Review

Vascular imaging as an endpoint in clinical trials of giant cell arteritis

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ABSTRACT

Giant cell arteritis (GCA) is a form of large-vessel vasculitis that can affect the head and/or neck vessels as well as the aorta and its major branches. Vascular imaging techniques like ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), magnetic resonance angiography (MRA), and ultrasound (US) are gaining significant attention as potential endpoints in clinical trials of GCA. Imaging is crucial not only for diagnostic purposes, but also for potential accurate and reliable assessment of disease activity, especially when evaluating treatment response to novel targeted therapies in GCA. Imaging scoring systems can assist with tracking changes in vascular inflammation and damage over time. Vascular imaging is also a valuable tool for detection of subclinical inflammation and/or vascular remodelling that is not possible with clinical assessment. Furthermore, vascular imaging might predict angiographic progression. In this article, we review the utility of vascular imaging as an endpoint in GCA clinical trials highlighting the challenges that are associated with its application.

Introduction

Giant cell arteritis (GCA) is a form of large-vessel vasculitis that affects the large and medium-sized vessels (1). GCA can affect cranial or extracranial arteries. While cranial GCA affects the temporal arteries and/or other branches of the external carotid arteries, extracranial GCA affects the aorta and its major branches (2). Currently, there are no well-established biomarkers to monitor disease activity or disease progression in GCA, especially when there is discordance between clinical assessment and inflammatory markers, or when IL-6 receptor inhibitors such as tocilizumab directly block CRP production from the liver.

Vascular imaging modalities such as ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) with or without computed tomography (CT) angiography, magnetic resonance angiography (MRA) or magnetic resonance imaging (MRI), and vascular ultrasound (US) can detect vascular inflammation in GCA. Vascular imaging is important not only for diagnostic purposes, but also for disease monitoring, as it can assist with evaluating inflammation, disease progression and damage in different arterial territories (3). Silent angiographic progression with development of new lesions in arterial territories, and persistently active disease have been observed in patients with GCA on tocilizumab, despite apparent clinical and biochemical remission, making it challenging to distinguish between active disease and remission by relying only on clinical and laboratory assessment (4). Vascular imaging might be more sensitive in demonstrating response of inflammation to therapy compared to reliance on clinical assessment and inflammatory markers. Thus, it has the capacity to assist with the detection of disease activity and progression in addition to treatment effectiveness (4-6). This is particularly important, when conducting clinical trials of novel therapies, as vascular imaging can potentially be utilised as an endpoint to assess disease activity and objectify the response to therapy in patients with GCA. In this review article we discuss in detail the role and utility of vascular imaging as a potential endpoint in GCA clinical trials.

FDG-PET/CT as an endpoint in clinical trials of giant cell arteritis

While temporal artery biopsy used to be considered the gold standard for the diagnosis of GCA, it is not suitable as an endpoint in clinical trials as the bi-

opsied arterial segment cannot be examined before and after treatment. Additionally, its sensitivity is low because of the occurrence of skip lesions (7). In contrast, repeated vascular imaging with ^{18}F-FDG PET/CT can offer a more comprehensive and non-invasive method to assess disease extent and activity (8). ^{18}F-FDG PET/CT is frequently used in the assessment and evaluation of patients with extracranial, large vessel GCA (LV-GCA), providing information about active vascular inflammation, and structural damage when conjugated with CTA (9). With the introduction of high-resolution scanners, ^{18}F-FDG-PET/CT can also assess the cranial arteries (10), but specialised scanning protocols are lacking.

^{18}F-FDG PET/CT can be used as a surrogate marker for arterial inflammation by demonstrating metabolic activity within the arterial wall and can help monitor disease activity but also assess treatment responses in patients with GCA (11-13) (Table I). It can be combined with CT angiography, a valuable tool providing detailed images of the aorta and other large arteries. CTA allows for the evaluation of structural changes such as stenosis, occlusion, dilatation, aneurysm formation, and mural thrombi that can be associated with disease progression in GCA, reflecting cumulative vascular damage rather than acute inflammatory activity (14). ^{18}F-FDG PET when combined with CT angiography, might provide synergistic value for diagnostic purposes, monitoring of disease activity, and progression of disease (15).

In clinical trials of patients with GCA, the primary outcome often focuses on sustained remission, while the imaging assessment of the arterial disease is often viewed as a secondary endpoint to assess the efficacy of new therapies, such as tocilizumab and upadacitinib in decreasing disease activity, and is usually incorporated when patients are in remission and not at the time of the diagnosis (16, 17).

