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Advances in PET Imaging of Large Vessel Vasculitis: An Update and Future Trends

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Systemic vasculitides are autoimmune diseases characterized by inflammation of blood vessels. They are categorized based on the size of the preferentially affected blood vessels: large-, medium-, and small-vessel vasculitides. The main forms of large-vessel vasculitis include giant cell arteritis (GCA) and Takayasu arteritis (TAK). Depending on the location of the affected vessels, various imaging modalities can be employed for diagnosis of large vessel vasculitis: ultrasonography (US), magnetic resonance angiography (MRA), computed tomography angiography (CTA), and [^{18}F]-fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography (FDG-PET/CT). These imaging tools offer complementary information about vascular changes occurring in vasculitis. Recent advances in PET imaging in large vessel vasculitis include the introduction of digital long axial field-of-view PET/CT, dedicated acquisition, quantitative methodologies, and the availability of novel radiopharmaceuticals. This review aims to provide an update on the current status of PET imaging in large vessel vasculitis and to share the latest developments on imaging vasculitides.

Introduction

Systemic vasculitides are characterized by inflammation of blood vessels. These autoimmune diseases are categorized based on the size of the preferentially affected blood vessels: large-, medium-, and small-vessel vasculitides.[1] The main forms of large-vessel vasculitis include giant cell arteritis (GCA) and Takayasu arteritis (TAK). Both GCA and TAK are characterized by a mononuclear and granulomatous infiltration of the vessel wall.[2,3]

The clinical presentation differs between GCA and TAK. GCA is more prevalent among Caucasians and occurs in individuals over the age of 50. It can affect both large systemic arteries (large vessel GCA; lvGCA) and medium-sized cranial arteries (cranial GCA; cGCA). Consequently, the associated morbidity can range from permanent blindness and stroke in cGCA to aortic aneurysm dissection in lvGCA.[4] On the other hand, TAK is predominantly observed in female patients under the age of 40, with a predilection for individuals of Asian descent. Beyond the clinical presentation, they differ in terms of the extent and localization of vessel involvement, with a wider range of affected arteries in TAK patients, including the mesenteric, renal, and ilio-femoral arteries, while sparing the medium-sized cranial arteries.[5] Overall, TAK has a greater propensity for causing severe focal stenotic lesions than GCA.

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The diagnosis of vasculitis necessitates a comprehensive clinical and laboratory evaluation. Laboratory tests are non-specific and reveal an elevation of inflammation markers in the blood. A biopsy of affected vessels/organs can offer direct evidence of vascular inflammation. However, not every vessel or tissue is easily accessible for biopsy. Imaging can serve as a valuable alternative to an invasive biopsy. Imaging not only provides evidence for vascular inflammation but can also identify vascular complications, such as aneurysm formation, stenosis, and occlusion.

Depending on the calibre and location of the affected vessels, distinct imaging modalities can be employed for diagnosing vasculitis: ultrasonography (US), magnetic resonance angiography (MRA), computed tomography angiography (CTA), and [^{18}F]-fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography (FDG PET/CT). Large vessel vasculitides were among the initial major indications for the use of FDG PET/CT in inflammatory disorders.[6] CTA and MRA can aid in detecting inflammation in large arteries located in the neck, chest, abdomen, and pelvic region,[7] while MRI also allows assessing the cranial arteries.[8] The various imaging tools for large vessel vasculitis offer complementary information. US, CTA and MRA may reveal thickening of the arterial wall and the presence of stenosis and/or aneurysm. US gives additional information on the severity of the stenosis and direction of the flow, while CTA and MRA can reveal mural contrast enhancement of the affected arteries. FDG-PET/CT offers demonstrates enhanced metabolic activity in affected arteries rather than insight into the structural changes of the vessel wall.

Recent advances in PET imaging in large vessel vasculitis include the introduction of digital long axial field-of-view (LAFOV) PET/CT, dedicated acquisition, quantitative methodologies, and the availability of novel radiopharmaceuticals, making it nowadays possible to also accurately detect cGCA. This review aims to provide an update on the status of PET imaging in large vessel vasculitis and to share the latest developments in this field.

