm these findings. Overall, the new understanding of VAP-1's role in GCA and PMR underscores the necessity for continued research to further elucidate its mechanisms, paving the way for improved disease management of these conditions.

Author contributions

SP: Conceptualization, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. C-JB: Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. VS: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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TYPE Review
PUBLISHED 14 October 2024
DOI 10.3389/fmed.2024.1469964

OPEN ACCESS

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RECEIVED 24 July 2024
ACCEPTED 26 September 2024
PUBLISHED 14 October 2024

CITATION
Thibault T, Alberini J-L, Billet A-C, Greigert H, Ramon A, Devilliers H, Cochet A, Bonnotte B and Samson M (2024) An overview of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in giant cell arteritis.
Front. Med. 11:1469964.
doi: 10.3389/fmed.2024.1469964

An overview of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in giant cell arteritis

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PET/CT is an imaging modality that is increasingly being used to diagnose large-vessel vasculitis. In the case of giant cell arteritis, it was first used to demonstrate inflammation of the walls of large arterial trunks such as the aorta and its main branches, showing that aortic involvement is common in this vasculitis and associated with the occurrence of aortic complications such as aneurysms. More recently, with the advent of digital PET/CT, study of the cranial arteries (i.e., temporal, occipital, maxillary and vertebral arteries) has become possible, further increasing the diagnostic interest of this examination for the diagnosis of GCA. Despite these advantages, there are still limitations and questions regarding the use of PET/CT for the diagnosis and especially the follow-up of GCA. The aim of this review is to take stock of currently available data on the use of PET/CT for GCA diagnosis and follow-up.

KEYWORDS

giant cell arteritis, 18F-fluorodeoxyglucose positron emission tomography/computed tomography, diagnosis, monitoring, prognostic

Introduction

Giant cell arteritis (GCA) is a large-vessel vasculitis (LVV) affecting people over the age of fifty (1, 2) and especially targets the aorta and branches of the external carotid arteries. The disease can cause vascular complications, particularly vision loss or stroke at diagnosis (3, 4), or aortic aneurysm in long-term follow-up (5).

GCA diagnosis is based on the combination of clinical signs of GCA with an increase in acute phase reactants (CRP, ESR) and evidence of vasculitis. Historically, temporal artery biopsy (TAB) was the gold standard to demonstrate granulomatous vasculitis (6). However, this examination is invasive (7) and lacks sensitivity (8), which led to vascular imaging's

growing role in confirming the diagnosis of GCA. Ultrasonography has been recommended by EULAR for several years as a first-line test to assess the temporal arteries in suspected GCA (9). This is also supported by the most recent EULAR guidelines, which state that ultrasonography of the temporal and axillary arteries is the first-line imaging test to be performed in this context (10). However, GCA does not always affect temporal arteries and sometimes targets large vessels, especially the aorta and its main branches, often in the upper limbs (11), and these areas are not readily accessible by ultrasound.

Along this line, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) has emerged as a very sensitive examination to detect LVV in GCA patients. More recently, newer generations of PET/CT have shown their good performance in demonstrating vasculitis of cranial arteries, including the temporal, occipital and maxillary arteries, allowing a more comprehensive assessment of vascular involvement (12–15), and are recognized in the new EULAR recommendations on imaging's use in GCA (15) (Figure 1).

PET/CT is now widely used for GCA diagnosis, but there are still limitations to its application and interpretation. Indeed, PET/CT is highly sensitive to glucocorticoids and should therefore be performed before or as soon as possible after the start of treatment. A previous study showed that the hypermetabolic signal in large arteries decreased significantly after 72 h of treatment, meaning that this limit is often used as a quality criterion for PET/CT (16). However, it has been clearly demonstrated that arterial hypermetabolism can persist for many months after treatment begins, so this rule is not absolute.

PET/CT was first used to detect LVV but has since expanded beyond that setting and been evaluated in different contexts. Therefore, in addition to the diagnosis of GCA, PET/CT has been used for disease monitoring.

This report aims to provide an update on the performance of PET/CT in the diagnosis and monitoring of GCA.

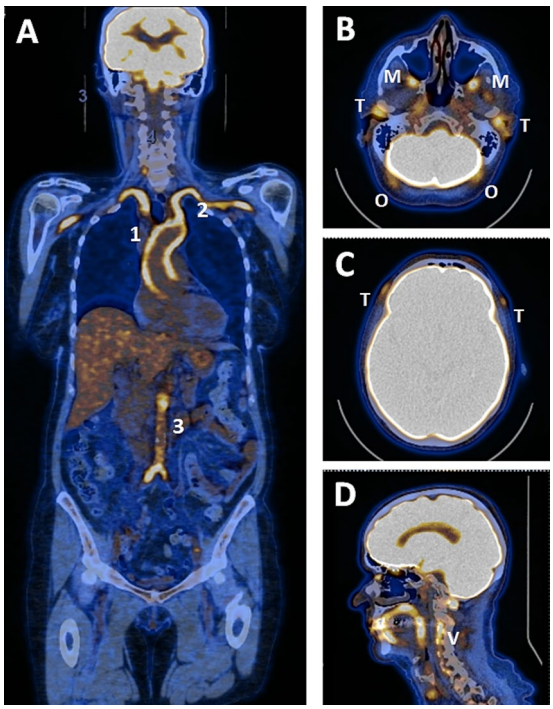

FIGURE 1
PET/CT study of a patient with GCA involving cephalic and large arteries. **(A)** study of large arteries showing grade 3 hypermetabolism of the ascending aorta (1), subclavian and axillary arteries (2) and from the abdominal aorta to the origin of the iliac arteries (3). **(B–D)** study of cephalic arteries showing significant hypermetabolism of the temporal (T), maxillary (M), occipital (O) and vertebral (V) arteries. **(C)** hypermetabolism of the frontal branch of the temporal artery (T).

Generalities about PET/CT

The latest EULAR guidelines indicate that, in cases of high clinical suspicion and positive imaging, the diagnosis of GCA can be confirmed without additional tests, including TAB. The first-line imaging test to achieve this goal is ultrasonography of the temporal and axillary arteries. Furthermore, PET/CT remains the test of choice for evidencing LVV in extracranial arteries (aorta and proximal branches). PET/CT and MRI are also becoming an alternative to ultrasonography for the study of cranial arteries (10).

Protocol procedure

With the aim of standardising procedures and optimising diagnostic accuracy, the recommendations reiterate good practice with regard to the protocol for performing PET/CT, including the acquisition of cranial artery imaging (Table 1) (15).