Currently, there are no standardised imaging outcome measures available that can be incorporated in disease activity [(*i.e.* Birmingham Vasculitis Activity Score (BVAS), Indian Takayasu Arteritis Score (ITAS)], or damage indices of the disease (*i.e.* Vasculitis Damage Index, Large-Vessel Vasculitis Index of Damage) (18, 19). Recent longitudinal studies demonstrated that FDG uptake in the vasculature was significantly reduced over time in response to treatment, and that persistent vascular activity was associated with an increased risk of future clinical relapses (11), but in some cases it can be an early indicator of subsequent angiographic change (20).

Interestingly, in a recent systematic review and meta-analysis FDG-PET/CT was able to identify relapsing/refractory disease with a sensitivity of 77% (95%CI 57–90%) and specificity of 71% (95%CI 47–87%) (21). However, other studies found that FDG-PET/CT did not predict relapses after stopping treatment, as patients that experienced a relapse had no active vasculitis on the FDG-PET/CT (22, 23). In another prospective longitudinal study of patients with GCA, the FDG uptake decreased after 3 and 6 months of glucocorticoid treatment, but there was still persistent arterial wall FDG uptake in cases of clinical remission (24). Reduction of arterial wall FDG uptake, rather than complete normalisation, could be an indicator of good treatment response. In contrast, new or worsening FDG-uptake compared to previous scans could be a potential warning of treatment failure if it is used as an endpoint in ongoing clinical trials**.** However, further research is needed to better understand whether persistent, low grade FDG uptake indicates subclinical inflammation or vascular remodelling, and whether it can truly predict future relapse of the disease, or angiographic damage over time. Currently, FDG-PET/CT should not be used to guide treatment decisions in patients in unequivocal clinical remission, and imaging abnormalities should be interpreted in the context of clinical assessment, inflammatory markers, and individual patient risk factors.

FDG-PET can also be helpful when a patient develops atypical manifestations such as abdominal angina, anorexia, blurred vision, diplopia, odynophagia, hearing loss, dry cough or weight loss with normal inflammatory markers that could be concerning for active disease (25). In these cases, new or worsening FDG-uptake compared to previous scans could be a potential warning of treatment failure if it is used as an endpoint in ongoing clinical trials.

To grade vascular inflammation using PET, several scores have been proposed including a visual qualitative score called total vascular score (TVS) that can grade the metabolic activity by summing up the FDG uptake in 14 different arterial territories, including bilateral carotid, subclavian, axillary, iliac and femoral arteries as well as the ascending thoracic aorta, the aortic arch, the descending thoracic and the abdominal aorta, and can range from 0 to 42 points (26).

In contrast to TVS, PET Vascular Activity Score (PETVAS) that is another qualitative score does not involve lower limb arteries where atherosclerosis might be misinterpreted as inflammation and is a quantitative score of FDG uptake throughout nine main susceptible arteries (ascending aorta, aortic arch, descending thoracic aorta, abdominal aorta, right axillary artery, left axillary artery, innominate artery, right subclavian artery and left subclavian artery). Each of these nine arterial territories is scored between 0 and 3 based on the FDG uptake separately, with the FDG-uptake being graded as 0=no uptake, grade 1=less than liver uptake, grade 2=equal involvement to the liver, grade 3=greater than liver uptake. PETVAS ranges from 0 to 27. Complete normalization in follow-up imaging is considered when total PETVAS equals 0 (27, 28). A PETVAS ≥10 can differentiate between active disease and remission with 60.8% sensitivity and 80.6% specificity (29). In a different study, a cut off value of 12 distinguished active from inactive disease with a sensitivity of 74% and specificity of 76% (30).

A recent study demonstrated the effectiveness of tocilizumab in decreasing FDG vascular activity, by using the PETVAS scoring system, upon 2 years of treatment in patients with GCA that had active vasculitis on the PET/CT imaging modality at their baseline visit (31).

Table I. Advantages and limitations of different vascular imaging modalities as endpoint in clinical trials of GCA.