FDG PET for Diagnosis and Treatment Monitoring

Current recommendations by the European Alliance of Associations for Rheumatology (EULAR) underscore the importance of an early imaging test to support the clinical diagnosis, assuming high expertise and prompt availability of the imaging technique. Ultrasonography is considered as the first-line diagnostic test for suspected GCA. Although the guideline of the American College of Rheumatology (ACR) also supports this practice, it gives preference to temporal artery biopsy due to limited experience with ultrasonography in the USA.[9] If available, FDG PET/CT (Fig. 1) and MRI/MRA are considered important alternatives for diagnosis of both lvGCA and cGCA.[10] CTA only allows for assessment of lvGCA. MRI/MRA has been suggested as first imaging test for suspected TAK, although ultrasonography, CTA, and FDG PET/CT are plausible alternatives.[10]

Therapy monitoring usually relies on comprehensive clinical and laboratory assessment. However, doubt regarding disease activity is not uncommon and certain targeted therapies (i.e., IL-6 receptor targeted therapy) compromise the sensitivity of CRP and ESR measurements, since the IL-6 pathway is needed for these inflammatory markers to rise. In those circumstances, imaging can provide important information regarding disease activity. Ultrasonography and MRI/MRA of cranial arteries may show improvement upon treatment, while arterial wall thickening, stenosis, and aneurysms of the large vessels usually persist. Progression of the latter lesions may raise suspicion for inadequately controlled disease. Especially in TAK regular imaging by MRA, potentially

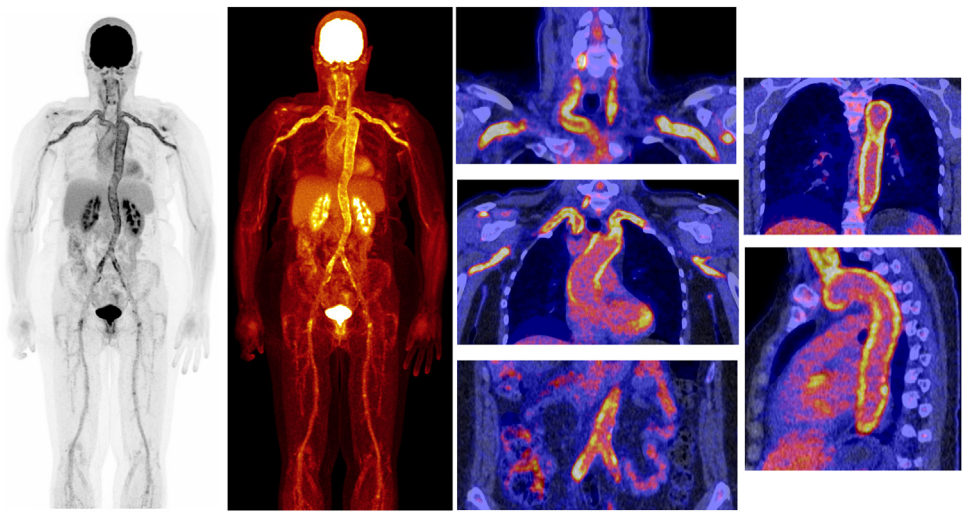

Figure 1 FDG TBPET in GCA. FDG LAFOV QUADRA PET/CT of GCA with vasculitis activity of the thoracic and abdominal aorta, carotid, subclavian, axillary, and iliac arteries. On the left MIP in colour, in the middle and on the right fused FDG PET and low dose CT images.

supplemented by ultrasonography, is needed to monitor progression of damage. These imaging tools are preferred, as they do not pose any radiation risk to young patients with TAK. The application of US, CTA, MRI/MRA during treatment for GCA is less well established. CTA and MRA may demonstrate thoracic aorta aneurysm formation, but guidelines for monitoring aortic damage in GCA are currently lacking. Upon treatment, FDG PET/CT usually shows a decrease in arterial wall FDG uptake, but not always a normalization.[11] As such, residual FDG uptake during treatment should not be considered as absolute evidence for ongoing disease activity, but could represent vascular healing/remodeling. Overall, FDG PET/CT has a sensitivity of 77% and specificity of 71% for detecting relapsing/refractory disease in patients with GCA/TAK.[12] Thus, findings on imaging should be carefully interpreted within the clinical context.