In particular, it is specified that the time between FDG infusion and image acquisition should be at least 60 min. Most studies on PET/CT in LVV have been conducted in these conditions. Delayed imaging at 3 h may provide a more detailed image of the arterial wall, mainly due to decreased blood pool activity, according to only one small prospective study of 23 patients with suspected LVV (17). However, there is little evidence to support a possible extension of this timeframe, in contrast to the recommended delay of 2 h for assessing the metabolic activity of atherosclerosis (18). Therefore, further studies extending the time between FDG infusion and imaging are

TABLE 1 Imaging modalities for PET/CT in LVV, according to EULAR recommendations (15).

⇒ Position of patient is supine, position of the arms should be arms down.
⇒ Body parts to include from top of head to at least mid-thigh, preferably to below the knees.
⇒ Blood glucose levels: preferred <7 mmol/L (126 mg/dL), <10 mmol/L (180 mg/dL) acceptable.
⇒ Interval between FDG infusion and image acquisition should be at least 60 min, preferably 90–120 min.
⇒ For evaluation of the cranial arteries, 5 min instead of 2–3 min acquisition time of the head should be used in cases of non-digital FDG-PET imaging.
⇒ Scoring of [18 F]-FDG-uptake: qualitative visual grading; if result is unclear, compare it to the liver background (grading 0–3).
⇒ Digital FDG-PET may be used in order to reduce imaging time, radiation dose and to improve the image quality.
⇒ FDG-PET is commonly combined with low-dose CT, optionally with CT-angiography (CTA). It can also be combined with MRI or MRA.

MRI, magnetic resonance imaging.
MRA, magnetic resonance angiography.

needed to determine whether performance can be optimized in the diagnosis of GCA and LVV in general.

Before PET/CT, blood glucose levels should be closely monitored, especially in diabetic patients and after the introduction of glucocorticoids, as FDG uptake is reduced when serum glucose levels exceed 7 mmol/L (126 mg/dL) (19, 20).

According to Nielsen et al., diagnostic accuracy is not significantly affected when PET/CT is performed 3 days after the start of GC therapy, whereas it is significantly reduced when PET/CT is performed 10 days later (21). Therefore, PET/CT should be performed before or within this three-day period after starting GC to ensure good performance (16). The availability of PET/CT is one of the main limitations to its use in clinical practice, as it is often inappropriate to wait for a suspected GCA diagnosis before initiating glucocorticoid therapy due to the risk of ocular complications (16).

PET/CT interpretation

There are several interpretation methods for assessing vascular hypermetabolism: the qualitative method, visual grading and semi-quantitative methods (19):

- The global qualitative method is still preferred in daily clinical practice due to the speed with which it can be initiated, as it is based on the clinician's experience and overall visual assessment. PET/CT is defined as negative or positive according to the presence or absence of evidence of active LVV. However, particularly in the context of clinical research, standardization of interpretation and intra- and inter-observer reliability are not guaranteed with this approach.
- Qualitative visual grading is recommended in clinical practice when the result of the global qualitative method is unclear. Visual grading is based on comparing the intensity of vascular FDG uptake in each vascular segment with the background uptake in the liver. The resulting score ranges from 0 to 3: 0 = no FDG uptake (lower than the mediastinal blood pool); 1 = low-grade uptake (< liver uptake); 2 = intermediate-grade uptake (similar to liver uptake), 3 = high-grade uptake (> liver uptake). This score should be interpreted with caution due to frequent false positives related to atherosclerotic vascular uptake, particularly in the iliac and femoral arteries. According to guidelines, a score of 3 should be considered positive for active LVV and a score of 2 indicative of possible LVV (20). Lower scores are considered as negative for LVV. It should be noted that most PET/CT studies (extracranial and cranial PET/CT) use a visual grading of ≥2 to define PET/CT as positive.
- Semi-quantitative methods consist of directly measuring the SUVmax of vascular FDG uptake in each vascular segment. The target is defined by drawing a manually delineated volume of interest (VOI) that includes each vascular segment and avoids areas of atherosclerosis. Target-to-liver and target-to-blood pool ratios are calculated by dividing the SUVmax by liver or superior vena cava background, respectively. These ratios were proposed because the simple SUV metric does not seem relevant for initial diagnosis due to the high overlap between patients and controls (22), and the potential loss of specificity (23).

Scores

Scores can be calculated by adding each vessel's visual grading (from 0 to 3 points). Two scores are mainly used: TVS (Total Vascular Score) and PETVAS (PET Vascular Activity Score). TVS is defined by the addition of the Meller score (24), which is composed of 14 arterial territories ranging from 0 to 42 points, including the carotid arteries [$n = 2$], subclavian arteries [$n = 2$], axillary arteries [$n = 2$], ascending thoracic aorta [$n = 1$], aortic arch [$n = 1$], descending thoracic aorta [$n = 1$], abdominal aorta [$n = 1$], and the iliac arteries [$n = 2$] and femoral arteries [$n = 2$] (23). PETVAS includes 9 arterial territories, ranging from 0 to 27 points, including the ascending thoracic aorta [$n = 1$], aortic arch [$n = 1$], descending thoracic aorta [$n = 1$], abdominal aorta [$n = 1$], brachiocephalic trunk [$n = 1$], carotid arteries [$n = 2$] and subclavian arteries [$n = 2$] (25). Unlike TVS, PETVAS does not include the arteries of the lower limbs, where atheroma can interfere with interpretation of the uptake (24). The scores' value is well correlated with vasculitis activity. Therefore, TVS and PETVAS are higher at GCA diagnosis than in treated GCA (26, 27). In addition, PETVAS is able to discriminate clinically active from inactive LVV with a sensitivity of 60% and specificity of 80% for a threshold of ≥10 points (28).

Dashora et al. (29) compared PETVAS with SUV semiquantitative metrics in 52 GCA and 43 Takayasu's arteritis patients. Intra-rater reliability showed a better intraclass correlation (ICC) for the semiquantitative method [0.99 (range 0.98–1.00)] than for the visual grading by PETVAS [0.82 (range 0.56–0.93)]. When compared to physician assessment of clinical disease activity, the target-to-liver ratio had the highest area under the receiver operating characteristic curve (AUROC). The authors suggested that visual grading (such as PETVAS or TVS) should be used in clinical practice or observational studies when ease of interpretation is preferred, and SUV metrics should be used in randomized clinical trials or translational research when precision is mandatory.

Diagnostic accuracy

Guidelines have specified that PET/CT can be used to detect mural inflammation or luminal changes affecting extracranial arteries in patients with suspected GCA (28).