Imaging modality	Advantages	Limitations
FDG-PET/CT	- Directly demonstrates the metabolic activity in the arterial wall. - May predict future clinical relapses or angiographic changes if persistent vascular activity. - Allows evaluation of treatment response and therapeutic effectiveness. - Utilises objective imaging metrics such as visual qualitative scoring system, and semi-quantitative assessments. - Identifies structural damage (arterial stenosis, occlusion or aneurysm formation) in conjugation with CT angiography. - Serves as an alternative to biopsy in the diagnosis of GCA. - Identifies patients with specific disease phenotypes (LV-GCA). - Standardises patient recruitment into enrolment of clinical trials. - Allows long-term monitoring.	- Offers short "window of opportunity" (lower sensitivity if per formed more than 3 days of glucocorticoids). - Requires optimal patient preparation (overnight fasting). - Lacks standardisation in interpretation of results among different centres. - Reduced availability and high cost. - Risk of radiation exposure. - Cannot identify patients with cranial GCA (unless new generation, high resolution scanners are used) - Can be difficult to differentiate atherosclerosis from vasculitis.
MRA/MRI	- Directly detects vessel wall thickness, mural enhancement, as well as arterial damage. - Monitors vascular inflammation at suitable endpoints for longitudinal clinical studies. - Identifies subclinical disease in asymptomatic patients. - Offers a strong surrogate endpoint for changes in stenosis scores in clinical trials. - No radiation exposure.	- Decreased sensitivity if performed more than 4 to 5 days of therapy. - Not suitable for patients with claustrophobia, end stage kidney disease or pacemakers. - Increased cost and limited availability. - Inaccurate correlation with disease activity - Lengthy examination sensitive to motion.
Vascular ultrasound	- Non-invasive imaging modality. - Provides immediate results. - Inexpensive imaging modality compared to PET/CT and MRA/MRI. - Provides a standardised scoring system (OGUS score) for disease activity and treatment response in clinical trials. - Differentiates between remission and relapse and forecasts the likelihood of relapse in GCA. - No radiation risk.	- Requires specialised training. - Not available in all centres. - It is operator dependent. - Inability to access the thoracic aorta and its major branches. - Sensitivity decreases within three days of glucocorticoids.

The RIGA study showed equal improvement of PETVAS scores in patients treated with monotherapy glucocorticoids and those treated with glucocorticoid-sparing therapies, including methotrexate and tocilizumab (32).

Standardization of vascular imaging techniques is vital for precise and replicable results when used in GCA clinical trials. Semi-quantitative assessments such as Target-to-Background Ratio (TBR) and SUV are also useful in evaluating and monitoring vascular inflammation. Recent studies found that semi-quantitative methods might offer superior reliability, and better discrimination of treatment response compared to qualitative assessments such as PETVAS (33, 34). Semi-quantitative methods also correlated better with systemic inflammatory markers, but the correlation was weak. Also, qualitative metrics might not identify important variability among patients with severe vascular inflammation, and therefore semi-quantitative metrics might be preferable (34), when evaluating outcome measurements in clinical trials (Table 2). However, new scoring systems that calculate the total inflammatory vascular volume (TIVV) as well as the total inflammation glycolytic volume (TIGV) obtained by multiplying TIVV by the mean standardized uptake value (SUVmean) may offer diagnostic advantages (35). FDG-PET uptake in the aorta might also predict development of thoracic aortic aneurysms, as higher total vascular score (TVS) was associated with greater yearly increase in aortic dimensions (36). Automated analysis methods could make more advanced analysis of FDG-PET data more practical and achievable in the future (37).

Use of vascular imaging with FDG-PET/CT angiography might have some limitations. It can be expensive and is not suitable for all patients, *i.e.* those that are obese, have contrast allergies or hyperglycaemia leading to altered FDG biodistribution (38). It might also not be a good fit for patients that are unable to adhere to pre-imaging instructions such as fasting or fat-enriched and low carbohydrate diet. Nephrotoxicity of iodinated contrast agent is also an important consideration when combining 18F-FDG-PET with CT angiography. Other limitations include the risk of radiation, the requirement for extensive expertise, and experience when interpreting FDG-PET imaging studies, that could vary among institutions. At diagnosis, it should be performed within 3 days of starting glucocorticoids, as treatment rapidly reduces sensitivity (Table I) (40), although delayed imaging at 180 minutes might potentially improve the sensitivity (41).

In conclusion, FDG-PET with CT angiography might play an important role in GCA clinical trials as a useful endpoint measure, by incorporating qualitative or semi-quantitative scoring systems in our assessment, that could provide a more objective and detailed visualisation of disease activity, and extent of arterial damage. These scoring meth-

ods can also be utilised as a metric of therapeutic response in serial imaging studies compared to solely relying on clinical assessment and inflammatory biomarkers in clinical trials.