Technical Trends (Table 1)

Advanced Image Acquisition

Although conventional static FDG PET/CT has been demonstrated to diagnose treatment naïve GCA with a high diagnostic accuracy,[13] certain features inherent to both image acquisition and interpretation may in some cases hamper correct identification of pathological vessel wall FDG uptake. Importantly, FDG uptake and intracellular accumulation by activated macrophages and other leukocytes involved in vessel wall inflammation is a progressive process that may not have reached a maximal plateau at the usual timing of the static PET scan (60 minutes post injection).[14] Thus, a short static FDG PET scan does not contain sufficient temporal information about tracer blood clearance or tissue accumulation.[15] Substantial residual radioactivity may therefore still be present in the blood pool at the time of image acquisition resulting in suboptimal target-to-background ratio with significant vessel wall spill-in from the blood pool. This is less of a problem in large caliber arteries such as the aorta, subclavian and axillary, but may significantly impact the reading of vessel wall uptake in arteries with diameters approaching the maximal resolution of the PET scan (3-5 mm on contemporary PET systems).[16] Discriminating between luminal and vessel wall uptake is therefore almost impossible in arteries such as the temporal, occipital, maxillary and to some extent also the vertebral arteries. Residual blood pool activity may be even more increased in individuals with diabetes,[15] where increased levels of circulating glucose and FDG compete for uptake by all tissues and cells, or in patients with impaired liver function, where the metabolism of FDG may be delayed. In addition, although vessel wall FDG uptake may be exceptionally avid in some patients at the time of diagnosis, others may have less pronounced FDG uptake either due to the timing of the PET scan (early disease) or disease severity.[14]

Some of these problems may be circumvented by more advanced PET acquisition techniques and modelling. Notably, dynamic PET scans with acquisition of both the blood input function and the tissue time-activity-curves (TAC) from the time of tracer injection permit for a full kinetic analysis of FDG uptake. This allows the creation of parametric images that contain more detailed information on tracer kinetics compared to accumulated radioactivity at a single time point. Since FDG uptake is largely an irreversible process, uptake can be calculated using simple linearization methods. For example, the Gjedde-Patlak plot can discriminate between tracer actively transported into tissue (metabolic rate of FDG uptake [MRFDG]) and free unbound tracer still in the blood pool (distribution volume [DV]). For decades, dynamic PET scans have been performed in research environments using FDG as well as a wide range of other tracers but have only rarely been used in a clinical context and to our knowledge never in GCA patients (Fig. 2). The need to obtain both a robust measurement of the input function and tissue uptake for the entire duration of the scan with limited field-of-view scanners (up to 25 cm) is an obvious drawback in a disease such as GCA, where disease extent may vary from isolated cranial arteries over widespread involvement of the aorta and large branches to disease restricted to singular arteries in the abdomen.