Evaluating the diagnostic accuracy of PET/CT in GCA is challenging because no other available test, especially TAB, is a perfect gold standard due to lack of sensitivity (30). In some patients, only PET/CT can confirm the diagnosed GCA by showing high vascular uptake in cranial or extracranial arteries. To avoid this difficulty, recent studies have used a reference clinical diagnosis as a gold standard, i.e., a diagnosis maintained by the treating physician after 6 months of follow-up with no alternative found. These studies are compiled in the systematic review and metanalysis by Bosch et al. (31). Four studies with a low risk of bias (12, 15, 32, 33) which evaluated the diagnostic accuracy of PET/CT in suspected GCA compared with the reference clinical diagnosis were included. The four studies' pooled results support high diagnostic accuracy (sensitivity 76% and specificity 95%). It should be noted that some of the studies include vascular FDG uptake in the cranial arteries to consider a positive PET/CT.

After evaluation of the diagnostic accuracy of PET/CT, there is a need for comparison of PET/CT with other imaging tests, particularly ultrasound of the temporal and axillary arteries. However, data about direct comparison between these two tests are lacking. Most published studies have included patients who had PET/CT or temporal ultrasound as the gold standard test (33–35). Therefore, the two tests cannot be compared. Other published trials evaluated the diagnostic accuracy of PET/CT and ultrasound using the clinical diagnosis confirmed after 6 months of follow-up as the gold standard. Unfortunately, at least one test was not performed in the whole population, which makes it difficult to draw firm conclusions in these studies (36, 37). Moreel et al. (38) published a systematic review and meta-analysis in 2023 with the aim of comparing PET/CT, ultrasound and MRI for the diagnosis of GCA. Eleven studies (including 1,578 patients) and three studies (including 149 patients) were included to evaluate ultrasound and PET/CT, respectively. The results showed a sensitivity of 86% (76–92%) and a specificity of 96% (92–98%) for cranial and large vessel ultrasound, and a sensitivity of 82% (61–93%) and a specificity of 79% (60–90%) for cranial and extracranial PET/CT. However, at the time of the meta-analysis, the authors could not identify any studies that assessed both PET/CT and ultrasound, which prevent head-to-head comparison. More recently, van Nieuwland et al. (39) included patients with suspected GCA in a nested case–control pilot study. Ultrasound, cranial and extracranial FDG-PET/CT, and cranial MRI were performed within 5 days of the initial clinical evaluation, and clinical diagnosis after 6 months of follow-up was used as gold standard. A total of 23 patients with GCA and 19 patients with suspected but undiagnosed GCA were included. The sensitivity was 69.6% (95%CI 50.4–88.8%) for ultrasound, 52.2% (95%CI 31.4–73.0%) for PET/CT and 56.5% (95%CI 35.8–77.2%) for MRI. The specificity was 100% for CDUS, FDG-PET/CT and MRI.

Another advantage of PET/CT is the ability to detect other diagnoses of interest. Firstly, PET/CT could detect neoplasms or infections that may mimic GCA. Secondly, polymyalgia rheumatica (PMR), a rheumatic disease that is often associated with GCA, can be confirmed or excluded by PET/CT. In PMR, PET/CT shows high FDG uptake in the scapula and pelvic girdles, and also in the lumbar and cervical interspinous bursae. Thirdly, PET/CT could aid the differential diagnosis of inflammatory rheumatic diseases occurring in the same age group, such as elderly-onset rheumatoid arthritis (EORA), spondyloarthropathies, crystal-induced arthropathies or remitting seronegative symmetrical synovitis with pitting oedema (RS3PE), by showing typical patterns of each disease (40).

Finally, in the case of large-vessel GCA (LV-GCA), a specific subset of GCA usually revealed by nonspecific symptoms (fatigue, fever, weight loss) and in the absence of typical signs of cranial GCA, PET/CT may be the only test that can diagnose GCA by showing vascular FDG uptake in the aorta and its main branches (39, 40).

Prognostic accuracy

FDG uptake evolution during follow-up

Some studies have focused on the evolution of vascular FDG uptake on therapy (mainly with glucocorticoids) by performing repeated PET/CT during follow-up. These studies showed that vascular FDG uptake decreases significantly, especially after 8 months of follow-up (41, 42), and this metabolic regression generally correlates with clinical and biological improvement (24, 43). However, other studies have observed persistent vascular uptake in patients in clinical and biological remission, defined by the absence of clinical signs and normal C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) (44). For example, about 80% of GCA patients who are in remission still have significant vascular uptake on PET-CT (45). In addition, Prieto-Pena et al. (46) reported a significant reduction in vascular FDG uptake in 30 LV-GCA patients followed for 10.8 ± 3.7 months, but less than one third achieved complete normalization of vascular uptake. Some authors have hypothesized that the persistence of low-grade vascular uptake may reflect smouldering inflammation or post-inflammatory vascular remodeling (45). Moreover, thoracic aortic histopathology from aortic surgery revealed active aortitis in most GCA patients despite clinical remission several years after GCA diagnosis, lending credence to the hypothesis of smouldering vasculitis persisting in patients in clinical and biological remission (47). Therefore, the value of follow-up PET/CT to predict the risk of relapse or the occurrence of aortic complication is questionable.

PET/CT for predicting relapse

Some studies have focused on the risk of subsequent relapse in relation to persistent FDG uptake on repeat PET/CT (Table 2). Only the study by Grayson et al. (46) suggests that the value of PETVAS can be used to predict the risk of relapse during follow-up. In this study, the authors prospectively analysed patients with Takayasu's arteritis ($n = 26$) and GCA ($n = 30$) who underwent serial PET/CT every 6 months. A total of 170 PET/CT from 56 patients with LV-GCA were analysed. PETVAS ≥20 during follow-up was associated with an increased risk of recurrence compared to patients with PETVAS <20 (55% vs. 11% of relapse, $p = 0.003$). Interpreting the study may be challenging. Firstly, patients with GCA and Takayasu's arteritis were included. Secondly, the 30 patients with GCA were enrolled 2.6 +/− 2.7 years after diagnosis. Therefore, the patients included may have been more refractory than usual patients and at higher risk of relapse. This may explain why some of them had a PETVAS ≥20 points during follow-up, which is particularly high.

Billet et al. (48) included 55 patients with LV-GCA who underwent 2 PET/CT during the course of the disease (the first at diagnosis and the second 3–12 months later) and who were in clinical and biological remission at the time of the second PET/CT. Only 4/55 (7%) patients had a PETVAS >20 at the time of the second PET/CT. All AUROCs calculated from the time-dependent ROC curves up to 2 years after the second PET/CT were close to 0.5 for both scores (TVS and PETVAS), which means poor discriminatory power to predict relapse. However, this study also has several limitations. Firstly, patients were recruited between 2009 and 2020 in different centres with different PET/CT techniques and resolutions. Therefore, the study's retrospective nature precluded systematic, centralized double-reading of all PET/CT images. Finally, the clinician prescribing the second PET/CT was aware of the imaging results, which may have influenced subsequent treatment decisions and relapse risk.