MRA and MRI as an endpoint in clinical trials of giant cell arteritis

MRA of large vessels and high-resolution MRI of cranial arteries are other imaging modalities that could be implemented as a valuable tool when conducting clinical trials in GCA. They can be used for the evaluation of both cranial and extracranial GCA via visualisation of cranial or large arteries such as the aorta, subclavian, and axillary arteries that are commonly affected in extracranial GCA (3, 42).

A combined MRA and MRI exam can evaluate both vascular inflammation by identifying vessel wall thickness, and oedema with mural enhancement, as well as detect arterial damage by demonstrating arterial anatomic abnormalities including stenosis, occlusion or aneurysmal formation (43, 44). This is useful for evaluating disease progression, response to treatment, and structural damage over time in patients with large vessel involvement (Table I).

Vessel wall (VW)-MRI demonstrated a sensitivity of 91%, and specificity of 78% in detecting GCA, as compared to temporal artery biopsy in a recent retrospective study (45). MRA can monitor vascular inflammation by identifying vessel wall thickness, and oedema with mural enhancement, as well as detect arterial damage by demonstrating arterial anatomic abnormalities including stenosis, occlusion or aneurysmal formation (44). This is useful for evaluating disease progression, response to treatment, and structural damage over time in patients with large vessel involvement (Table I). By periodically comparing MRA scans, clinicians can assess whether there is worsening vascular inflammation as well as monitor treatment effects to indicate improvement or deterioration in arterial stenosis in patients with GCA (46, 47). In a randomised controlled trial of tocilizumab in GCA, MRA vessel wall signal showed normalisation in only one third of the participants after 52 weeks (5).

The intensity of contrast enhancement and mural thickening of the cranial and extracranial arteries on MRI can be graded visually and potentially be used as an endpoint in clinical trials. Each of these cranial and/or extracranial arteries can be graded as 1 with the absence of contrast enhancement or mural thickening, as 2 with slight mural contrast enhancement, as 3 with evident enhancement or as 4 with strong enhancement, with the latter two grades representing pathologic inflammatory changes (47). Although this scoring system has not been yet validated, further research is required to evaluate the impact of spatial resolution in T2 images to enhance the detection of moderate GCA-related changes in vessel inflammation.

Similarly to FDG-PET, patients with GCA may have evidence of persistent vascular lesions on MRI or MRA, but in the absence of clinical symptoms and normal inflammatory markers it may indicate remission of the disease or remodelling (5, 47, 48). Interestingly, in a recent study cranial vascular segments normalised on MRI after 52 weeks of treatment with ultra-short glucocorticoids and tocilizumab, whereas MR segments of large vessels showed persistent vasculitic changes despite full sustained clinical remission (49). These results suggest that imaging findings may not be directly related to acute inflammation or that imaging findings might persist even after symptoms resolve.

A novel standardised scoring system, the Magnetic Resonance Vasculitis Activity Score (MRVAS) that assesses the extent of vascular inflammation in cranial vessels, and the aorta with its branches in a binary fashion, demonstrated high levels of interrater agreement rates. It could potentially be incorporated in clinical trials for risk stratification purposes, as a worsening score might be indicative of disease activity (50). Although MRVAS score is promising it has not yet been prospectively validated as a treatment response measure and its role could be limited as a potential endpoint for disease activity. Moreover, persistent contrast enhancement on MRI may not necessarily reflect ongoing active inflammation and may instead represent vascular remodelling, fibrosis, or post-inflammatory changes.

A novel scoring system called the Vasculitis Activity using MR PET (VAMP) score combines 12 arterial territories from PET metrics by utilising SUV mean with the presence or absence of T2-weighted mural signal in major aorta and great vessels and showed excellent intra-and inter-operator reliability. A cut-off of 0.985 was able to differentiate active from inactive disease with a sensitivity of 96% and specificity of 82%, which surpassed blinded assessment by clinician experts and displayed response to treatment (30).

On the other hand, arterial stenosis and aneurysm formation on MRA reflect damage rather than disease activity. The degree of arterial stenosis can be characterised after dividing the arterial tree into the following segments: aortic arch, innominate artery, left prevertebral subclavian, right subclavian, left subclavian (postvertebral), right common carotid, left common carotid, right vertebral, left vertebral, right axillary and left axillary. A 5-point grading scale can then be implemented on each of these segments: grade 0 would indicate a normal segment (absence of stenosis); grade 1, mild arterial disease (50% luminal stenosis); grade 2, moderate arterial stenosis (50–69% luminal narrowing); grade 3, severe arterial stenosis (70–99% luminal stenosis); and grade 4, complete arterial occlusion (100% luminal stenosis) (40).