However, the introduction of automated dynamic whole body (D-WB) PET imaging may solve this problem.[17] The technique involves multi-pass, multi-bed PET acquisition covering the desired part of the body, usually from the vertex to the thighs. The parametric images (MRFDG and DV) can be calculated directly from PET sinogram data using recent reconstruction algorithms and an image-derived input function from the aorta or left ventricle.[18,19] The resulting MRFDG images show surprisingly little inter-individual variation in organ and tissue uptake[20] and have virtually no luminal activity in the large vessels (see Fig. 1). However, to correctly use Gjedde-Patlak linearization to estimate irreversible tissue FDG uptake, both the late D-WB tissue data (50-70 minutes) and the full arterial 70-minute input function must be measured[21,22] resulting in very long and therefore not clinically feasible PET scans. This problem has recently been addressed by introducing a population-based input function (PIF). The shape of the FDG input function varies only little between individuals and can be described by a four-exponential model[15] scaled to residual blood radioactivity during the final 50-70 minutes of the scan. As a result, complete D-WB PET scans yielding parametric images with substantial reduction of the blood pool signal and covering the entire relevant part of the body from the vertex to the thighs can be performed using about 15-minute scan protocol commencing 50 minutes after radiotracer injection.[15,23] The availability of LAFOV PET scanners, which include a CE-marked option for parametric reconstruction using the PIF, makes D-WB FDG PET scans a feasible option for LVV. However, there are two important aspects to consider: (1) spill-over activity from high uptake in the vessels due to inflammation, may cause inaccurate estimation of the blood signal, therefore the region of interest to extract the blood curve should be carefully chosen; and (2) motion during the scan may bias Gjedde-Patlak plot analysis.[24,25]

Using D-WB FDG PET in patients with suspected GCA may yield more advantages than just the elimination of

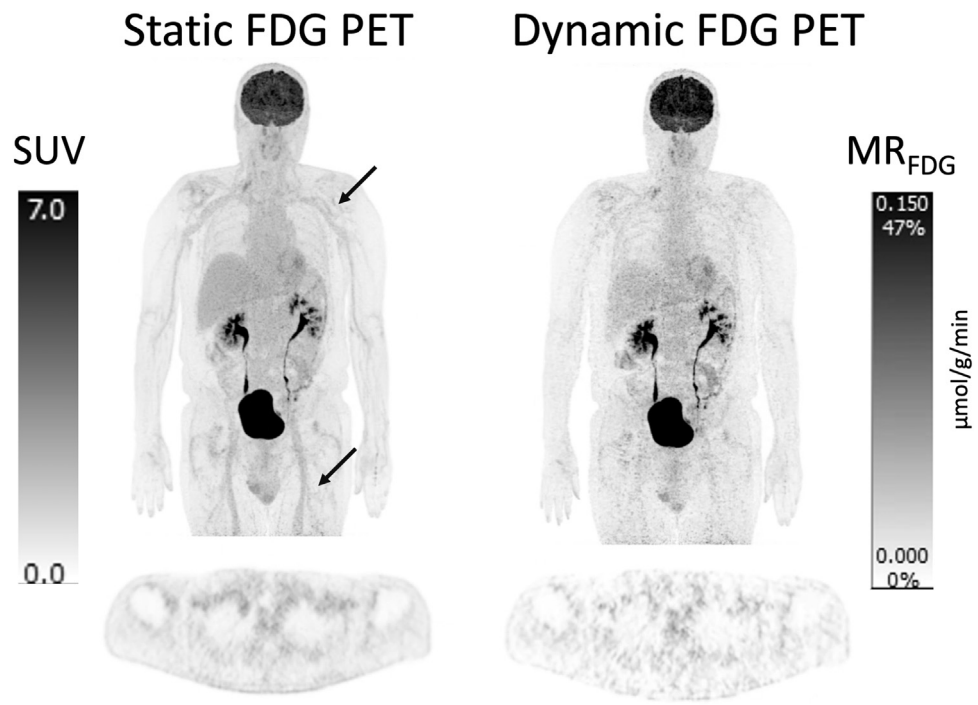

Figure 2 The 55-y old man with suspected GCA scanned using a shortened D-WB PET scan protocol. No GCA was suspected after inspection of the PET scans. As seen in the left panel, the static SUV was characterized by luminal uptake in the large vessels, particularly evident in the subclavian/axillary and femoral arteries (arrows). By contrast, the MRFDG image from the D-WB PET in the right panel showed no uptake above background in the subclavian and femoral arteries.