The study by Hemmig et al. (49) aimed to investigate the value of PET/CT and MRI in predicting relapse after stopping treatment in patients with LV-GCA (25 patients underwent PET/CT and 15 underwent MRI). A relapse occurred in 11/40 patients (27.5%) after

TABLE 2 Summary of studies assessing the prognostic value of PET/CT for subsequent relapse.

Studies	Design	Population	PET/CT	Results for predicting relapse
Blockmans et al. (26)	Prospective	35 GCA patients with PET/CT performed at diagnosis	TVS calculated from PET/CT performed at diagnosis, then at 3 and 6 months if the previous PET/CT showed vascular FDG uptake	Relapse versus no relapse, mean (SD): TVS at diagnosis: 5.2 (5.0) versus 7.5 (7.3), p = NS TVS at 3 months: 1.8 (2.0) versus 3.3 (4.3), p = NS TVS at 6 months: 2.8 (3.7) versus 4.8 (3.6), p = NS
Grayson et al. (25)	Prospective	56 LVV patients (30 with GCA and 26 with Takayasu)	PETVAS calculated from PET/CT performed at six-month intervals in patients in clinical remission	More frequent relapse in patients with PETVAS >20 (45% versus 11%, p = 0.03)
Sammel et al. (27)	Prospective	21 consecutive GCA patients who had PET/CT at diagnosis	TVS computed from PET/CT at diagnosis and after 6 months of follow-up	7 out of 12 (58%) patients with a TVS ≥ 10 at diagnosis relapsed compared with 5/9 (56%) with a TVS < 10
Galli et al. (47)	Retrospective	100 LVV patients (51 with GCA and 49 with Takayasu) who underwent at least one PET/CT (81 patients included in the prognostic analysis)	PETVAS computed from PET/CT performed during clinical remission with at least 6 months of follow-up	PETVAS not associated with subsequent relapses [age- and sex-adjusted HR 1.04 (95% CI 0.97, 1.11)]. AUC PETVAS in predicting subsequent relapses = 0.60 (95% CI 0.50, 0.69)
Hemmig et al. (49)	Prospective	40 GCA patients, but 25 patients included in the prognosis analysis (patients in clinical remission with PET/CT performed at treatment stop)	PET/CT positive if SUVmax artery/liver ratio > 1 for the supra-aortic region and > 1.3 for the aorta and femoral region	PET/CT positive: 4/6 (66.7%) patients who relapsed and 8/19 (42.1%) patients who remained in remission after 4 months of follow-up (p = 0.378)
Billet et al. (48)	Retrospective	65 patients with LVV-GCA diagnosed on PET/CT who underwent a second PET/CT after 3 to 12 months of follow-up	TVS and PETVAS calculated from the first PET/CT and second PET/CT in 55 patients in clinical and biological remission	Time-dependent ROC curves: All AUCs close to 0.5 for TVS and PETVAS calculated at first PET/CT and second PET/CT after different follow-up time

4 months of follow-up (time to relapse 1.9 months, IQR 1.4–3.3). Patients experiencing a relapse had no more active vasculitis on MRI and/or PET/CT (54.5% versus 58.6%, p = 1.0). These results are consistent with other studies detailed in Table 2, which often included patients with GCA and Takayasu's arteritis and calculated TVS (26, 27), PETVAS or both (41).

In summary, PET/CT does not appear to predict relapse and may not be suitable for guiding treatment decisions in patients with LV-GCA in clinical remission.

PET/CT for predicting vascular complications

Large-vessel involvement is known to be associated with an increased risk of vascular complications, particularly aortic dilatation in GCA (43). Therefore, the guidelines specify the need to monitor for structural damage, particularly at sites of previous vascular inflammation (48). This recommendation is supported by several studies.

First, the one of Quinn et al., who reported that in 32 GCA and 28 TAK patients, 80% of vascular territories with significant FDG uptake at baseline developed stenosis or aneurysms during follow-up (50). Then Blockmans et al. (51) also showed in 46 patients with a positive GCA biopsy who underwent PET/CT at diagnosis and a CT scan of the aorta during follow-up with a delay of 46.7 (29.9) months [mean (SD)] that increased FDG uptake was associated with a significantly larger diameter of the ascending and descending aorta and a significantly larger volume of the thoracic aorta. Along this line, Muratore et al. (52) reported that aortic FDG uptake grade 3 at diagnosis was associated with an increased risk of aortic dilatation compared with aortic FDG uptake ≤2. Retrospective data from the French cohort involving 549 GCA patients confirmed the results by showing that in LV-GCA, aortic dilatation occurred in a previously inflamed segment in 94% of cases (51).

More recently, Moreel et al. (53) included 106 GCA patients who had undergone PET/CT at diagnosis, within 3 days of starting glucocorticoid therapy, and who were followed by performing annual CT scans of the aorta over a ten-year period. The TVS at diagnosis was associated with a greater annual increase in thoracic aortic diameter and volume. A positive PET/CT at diagnosis was associated with a

higher risk of thoracic aortic aneurysm [adjusted hazard ratio = 10.24 (CI 95%: 1.25 to 83.3)]. The authors concluded that the intensity and extent of the initial inflammation determine the risk of subsequent aortic dilatation, as no association was observed between the development of thoracic aortic aneurysm and treatment regimen or relapse rate (53). Blockmans et al. (54) performed a post-hoc analysis of this study, including 52/106 patients who had at least one further PET/CT during follow-up. A total of 88 PET/CT were analysed during follow-up, 55 during relapse and 33 during remission. Overall, 9/10 patients with thoracic aortic aneurysms had a positive PET/CT both at diagnosis and during follow-up. However, the authors emphasize that no conclusions can be drawn about FDG uptake in remission because most patients underwent repeat PET/CT during a relapse (54). Therefore, the hypothesis that persistent aortic inflammation may contribute to the development of thoracic aortic aneurysms in GCA contrasts with the lack of association between thoracic aneurysm occurrence and treatment regimen or relapse rate shown in the first part of this study (53).

In conclusion, the results of numerous studies converge on the fact that large-vessel vascular FDG uptake at GCA diagnosis is associated with an increased risk of vascular complications (mainly dilatation and aneurysm) during follow-up. Whether persistent smouldering vascular inflammation or post-inflammatory vascular remodeling is responsible for the development of aortic aneurysms is still unclear.

Cranial PET/CT

Assessment of the cranial arteries (including temporal, occipital, maxillary and vertebral arteries) to diagnose GCA was not part of the original 2018 EULAR recommendations due to a lack of sufficient data (42). Following the publication of several studies evaluating cranial PET/CT (12–15), the updated recommendations include PET/CT alongside MRI as an alternative to ultrasonography for the examination of cranial arteries (46). Comparing these studies is challenging because different criteria were used to define a positive PET/CT and the gold standard diagnosis of GCA.