In a recent study, increases of ≥1 in the stenosis scores on MRA was considered a reliable marker for arterial disease progression (51), and these changes in stenosis scores could be used as an endpoint in GCA clinical trials (Table I). Another study developed a numerical damage assessment score, the Combined Arteritis Damage Score (CARDS) based on radiologic lesions in 25 vessels that were acquired by enhanced CT or MRA in patients with large-vessel vasculitis. This tool could be of potential utility in GCA clinical trials as well (52).

MRA and MRI use have some limitations. Assessment of disease activity by MRA and MRI could be unreliable as they do not always align well

with clinical status (53). The use of glucocorticoids affects the sensitivity of baseline MRA or MRI after 4 to 5 days of therapy (54), posing challenges when comparing follow up scans for disease monitoring. These examinations can be lengthy which may limit their use in patients who find it difficult to remain prone for long stretches of time. Also, the interpretation of MRA or MRI images can vary based on the expertise of the radiologist, though a recent study showed high reproducibility in VW-MRI interpretation even among less experienced readers (45). Arterial pseudo-stenoses due to early arterial phase angiography can commonly occur within the upper extremity arteries in patients with large vessel vasculitis and can look like a true stenosis. Thus, high-resolution delayed imaging of the subclavian arteries is recommended to confirm that the pseudo-stenosis is attributed to an artifact (55).

Another limitation is the high cost and the availability of the MRA or MRI machine equipped with specific scan protocols for GCA, that could be limited in some academic or community settings. Finally, some patients may be claustrophobic or may have metallic devices, and therefore not be eligible for MRA or MRI studies (Table I).

In conclusion, MRA and MRI could be used as a serial marker of disease activity, and/or damage in GCA clinical trials, by integrating contrast enhancement and stenosis scores in the overall disease assessment. By tracking changes in these scores over time, MRA and MRI can complement clinical, laboratory and other imaging-based assessments to monitor disease activity or damage, progression or relapse, and/or treatment response in a more objective manner compared to reliance on clinical and laboratory assessment. For example, a reduction in mural contrast enhancement or stenosis may suggest a response to therapy and may provide valuable information for decision making in the clinical setting at the time point that the imaging was conducted.

Vascular US as an endpoint in clinical trials of giant cell arteritis

Vascular US is a valuable imaging modality that can be used to confirm the diagnosis of GCA by visualising vascular inflammation but also evaluate morphological changes in the vessel wall thickness as well as vascular damage in follow-up visits (56). In GCA, thickening of the arterial wall due to intimal hyperplasia is a key feature (57), and together with oedema, this causes the hypoechoic wall thickening on US that is known as 'halo sign' (58).

US with high frequency transducers enables the measurement of intima-media thickness (IMT) in temporal arteries. However, IMT measurement should not be used solely for diagnostic purposes, as older population particularly those with severe arteriosclerosis may demonstrate higher IMT values independently of vasculitis (59). On the other hand, established cut-off IMT values can be useful for disease monitoring or response to therapy in GCA (60, 61).

Interestingly, the OMERACT Giant Cell Arteritis Ultrasound Score (OGUS) was developed based on these established cut-off IMT values. The cut-off of IMT is 0.4 mm for common superficial temporal artery, 0.3 mm for parietal branch, 0.3 mm for frontal branch, and 1.00 mm for axillary artery. OGUS is a composite score that cannot be used for the diagnosis of the disease but can evaluate the extent of arterial inflammation in patients with GCA through averaging the score by the number of segments that are assessed. It has a good inter-reader and intra-reader reliability among US operators (62). The optimal cut off point for OGUS to separate active from inactive disease is 0.81 with a sensitivity of 79.07% and specificity of 97.22% (63). Thus, the OGUS could be used as an outcome measure and endpoint for treatment response in clinical trials. However, it is important to have prior measurements, as changes in OGUS are more indicative of disease activity than single point measurement, and might predict the risk of relapse in patients with GCA (Table I) (64). At relapses, the mean IMT and OGUS tend to be higher compared to prior US assessments in a phase of clinical remission, as recently demonstrated in a prospective study (65).