luminal blood pool radioactivity and easier identification of the vessel wall. Thus, conventional static FDG imaging entails a range of potential errors and variations in maximum standardized uptake values (SUV_{max}) caused by differing reconstruction methods (filtering, PSF, iterations), quality issues in older PET systems, varying blood glucose values, and retained radiotracer at the injection site.[26,27] MRFDG values are calculated based on the slope of the tissue FDG uptake curve rather than a single estimate of retained radioactivity and are therefore less prone to variations between scanner systems and reconstruction methods. In theory, this allows for a more robust thresholding of vessel wall pathology than the commonly used visual approach, the 4-point Meller score (described in the next section).[28,29] Thus, newer PET/CT systems tend to have a significantly higher sensitivity and low-grade vessel wall inflammation as in atherosclerosis, systemic lupus erythematosus, or psoriasis[30] may therefore mimic GCA patterns. It is possible that introduction of more precise and robust MRFDG thresholds may reduce this problem.

Although D-WB PET seems a promising technique in GCA diagnosis and was introduced some years ago, no studies on its usefulness in GCA have to our knowledge been published. In Aarhus, a comparative study between static SUV and dynamic PET in patients with suspected GCA is ongoing with encouraging preliminary results (data not published). MRFDG values in inflamed cranial vessels are high, resulting in excellent lesion-to-background ratios and more easy interpretation of the MRFDG images (see Fig. 2). Since the luminal activity is markedly reduced, it is possible that introduction of D-PET in patients with suspected GCA could potentially reduce the number of false positive reports of possible LVV, particularly in the subclavian and axillary arteries.

Advanced Scoring, Quantification, and Software

A variety of methods for interpreting FDG PET exams exist in this clinical indication. All those methods are based on the intensity of FDG uptake going from intuitive visual assessment to structured visual scoring and finally semi-quantitative evaluation. Visual interpretation is usually done by a 4-point visual scale (ranging from 0 to 3) in which the vessel uptake is compared to liver background as recommended by the European Society of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI).[29] Additionally, a visual-based composite score, the total vascular score (TVS), evaluating uptake in 7 to 11 different vascular regions, has been developed for diagnosing lvGCA.[29] Last, semi-quantitative or quantitative approaches have been developed and evaluated, such as aorta to liver SUVmax ratio, vascular/liver ratio, vascular/lung ratio, and arterial/venous ratio.[31] Despite the compelling rationale advocating for more objective metrics compared to visual analysis, a limited number of studies directly compared visual analysis with quantitative metrics. Moreover, disparate metrics have been used in these investigations. It is noteworthy to mention that measurement of SUV or TBR values

necessitates VOI segmentations, a time-intensive process susceptible to variability.

Recently, accurate and robust artificial intelligence (AI) organ segmentation models have been published that include large vessels.[32-34] These models anatomically delineate large vessels on CT scans and exhibit proficiency in handling low-dose, non-contrast enhanced CT images. Leveraging these segmentations, quantitative metrics can be computed on the overlaid PET image, facilitating swift analysis of such metrics within extensive datasets. For example, it could be investigated whether global inflammatory uptake in the vessels is of added diagnostic value without the labor-intensive task of manual segmentation. However, it is imperative to establish standardized metrics for homogeneous evaluations and to collect robust evidence supporting the efficacy of these metrics.

Additional technical advancements, such as radiomics, can provide valuable quantitative information about LVV and FDG uptake. Radiomics involves the extraction and analysis of quantitative features from medical images that are imperceivable by the human eye. In combination with machine learning models, PET images can be automatically analyzed. This could potentially be helpful as a diagnostic tool or to differentiate inflammatory uptake associated with LVV from atherosclerosis. Duff et al. demonstrated the potential of radiomics in diagnosing aortitis.[35,36]

PET/MRI

PET imaging integrated with MRI may create new opportunities compared to CT and especially low-dose CT, the current standard for lvGCA imaging. First, MRI offers more precise anatomical localization of PET tracer uptake.[10] This may be especially useful in patients with cGCA, where FDG uptake of the cranial arteries may be difficult to separate from physiologic uptake in surrounding tissues (Fig. 3).[10,29] Similarly, the ability to better localize PET uptake in soft tissues may benefit investigations of more specific novel PET tracers.