Two prospective studies by Sammel et al. (48) and Thibault et al. (15) used the clinical diagnosis as the gold standard, based on the absence of an alternative diagnosis and a favorable outcome with glucocorticoid treatment after 6 months of follow-up. Sammel et al. (48) considered the PET/CT to be positive based on a qualitative subjective evaluation of the cranial and thoracic segments. Thibault et al. (15) considered the PET/CT to be positive if at least one cranial segment had a visual grading ≥2 compared to liver FDG uptake. In the studies by Nienhuis et al. (49) and Nielsen et al. (53), patients with metastatic melanoma were used as a control group. Nienhuis et al. (55) included GCA cases with a positive TAB and Nielsen et al. (53) included GCA cases that met the ACR criteria confirmed after 6 months of follow-up. In these two case–control studies, the PET/CT was defined as positive if at least one cranial segment had a higher FDG uptake than the surrounding tissue.

The two prospective studies showed sensitivity of 71 and 73.3% and specificity of 91 and 97.2% for Sammel et al. (12) and Thibault et al. (15), respectively (54). An advantage of the study by Thibault et al. (15) was the combination of cranial PET/CT with extracranial PET/CT in a single examination. The combination of the two examinations optimized sensitivity (73.3% for cranial PET/CT, 66.7% for extracranial PET/CT and 80% for the combination) at the expense of specificity (97.2% for cranial PET/CT, 80.6% for extracranial PET/CT and 77.8% for the combination).

In conclusion, the advantage of cranial PET/CT is that it increases diagnostic sensitivity when combined with extracranial PET/CT. In addition to the temporal arteries, other cranial vessels such as the vertebral, maxillary or occipital arteries can also be studied. The correlation between the involvement of certain arterial segments and the risk of ischemic complications, for example between vertebral arteries and stroke, still requires further research. Table 3 summarises the studies' characteristics.

Perspectives

How PET/CT involvement and the extent of inflammation might guide treatment remains uncertain. Therefore, we believe that prospective evaluation of PET/CT in GCA is needed. This is especially true in clinical trials evaluating immunosuppressive therapy, where data on PET/CT assessment are lacking. In addition, the management of patients with GCA may benefit from the development and evaluation of new technologies. Examples include PET/MRI and new tracers that target the somatostatin receptor.

Combining FDG-PET with MRI may allow more precise anatomical localization of PET tracer uptake and better characterization of the inflamed arterial wall (56), while reducing radiation exposure (57). However, availability is poorer than with PET/CT and no prospective study has investigated the diagnostic performance of FDG-PET/MRI. Laurent et al. (58) defined three different patterns according to the positivity of MRI and/or PET in 13 retrospectively recruited patients with LVV who underwent 18 PET/MRIs at different follow-up times. The "inflammatory" pattern was defined as positive PET (visual grading = 3) and abnormal MRI (stenosis and/or wall thickening), the "fibrous" pattern as negative PET (visual grading = 1 or 2) and abnormal MRI (stenosis and/or wall thickening), and the "normal" pattern when both PET and MRI are negative. In a retrospective study, 14 patients with aortitis defined by PET/CT as the gold standard (11 GCA and 3 Takayasu patients) were compared with 14 control patients without aortitis (59). The sensitivity and specificity of PET/MRI were 85.7 and 100%, respectively. Sensitivity limitations were observed in the thoracic part of the aorta due to motion artefacts.

False-positive results from FDG PET/CT may be due to the metabolic activity of atherosclerosis, which is sometimes difficult to distinguish from persistent smoldering vascular inflammation or vascular remodeling, calling for the development of new, more specific radiotracers. Targeting the somatostatin receptor expressed by inflammatory macrophages, which play a major role in the pathophysiology of GCA, is an interesting prospect that could meet this need. Among these, somatostatin receptor PET/MRI using ^{68}Ga-DOTATATE or ^{8}F-FET-βAG-TOCA are candidates for more specific evaluation of large vessel vasculitis (60). In this prospective study, Ćorović et al. (60) compared 61 patients, including 27 with LVV (GCA = 13, Takayasu = 13, unspecified LVV = 1), 25 with recent atherosclerotic myocardial infarction and 9 patients with

TABLE 3 Summary of studies assessing PET/CT for cranial arteries in GCA.

	Sammel et al. (11)	Thibault et al. (15)	Nienhuis et al. (12)	Nielssen et al. (13)
Design	Prospective		Retrospective/Case–control	
Population	Clinical suspicion of GCA		Control group: PET/CT for follow-up of metastatic melanoma	
	64 patients, including 21 with GCA (12 positive TAB)	51 patients, including 15 with GCA (10 positive TAB)	48 patients (24 biopsy proven GCA and 24 controls)	88 patients (44 GCA including 35 with positive TAB and 44 controls)
Gold standard	Clinical diagnosis retained after at least 6 months of follow-up without alternative diagnosis		GCA confirmed by a positive TAB	GCA defined according to ACR 1990 criteria
Definition of positive PET/CT	Qualitative subjective assessment of the cranial and thoracic segments	At least one cranial segment with a visual grade ≥ 2 (≥ hepatic fixation)	At least one cranial segment with FDG uptake > surrounding tissue	A least one cranial segment (excluding occipital) with FDG uptake > surrounding tissue
Sensitivity	71% [48–89%]	73.3% [51–96%]	83% [64–93%]	82% [67–92%]
Specificity	91% [78–97%]	97.2% [92–103%]	75% [55–88%]	100% [92–100%]
Positive predictive value	79% [54–94%]	91.7% [76–107%]	Not relevant due to case–control design	
Negative predictive value	87% [73–95%]	89.7% [80–99%]		

cancer. PET/MRI with ^{68}Ga-DOTATATE and ^{18}F-FET-bAG-TOCA discriminated active LVV from inactive LVV and active LVV from athrosclerosis with high diagnostic accuracy (AUROC = 0.89 and AUROC = 0.86, respectively).

Conclusion

PET/CT imaging has high diagnostic accuracy in GCA by demonstrating transmural vascular inflammation in large vessels. Recently, sensitivity has been improved by the ability to detect vascular FDG uptake in cranial arteries. LVV detected by PET/CT correlates with disease activity and could predict vascular complications such as aneurysms, suggesting that assessment of vascular damage by morphologic imaging during follow-up is warranted in these patients. However, PET/CT has several limitations. First, significant vascular FDG uptake may remain in some patients in remission on therapy. It is unclear whether this FDG uptake is due to persistent smouldering vascular inflammation or post-inflammatory vascular remodeling. In particular, the persistence of this FDG uptake does not appear to be predictive of future relapse and therefore should not be used to guide treatment decisions in patients in clinical remission. Secondly, the main limitation to the generalization of PET/CT is its availability in most centres less than 72 h after the introduction of glucocorticoids, after which the diagnostic accuracy decreases significantly. This limitation is very problematic because glucocorticoids must be started early after suspicions because of the risk of ophthalmological complications and blindness.