Also, in another study the lack of OGUS improvement at 3- and 6-months follow-up visits indicated the high probability of future relapses (66). Notably, a higher OGUS score at baseline predicted early relapses within the next twelve months, whereas an earlier reduction of the OGUS score (score <1), particularly over the first three weeks was linked to a lower risk of relapse in the long term. Similarly, an OGUS reduction over the first 12 weeks was associated with a lower likelihood of DMARD initiation (67) (Table II).

In another prospective study, vascular US detected relapses in patients with GCA with moderate sensitivity (61.2%) and specificity (72.3%). However, after using a composite score based on symptoms, vascular US activity and CRP levels, disease was considered active if at least two of the three components were positive (68).

Vascular US was also found to be a valuable tool for evaluating disease activity and treatment response in GCA. In a recent study, the "halo sign" surrounding the temporal arteries significantly decreased over a 26-week period of glucocorticoids. Interestingly, the decrease in the temporal artery halo sign correlated with inflammatory biomarkers, disease activity as assessed by Birmingham Vasculitis Activity Score (BVAS), and cumulative glucocorticoid exposure. However, there was no significant correlation found for the axillary halo sign, that was persistent even in cases of clinical remission (69). In another study, tocilizumab achieved a slow but steady decline of the IMT in the temporal arteries over a period of 52 weeks implicating the important role of US in monitoring disease activity in GCA (6).

Another important aspect of the vascular US is that it can detect stenosis and occlusions, as well as monitor development of aortic aneurysms in patients with large vessel involvement. Given that the ascending aorta is mostly involved in extracranial GCA, with the risk of thoracic aneurysm development as a potential complication, measurement of the aortic diameter around 6 cm distal to the aortic valve could be achieved with the help of ultrasound

Table II. Vascular imaging as an endpoint in clinical trials of GCA.

Imaging modality	Timing of scans	Scoring methods	Outcome measure
FDG-PET/CT	**Baseline scan (pre-treatment)** - glucocorticoid-naïve patients, or - within 3 days of glucocorticoid treatment initiation **Follow-up scans** - at 6–12-month intervals	**Semi-quantitative methods** - vessel-to liver SUVmax ratio - SUVmax ratios (vessel-to-blood pool) - TIVV - TIGV **Qualitative visual grading** - Grade 0: no FDG uptake - Grade 1: low-grade uptake, less than liver uptake - Grade 2=equal involvement to the liver - Grade 3=greater than liver involvement - TVS - PETVAS	**Remission** - reduction or normalization in FDG uptake - cutoff of PETVAS <10 **Active disease** - new or worsening FDG uptake - cutoff of PETVAS ≥10
MRA/MRI	**Baseline scan (pre-treatment)** - glucocorticoid-naïve patients, or - within 4-5 days of glucocorticoid treatment initiation **Follow-up scans** - at 6–12-month intervals	**Scoring for mural thickening/enhancement** - Grade 1: no mural thickening and no mural enhancement - Grade 2:no mural thickening with only slight enhancement - Grade 3: mural thickening and prominent enhancement - Grade 4: strong mural thickening and strong enhancement **MRVAS** 0: not inflamed 1: inflamed **Scoring for arterial stenosis** - Grade 0: normal segment (absence of stenosis) - Grade 1: mild arterial disease (50% luminal stenosis) - Grade 2: moderate arterial stenosis (50%-69% luminal narrowing) - Grade 3: severe arterial stenosis (70%-99% luminal stenosis) - Grade 4: complete arterial occlusion (100% luminal stenosis)	**Remission** - reduction or normalization of MRI lesions **Active disease** - mural thickening/enhancement - new or worsening structural lesions (stenosis, occlusion, aneurysm) - worsening MRVAS
Vascular US	**Baseline scan (pre-treatment)** - glucocorticoid-naïve patients, or - within 3 days of glucocorticoid treatment initiation **Follow-up scans** - at 3–12 weeks intervals	**Quantitative scoring systems** - No. of arteries with halo sign (halo count) - OGUS	**Remission** - improvement or normalization of US lesions in temporal arteries during first year - OGUS < 0.81 **Active disease** - new / worsening US lesions - OGUS ≥ 0.81

machine by using a parasternal longitudinal scan and echocardiography probes. However, this approach needs further validation in future prospective multicentre studies (70, 71), and aortic monitoring is usually performed via CTA or MRA.