Secondly, FDG PET/MRI may allow for better characterization of the inflamed arterial wall. Combined information on vessel wall thickening, luminal narrowing, and FDG uptake can help identify the stage of inflammation in the arterial wall.[37] For example, a study by Einspieler et al. reported an association between CRP and FDG uptake but not with MRI findings.[38] No prospective studies have yet investigated the diagnostic performance of FDG-PET/MRI so the diagnostic benefit of adding MRI is not yet known. An application of immediate clinical use for FDG PET/MRI concerns young TAK patients.[39] It may be a way to reduce radiation exposure in this group of patients who may need to undergo relatively frequent follow-up imaging.

Novel PET Tracers

FDG is an excellent radiotracer for diagnosing GCA/TAK prior to initiation of any treatment. However, interpretation of FDG PET/CT becomes more complex when patients receive high dose glucocorticoid treatment in the acute phase, but also during therapy monitoring. This is partly related to direct effects of glucocorticoids on the liver, the main reference organ for assessing vascular wall FDG uptake. Moreover, reminiscent FDG uptake later during the disease could potentially reflect vascular remodeling rather than active infiltration and inflammation of the arterial wall. Thus, a clear rationale exists for evaluating alternative radiotracers that specifically identify key immune cells or activated stromal cells in the arterial wall.[40] Macrophages, which are key

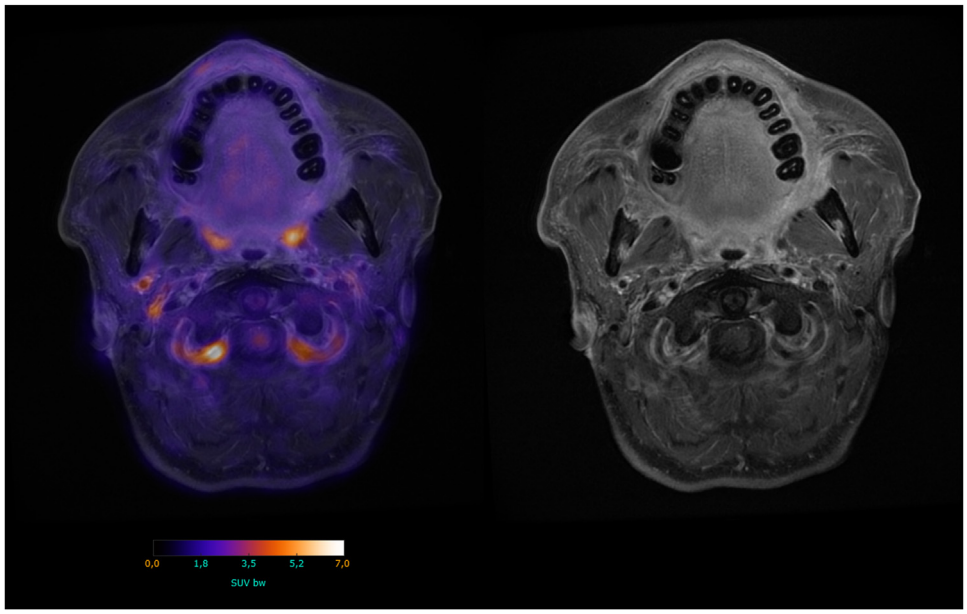

Figure 3 FDG PET/MRI in cranial GCA. Left: Axial fused FDG-PET/MRI image of a patient with cranial GCA. Increased uptake can be observed in the vertebral arteries, the proximal segment of the occipital arteries, and the right external carotid artery. Right: Axial MRI image (contrast enhanced T1-weighted) without FDG-PET. Vessel wall thickening and attenuation can be observed in the right external carotid artery and vertebral arteries.