Author contributions

TT: Writing – original draft, Writing – review & editing. J-LA: Writing – review & editing. A-CB: Writing – review & editing. HG: Writing – review & editing. AR: Writing – review & editing. HD: Writing – review & editing. AC: Writing – review & editing. BB: Writing – review & editing. MS: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

MS was employed by the AbbVie consulting, Argenx consulting, Boehringer Ingelheim consulting, GSK consulting, Novartis consulting and research grant, Roche–Chugai consulting, CSL VIFOR consulting, Fresenius consulting. BB was employed by the Roche–Chugai personal fees for consulting, Boehringer Ingelheim consulting. AR was employed by the Novartis research grant, Novartis consulting, AbbVie consulting, Boehringer Ingelheim consulting, Chugai consulting. HD declare Grants from GSK, Consultant for NOVARTIS, Consultant for GSK, Consultant for Jonhson & Jonhson.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Mini Review
PUBLISHED 31 October 2024
DOI 10.3389/fmed.2024.1495644

OPEN ACCESS

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RECEIVED 13 September 2024
ACCEPTED 17 October 2024
PUBLISHED 31 October 2024

CITATION
Ni R and Kohler MJ (2024) What is new in imaging to assist in the diagnosis of giant cell arteritis and Takayasu's arteritis since the EULAR and ACR/VF recommendations? *Front. Med.* 11:1495644. doi: 10.3389/fmed.2024.1495644

What is new in imaging to assist in the diagnosis of giant cell arteritis and Takayasu's arteritis since the EULAR and ACR/VF recommendations?

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Over the past decades, fundamental insights have been gained to establish the pivotal role of imaging in the diagnosis of large-vessel vasculitis, including giant cell arteritis (GCA) and Takayasu's arteritis (TAK). A deeper comprehension of imaging modalities has prompted earlier diagnosis leading to expedited treatment for better prognosis. The European Alliance of Associations in Rheumatology (EULAR) recommended in 2023 that ultrasound should be the initial imaging test in suspected GCA, and Magnetic Resonance Imaging (MRI) remains the first-line imaging modality in suspected TAK. We summarize the recent advances in diagnostic imaging in large vessel vasculitis, highlighting use of combination imaging modalities, and discuss progress in newer imaging techniques such as contrast-enhanced ultrasound, shear wave elastography, ocular ultrasound, ultrasound biomicroscopy, integration of Positron Emission Tomography (PET) with MRI, novel tracer in PET, black blood MRI, orbital MRI, and implementation of artificial intelligence (AI) to existing imaging modalities. Our aim is to offer a perspective on ongoing advancements in imaging for the diagnosis of GCA and TAK, particularly innovative technology, which could potentially boost diagnostic precision.

KEYWORDS

ultrasound, vasculitis, giant cell arteritis - large-vessel, Takayasu's arteritis, temporal arteries ultrasonography

Introduction

Giant cell arteritis (GCA) and Takayasu's arteritis (TAK) are the most common vasculitides that predominantly affect large- to medium-sized vessels (1, 2). GCA commonly affects temporal arteries, ophthalmic arteries, and vertebral arteries, known as cranial GCA, with potential complications of vision loss or ischemic stroke. GCA also involves extracranial arteries, such as subclavian and axillary arteries, known as large vessel vasculitis, associated with stenosis and aneurysm (2). TAK primarily impacts aorta and its main branches, more likely affecting subclavian, renal, mesenteric arteries (2). Early diagnosis and prompt treatment can significantly reduce the complications from vasculitis, preserve vision, and improve prognosis.

The European Alliance of Associations for Rheumatology (EULAR) updated large vessel vasculitis imaging recommendations in 2023 (3) stating that temporal and axillary artery ultrasound should be considered the first-line imaging test in all patients with suspected GCA. As an alternative to ultrasound, cranial and extracranial arteries can be examined by

[^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) or magnetic resonance imaging (MRI). For diagnosing TAK, MRI is the preferred imaging modality, with FDG-PET, computed tomography (CT), or ultrasound as alternatives. It is important to note that all imaging should be performed by a trained specialist using appropriate operational procedures and settings. Ultrasound is highly operator dependent. Generally, in the United States (U.S.), the majority of rheumatologists and radiologists have historically had little to no experience in utilizing ultrasound for diagnosing GCA, and only a few experts exist, compared to our European peers where the utilization of ultrasound for vasculitis among rheumatologists has been more accepted (4). The use of vascular ultrasound is increasingly recommended as a first-line diagnostic test for suspected GCA, and in some European institutions has replaced temporal artery biopsy (TAB) unless ultrasound findings are equivocal (3, 5). In the U.S., the preferred method for diagnosing GCA remained the TAB per 2021 American College of Rheumatology (ACR)/Vasculitis Foundation (VF) guidelines (6). As ultrasound education among U.S. rheumatologists continues to progress with the creation of the ACR Rheumatology Ultrasound (RhUS) supplemental curriculum for rheumatology fellowship training programs (7), hands-on ultrasound workshops and courses at the ACR annual meeting, and training through educational modules and Continued Medical Education (CME) courses via the Ultrasound School of North American Rheumatologists (USSONAR) (8), the utilization of ultrasound among rheumatologists in the U.S. continues to grow. And thus, the 2022 ACR/EULAR classification criteria for large vessel vasculitis now includes both TAB or a positive "halo sign" on ultrasound with equal weight scoring of 5 points toward criteria (9). Meanwhile, 2022 ACR/EULAR classification criteria for TAK emphasizes the equivalent diagnostic role of MRI, CT, ultrasound and PET on various vascular territories (10).

This review provides insights into recent advances in imaging for diagnosing GCA and TAK, including novel technology, which could potentially enhance diagnostic accuracy in clinical practice.