Use of vascular US in the diagnosis and monitoring of GCA has some limitations. Although it can be very useful to assess temporal and axillary arteries, it cannot evaluate all vessels, with limited access to the thoracic aorta (Table I) (72). Another limitation is that it is operator dependent, as the interpretation of the imaging findings depends on the experience of the ultra-sonographer (73). At diagnosis, the sensitivity of the US for the diagnosis of GCA can fall rapidly after the initiation of corticosteroid therapy as the halo sign can vanish within three days of corticosteroid therapy (Table I) (74, 75). This is important for disease monitoring, as baseline US needs to be performed early on for reliable assessment regarding improvement in follow up imaging studies.

In summary, while imaging is not routinely advised for follow-up (76), vascular US can be valuable for quantifying vascular inflammation and monitoring vascular response to new therapies, and relapses in GCA clinical trials upon adopting standardised protocols (77). Extensive validation is needed before using the scoring system with IMT and OGUS cut-off values in clinical practice and/or as a secondary endpoint in clinical trials.

Examples of use of vascular imaging as an endpoint in GCA trials and conclusions

Vascular imaging can potentially be used as a useful endpoint in clinical trials of GCA with the goal to monitor disease activity but also track changes over time in standardised scoring systems following treatment with novel investigational medical products.

The VEGA (Vascular MRI Evalua-

Table III. Comparative table of imaging modalities distinguishing disease activity *versus* damage.

	Surrogate markers of disease activity	Surrogate markers of structural damage
Imaging findings	Wall oedema or enhancement (MRI/MRA), FDG-uptake (PET), Hhlo sign (US)	Aortic dilation, aneurysm, stenosis, occlusion
Preferred modality	PET/CT or colour Doppler US or VW-MRI	CTA or MRA
Clinical value	Assessment of acute inflammatory disease activity	Long-term monitoring for cumulative vascular damage
Drawback	Can be suppressed quickly by steroids	May progress even when active inflammation is well controlled

tion in Giant Cell Arteritis) study (NCT05865054) is an example of a clinical trial that assesses the effectiveness of MRI on detecting mural inflammation and structural vascular changes in patients with suspected GCA with the aim to investigate the role of MRI in the diagnosis and treatment of patients with GCA. 'The Meteoritics Trial' utilises changes in IMT in vasculitic vessels as a secondary endpoint, when studying the efficacy of methotrexate in maintaining remission in patients with GCA following discontinuation of tocilizumab (78).

The TOPAZIO study prospectively demonstrated the utility of PETVAS as a predefined outcome measure in patients with GCA treated with ultrashort glucocorticoids and tocilizumab. It also showed that reduction in PET activity correlated with clinical response. However, a subset of patients with preexisting damage showed progression of disease despite metabolic improvement (79). The extension of this study showed that early changes in PETVAS after stopping tocilizumab treatment could help predict which patients were likely to develop a subsequent relapse (80).

Vascular imaging is increasingly embodied in clinical trials, playing a seminal role in assessing diagnosis, monitoring disease activity, detecting structural changes, and evaluating efficacy as well as effectiveness of both conventional and novel agents in GCA (Table III). Simultaneous performance of two or more vascular modalities can provide more distinct yet complementary insights into the assessment of GCA. It can also direct comparison of standardised mean differences for scoring systems with each one of these modalities between baseline and follow up visits (Table II). While MRA studies demonstrate more accurately the extent of structural changes and damage occurring in the affected arteries, PET imaging could be more valuable at revealing metabolic activity within the vessel walls and disease activity (52) (Table III). Vascular US could further assist with identifying both cranial and extra-cranial sites of the disease (81). Overall, combining multiple imaging modalities would enable comprehensive assessment of vascular involvement by capturing changes in both cranial arteries (*e.g.* with ultrasound, high-resolution MRI, or FDG-PET/CT) and large vessels (*e.g.* with ultrasound, MRA, CTA, or FDG-PET/CT). However, vascular US remains the imaging study of choice for cranial GCA due to its high resolution in temporal and axillary arteries (82), recognising that VW-MRI of temporal arteries also shows superior sensitivity for detecting cranial involvement. A recent study demonstrated that VW-MRI has potential for longitudinal disease monitoring of GCA, as there was evidence of increased cranial MRI contrast enhancement during relapses even in patients with normal inflammatory markers (83).

Future trial design in GCA should ideally incorporate a multi-dimensional composite endpoint based on absence of clinical symptoms, normalisation of inflammatory markers, and pre-defined reduction of standardised vascular imaging scores, rather than return to completely negative imaging reports. The development and validation of optimised vascular imaging scoring systems employing imaging guided treat-to-target strategies could objectively guide treatment decisions in the clinical practice, preventing catastrophic complications such as permanent vision loss and stroke.