Table 1 Challenges FDG PET/CT in Large Vessel Vasculitis

Challenges	Solutions/Research Agenda
Technical and Methodological	
Interference of drugs	
- Glucocorticoids (GC)	- Stop GC administration before PET if possible (2-4 weeks before?)
- Sodium-glucose cotransporter-2 inhibitors	- To be investigated
Time interval FDG injection and imaging	90-120 minutes to improve target-to-background[49]
Standardization & Quantification PET data	EARL/Recommendations
cCGA acquisition time	Dedicated longer head-and neck acquisition
Novel tracers	ligands targeting immune cell
Radiation dose	Ultralow dose CT,[50] highly sensitive PET scanner[51]
AI and dynamic quantitative metrics	Rapid developments[52]
Consensus reading	Recommendations
Development of online training modalities for interpretation	EULVIC (onsite) EANM/ESMIT
LAFOV PET/CT	Very low radiation burden, fast
PET/MRI	Low radiation burden
Costs	Imaging-driven (expensive) therapy
Clinical	
To investigate the association of imaging results with novel laboratory biomarkers in GCA and TAK	Clinical trials needed
Multi-disciplinary approach	To be stimulated
To investigate the value of imaging for response assessment and correlation with patient-reported outcomes in GCA and TAK	Clinical trials needed
To define remission of imaging results in GCA and TAK	Clinical trials needed
To investigate the value of imaging in a treat-to-target approach in GCA and TAK	Clinical trials needed
Risk of cardiovascular events/complications (atherosclerosis?)	Clinical trials (follow-up) needed
To study the association between vascular inflammation detected by FDG and vascular damage	Clinical trials needed
To evaluate the usefulness of an integrated disease activity index[53]	Clinical trials needed

players in the pathobiology of LVV, can be visualized by PET tracers targeting the somatostatin receptor or folate receptor.[41,42] T-cells might be another important target for imaging in large vessel vasculitis. This could be achieved via radiotracers targeting IL-2 receptor, CD4 and CD8 molecules on T-cells.[43,44] Moreover, imaging of fibroblast activation protein (FAP) on activated fibroblasts could be another interesting target.[45,46] Fibroblasts are stromal cells that play an active role in the recruitment and activation of immune cells to the vessel wall.[47] FAP can be detected by using radioactively-labelled FAP inhibitor (FAPI) using ^{68}Ga or ^{18}F.[48] Such specific radiotracers could potentially aid both diagnosis and therapy monitoring/disease relapse in cases where FDG-PET/CT findings are inconclusive.

Conclusion

The 2023 EULAR recommendations provide up-to-date guidance for the role of imaging in large vessel vasculitis.[10] The use of FDG PET/CT is highly recommended in the diagnosis of lvGCA.[10] The accuracy and clinical value of PET imaging is expected to improve due to important innovations such as highly sensitive PET camera systems (of added value in cGCA), PET/MRI, dynamic (kinetic) imaging and more specific radiopharmaceuticals targeting specific immune cells and activated stromal cells.

It is recommended to develop a multidisciplinary "round table" approach involving specialists in imaging, rheumatologists, internal medicine, and pathologists. This approach may reduce the delay of work-up of the patient suspected of LVV. The challenge of the imager within this multimodality team is to establish a new professional perspective: a new vision of the imager, no longer thinking as an individual, but as a part and contributor to the team, translating the image content into a clinical planning and decision-making process to deliver high quality care to patients within such complex contexts.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Kornelis S.M van der Geest: Writing — review & editing, Writing — original draft. **Olivier Gheysens:** Writing — review & editing, Writing — original draft. **Lars C. Gormsen:** Writing — review & editing, Writing — original draft. **Andor W.J.M. Glaudemans:** Writing — review & editing, Writing — original draft. **Charalampos Tsoumpas:** Writing — review & editing. **Elisabeth Brouwer:** Writing — review & editing. **Pieter H. Nienhuis:** Writing — review & editing, Writing — original draft. **Gijs D. van Praagh:** Writing — review & editing, Writing — original draft. **Riemer H.J.A. Slart:** Writing — review & editing, Writing — original draft, Resources, Conceptualization.

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