Ultrasound

Ultrasound of temporal and axillary arteries is considered the first-line imaging test of choice to evaluate patients with suspected GCA per EULAR recommendations (3). Gray scale and color Doppler mode are required (3). Using the clinical diagnosis as the reference standard, pooled sensitivities and specificities of color-Doppler ultrasound (CDUS) were 75% (95% confidential interval, CI: 66–83%) and 91% (95% CI: 86–94%), respectively (11). The diagnostic accuracy has further enhanced with the advancement of ultrasound technology and improved operator expertise (12). Temporal artery ultrasound was proven to serve as a cost-effective method for diagnosing GCA accurately in patients with strong clinical suspicion, which help minimize the necessity for TAB (13). A recent study by Monjo-Henry et al. observed increased intima-media thickness (IMT) in GCA by vascular ultrasound of the carotid, subclavian and axillary arteries compared to atherosclerosis (14). Cut-off values of IMT were proposed for diagnosing GCA when compared both to clinical evaluation and MRI findings with consideration of cardiovascular risks; these await further validation (15). Schäfer et al. compared GCA patients with healthy controls and suggested cut-off values of the common superficial temporal arteries, the frontal and parietal branches and the axillary arteries are 0.42, 0.34, 0.29, and 1.0 mm, respectively (16). This led to the development of different scoring systems such as the Southend Halo Score (17) and Outcome Measures in Rheumatology (OMERACT) GCA Ultrasonography Score (OGUS) (18). Southend Halo Score and OGUS were evaluated to assess the diagnostic accuracy and showed an optimal cut-off value of 14.5 (sensitivity of 74.4% and specificity of 97.2%) and 0.81 (sensitivity of 79.07%, specificity of 97.22%), respectively (19). A reduction of the IMT of the temporal artery can be observed within 2–3 days following treatment with pulse glucocorticoids (20). Meanwhile, the normalization of the mean IMT of the axillary artery was observed after 7 days (21). This suggests that temporal artery ultrasound should be performed as soon as possible for diagnostic purposes, even though the treatment itself should not be delayed.

In addition to training the ultrasonographer on how to scan to identify anatomic vessels, it is imperative to also have high quality ultrasound equipment available within the clinic with a high frequency probe to accurately visualize and measure IMT. Without knowledge to adjust ultrasound settings appropriately, false negatives or positives can be created. A standardized training program with theoretical knowledge, reader evaluation session and hands-on scanning workshop provided excellent inter-reader and intra-reader reliability (12, 22). As more rheumatologists receive standardized vasculitis ultrasound (VUS) training to specifically evaluate for vasculitis with presence of the halo sign, and better imaging quality of ultrasound equipment becomes more accessible, the opportunity for rheumatologists to incorporate VUS into their clinical practice will gradually increase, similar to the growth of musculoskeletal ultrasound among rheumatologists.

As more imaging is obtained and the use of Artificial Intelligence (AI) is incorporated into ultrasound equipment software, it may become easier to identify the correct anatomy and findings of GCA with more confidence and accuracy. This is already being explored with a minimum resolution requirement of 224 × 224 pixels for human experts to proficiently assess VUS images (23). This discovery served as the foundation for creating an AI-powered tool to assist in classifying ultrasound images for detecting GCA. Roncato et al. created and analyzed CDUS images in GCA via a convolutional neural network and detected halo sign with a sensitivity and specificity of 60% and 90%, respectively (24). AI also holds the potential to mitigate the operator-dependent limitations by enhancing the accuracy and consistency of ultrasound evaluations and offering a supplementary perspective to the examiner during image analysis as well as potential for more accurate measurements (25).

Contrast-enhanced ultrasonography (CEUS) may play a role in evaluating disease activity in large vessel vasculitis (26, 27). CEUS with administration of sulfur hexafluoride gas stabilized by a phospholipid and palmitic acid envelope was designed to improve the visualization of vasculature (28). The contrast-formed microbubbles within the thickened artery lesions represented neovascularization. ≥ 25% increased contrasted areas of axillary/subclavian and/or carotid arteries can distinguish active and inactive GCA with a sensitivity and specificity of 91.7% and 100%, respectively (29). CEUS of carotid artery was found to detect response and relapse correlated with clinical evaluation in TAK (30, 31).

Increased arterial stiffness is associated with complications, such as hypertension and accelerated atherosclerosis in TAK, which can be detected by shear wave elastography (SWE). SWE is a non-invasive

ultrasound technique that monitors and records the velocity of shear waves to assess the elasticity of blood vessels. Ucar et al. discovered that carotid artery stiffness is significantly higher in TAK along with increased IMT detected by SWE and CEUS (32).

Ultrasound biomicroscopy (UBM) of temporal artery, also known as very-high resolution ultrasound, may predict the result of TAB. The halo sign and or the intra-arterial middle reflexive filling, detected by 50–55 MHz probe on UBM, showed positive predictive value of 44.4% and negative predictive value of 100% (33). The IMT measurement by very-high resolution ultrasound was found more sensitive than conventional CDUS with maximum frequency of 22 MHz (34). UBM has been utilized to diagnose uveitis, glaucoma and cataract in ophthalmic diseases (35), which are related with glucocorticoid toxicity and can mimic as a visual disturbance in GCA.

Ocular ultrasound is currently used in the emergency medicine setting for identification of foreign body, retinal detachment (36). Clinical visual deterioration in GCA was correlated with absence of blood flow on CDUS of orbital vessels, including ophthalmic, central retinal, nasal and temporal posterior ciliary arteries (37, 38). Ocular ultrasound can also detect vitreous echoes and optic nerve sheath thickness (39). Future studies incorporating ocular ultrasound and UBM may be of interest to better understand predictive changes that may occur in GCA prior to vision loss.

Positron emission tomography

[^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has been proven to diagnose large vessel vasculitis with pooled sensitivities and specificities of 80% (95% CI: 70–97%) and 91% (95% CI: 67–98%), respectively (11). FDG-PET/CT can provide an accurate diagnosis within 3 days of initiating high-dose glucocorticoid treatment and the diagnostic sensitivity decreases after 10 days of treatment (40). A recent retrospective study revealed the utilization of ^{18}F-FDG-PET/CT in diagnosing GCA with negative temporal artery biopsy (41). Positive FDG uptake at the time of diagnosis of GCA had an increased risk for thoracic aortic aneurysm, stenosis or occlusion (42, 43). Adding iodine to FDG-PET/CT imaging may serve as a potentially synergistic tool that can concurrently concentrate on both vascular inflammation and the structural status of the blood vessels in TAK (44).

Several attempts have been made to rectify the shortcomings of conventional static FDG-PET/CT. Scoring systems using FDG uptake intensity compared to liver uptake and arterial wall calcification as semi-quantitative parameters were developed to optimize the evaluation of GCA and reduce the inconsistency between different readers (45, 46). The FDG-PET/CT is mainly valid in large vessels, including aorta, axillary/subclavian arteries instead of temporal or vertebral arteries due to disparity of imaging acquisition time in large- and medium-sized vessels (47). A prolonged 5-min acquisition time may provide a higher observer agreement than a regular 2-min acquisition time in diagnosing cranial GCA, along with usage of vascular scores (48). Dynamic-whole body FDG-PET/CT was introduced to remove the radioactivity in the luminal blood pool and better distinguish the walls of vessels (47).

Integration of PET imaging with MRI provides a more accurate anatomical visualization of PET tracer uptake, especially in cranial GCA (47). PET/MRI may better define active inflammatory from inactive fibrous large vessel vasculitis in GCA and TAK compared to PET/CT and has lower radiation (49, 50).