The longitudinal validation of standardised scoring systems, such as PET-VAS, MRVAS, and OGUS, as primary trial endpoints need to be the focus of future structured research endeavours. While such scores might show relatively good responsiveness to treatment, their biological significance for future outcomes such as relapse or vascular damage remains uncertain. It is unclear whether these scores truly measure active inflammation *versus* remodelling or vascular damage without ongoing active inflammation. It is also uncertain whether they can discriminate between true remission and subclinical inflammatory activity that may predict future relapses, particularly in patients treated with IL-6 receptor inhibitors.

A recent study proved the uncoupling of clinical and metabolic vascular activity using FDG-PET in patients with extracranial GCA treated with tocilizumab, where among those that achieved clinical remission less than one-third showed normalisation of vascular tracer uptake (84). Another study evaluated the prognostic impact of baseline aortitis on subsequent aortic dilation in patients with GCA and demonstrated that baseline aortic diameter and not just the presence of aortitis emerged as the strongest predictor of future aortic dilation and progression (85). Additionally, structural vascular damage may progress despite apparent control of inflammation. Indeed, aortic dilation may continue to progress in patients considered to be in clinical remission, that demonstrate chronic smouldering subclinical aortic inflammation on histopathologic evaluation (86). It remains to be further elucidated whether imaging scores correlate with

"hard" clinical outcomes such as mortality, aneurysm formation, or progressive aortic dilation, and thus whether they truly have predictive value.

A significant barrier to the adoption of imaging as primary endpoints is the inherent inter-centre variability in image acquisition and interpretation, and multicentre validation is still lacking. To assure that imaging data is robust enough for regulatory submission, future GCA trials must implement harmonised acquisition protocols and techniques (*i.e.* colour Doppler vascular US with high frequency probes of at least 18 MHz for temporal arteries, use of the same tracer dose of 18F-FDG with standard uptake time, and 3 Tesla MRI scanner). Other strategies include synchronised image uptake and scan timing, standardised preparation protocols for FDG-PET/CT with strict adherence to fasting, consistent interpretation methods with centralised reading (where appropriate) at core imaging centres, and quantitative scoring rather than simple binary (positive or negative) reads that represent a poor tool for monitoring early efficacy in clinical trials.

In GCA clinical trials, the optimal imaging schedule should include the diagnostic window where baseline imaging studies must ideally be performed within three to five days of starting high-dose glucocorticoid. It should also include early monitoring at week 24 using standardised scoring to assess metabolic response, followed by long-term disease activity and structural assessment at week 52 to detect vascular damage/remodelling that is a slower process than metabolic inflammation.

While the implementation of vascular imaging in clinical trials increases the total cost of trial budgeting, these modalities offer advantages as they can be employed as a gatekeeper for trial enrolment, ensuring a more homogenous study population at study entry, consistency, and data integrity among different imaging centres. To facilitate the integration of vascular imaging in clinical trials, dedicated research imaging slots need to be reserved to facilitate fast-track protocols, avoiding delays and trial screening hurdles. Care coordination between different imaging cores, and transportation assistance need also to be provided to ensure access and successful enrolment in the trial.

In conclusion, the primary endpoint in clinical trials of GCA needs to shift from subjective clinical and serological assessment towards objective precision imaging, by initiating prospective imaging-guided treat-to-target interventional trials. The integration of artificial intelligence (AI) algorithms to automatically calculate imaging scores might assist with reducing inter-operator variability and lead to reproducible quantitative metrics, allowing for accuracy and reliability across large-scale multicentre trials. Also, the transition to hybrid PET-MRI imaging with extended field of view might assist with comprehensive superior quantitative simultaneous assessment of both metabolic and morphological evaluation, while reducing radiation exposure. Finally, the transition from metabolic to molecular imaging with the introduction of novel PET tracers that target specific molecules on immune cells (87), might change the landscape of future clinical trials in GCA. For example, the C-X-C motif chemokine receptor 4 (CXCR4) on T cells and monocytes (88) in the CXCR4-PET trial (NCT05604482) shows lower uptake in atherosclerotic lesions, or the Somatostatin Receptor 2 localised to macrophages, pericytes, and perivascular adipocytes in vasculitis specimens (89) in the DOTATATE trial (NCT03812302) suggests better active inflammation compared to FDG in patients already on prednisone.

Competing interests

C. Dejaco has received honoraria for consultancies or speaker honoraria from AbbVie, Sanofi, Fresenius, Novartis, Janssen and Sparrow.

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