Discovering a novel tracer in PET is also intriguing to improve diagnostic accuracy in GCA. Tissues and cells vie for the absorption of both glucose and FDG. Hyperglycemia is not uncommon in patients with suspected large vessel vasculitis on empiric high dose glucocorticoids and elevated circulating blood glucose affects the interpretation of FDG-PET (40, 51). Somatostatin receptor 2, a macrophage marker involved in the pathogenesis of GCA and TAK, showed higher uptake in active large vessel vasculitis compared to inactive vasculitis and atherosclerosis (52). Given its extremely low background noise in the brain and heart, it may permit detecting the involvement of coronary artery in TAK and intracranial artery in GCA (52). Fibroblasts are also recruited in vasculitis while radiotracers based on fibroblast activation protein inhibitor and ^{68}Ga may detect active inflammation where results from ^{18}F-FDG-PET/CT are not definitive (53).

AI-based segmentation of vasculature can expedite pre-analysis processing steps in PET quantification, to improve molecular and structural accuracy and enhance inter-reader reliability (54).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) of cranial arteries has a pooled sensitivity of 82% (95% CI: 76–86%) and specificity of 92% (95% CI: 84–97%) with clinical diagnosis of GCA as reference standard (11). MRI remains the preferable imaging test to investigate mural inflammation or luminal changes in patients with suspected TAK (3, 55).

3D-compressed sensing T1-weighted black blood high resolution MRI (BB-MRI) allows precise visualization of intracranial vessel wall inflammation. The involvement of intracranial arteries, including internal carotid artery, vertebral artery, posterior cerebral artery and basilar artery, was discovered by BB-MRI in GCA without artery stenosis or occlusion (56). Additional research is needed to distinguish the findings from atherosclerosis and stratify the risks of stroke in this population.

Application of orbital MRI may assist in stratifying patients with high-risk of vision loss in GCA. Gadolinium-enhancement of the optic nerve sheath and ophthalmic artery wall was found to correlate with visual symptoms and fundoscopic examinations (57, 58). Pathologic orbital MRI findings were observed in asymptomatic patients, clinically unaffected eyes or fundoscopic-negative exams (59). This may indicate early ischemic changes and possible development of posterior ischemic optic neuropathy. Further studies are required to determine the clinical significance and prognosis of abnormal subclinical orbital MRI.

Computed tomography angiography, optic coherence tomography and fluorescein angiography

Computed tomography angiography (CTA) revealed a sensitivity of 73.3% and a specificity of 77.8% in patients with suspected

GCA. These results were based on the reference standard of clinical diagnostic criteria of GCA after 6 months (60). CTA can be utilized to screen at diagnosis for aneurysm, dissection, or stenosis.

Optic Coherence Tomography (OCT) has been utilized in patients with GCA to assess ocular manifestations. OCT can detect optic disc edema, thickening of the inner retinal nerve fiber layer and ganglion cell layer, and loss of layer structure in acute stages of optic neuropathy and retinopathy. In later stages, OCT can show diffuse atrophy of the inner retina (61). Full-field OCT of TAB shows potential for identifying characteristic pathological lesions of GCA within minutes (62). OCT angiography has been used to describe chorioretinal signs in GCA, including choroidal ischemia, which is a key angiographic indicator in the diagnosis of GCA (63).

Positive fluorescein angiography or indocyanine green angiography was found with a sensitivity and specificity of 88% (95% CI: 69–97%) and 74% (95% CI: 49–91%), respectively, when compared to clinical diagnosis (64). Positive imaging tests were identified as either a delay in the filling of choroidal vessels or the existence of choroidal areas without vascularization. Due to its invasiveness, catheter-based angiography is no longer the preferred initial imaging method.

Comparison and incorporation of multiple imaging modalities

Ultrasound of cranial and extracranial arteries showed high sensitivity and specificity to diagnose GCA compared to other imaging modalities. Adding ultrasonography of extracranial arteries to cranial arteries can increase sensitivity from 70% (95% CI: 59–79%) to 89% (95% CI: 73–96%) to detect GCA while preserve specificity around 91% (11). Extracranial involvement can be identified by both ultrasound and FDG-PET/CT (65, 66). FDG-PET/CT can detect aortitis in 33.3% of patients with positive ultrasound of extracranial arteries and 8.3% of patients with negative ultrasound findings were found with aortitis on FDG-PET/CT (67). Hemmig et al. concluded that MRI of subclavian/axillary arteries aligned with PET/CT findings but less frequent on ultrasound (68). Notably, vasculitis was defined qualitatively (69) and duration of steroid treatment varied before the imaging tests. The results of BB-MRI without contrast were consistent with FDG-PET/CT in diagnosing GCA (70). A recent nested-case control study compared CDUS, FDG-PET/CT and MRI with clinical diagnosis of GCA at 6-month follow up. CDUS had the highest sensitivity of 69.6% (95% CI: 50.4–88.8%) and equivalently high specificity among all the imaging modalities (71).

Multimodal imaging can improve diagnostic accuracy with a comprehensive assessment of both cranial and extracranial involvement (65). A diagnostic algorithm with ultrasound, MRI and retinal angiography was proposed to optimize the diagnostic performance of imaging in GCA (64). In this small sample study, it was proposed to initiate investigations with MRI, followed by ultrasound or retinal angiography to yield best diagnostic performance. This requires further validation in large populations. Multimodality imaging, including ultrasound, CT, MRI, and PET/CT, provides a more accurate and comprehensive diagnostic approach for GCA, which is essential for timely initiation of treatment to prevent serious complications. Additional studies are needed to investigate how multi-modal quantitative imaging to assess degree of disease burden may impact treatment response and relapse rates.

Conclusion

Progressive advances in imaging technologies hold promise for improving the accurate diagnosis and monitoring of large vessel vasculitis. VUS has already shown its clinical impact on expediting large vessel vasculitis diagnoses, however further ultrasound education to teach VUS expansively is needed to make this skillset more widespread and accessible, similar to what has happened with MSKUS use among rheumatologists. Utilization of various imaging modalities including ultrasound, CT +/− PET and MRI to evaluate vasculitis both qualitatively and quantitatively will continue to assist in expedited diagnosis in conjunction with a good history and clinical exam. Additional advances in ocular and orbital imaging may also provide new insights into earlier diagnosis of disease. In cases where vasculitis is suspected but the initial imaging test is negative, combination use of imaging should be considered to obtain the optimal diagnostic accuracy for large vessel vasculitis. Despite substantial technological advancements over the past decade, the validation of new imaging modalities and standardized protocols as well as potential for the concomitant use of AI are still needed before they can be incorporated into routine clinical practice.

Author contributions

RN: Writing – original draft, Writing – review & editing. MK: Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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