Is PET/CT essential in the diagnosis and follow-up of temporal arteritis?

Carlo Salvarani\textsuperscript{a,b,⁎}, Alessandra Soriano\textsuperscript{a,c}, Francesco Muratore\textsuperscript{a,b}, Yehuda Shoenfeld\textsuperscript{d}, Daniel Blockmans\textsuperscript{e}

\textsuperscript{a} Division of Rheumatology, Azienda USL - Istituto di Ricovero e Cura a Carattere Scientifico di Reggio Emilia, Viale Risorgimento 80, 42100 Reggio Emilia, Italy
\textsuperscript{b} Modena and Reggio Emilia University, Via Università 4, 41121 Modena, Italy
\textsuperscript{c} Campus Bio-Medico University of Rome, Via Álvaro del Portillo n° 200, 00128 Rome, Italy
\textsuperscript{d} Center for Autoimmune Diseases, Sheba Medical Center, affiliated to Tel-Aviv University, Israel.
\textsuperscript{e} Department of Clinical and Experimental Medicine, University Hospital Gasthuisberg, Leuven, Flanders, Belgium

\textbf{Abstract}

The increasing availability and improvement of imaging techniques are deeply influencing diagnosis and work-up of patients affected with vasculitis, particularly those with large vessel vasculitis (LVV). Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET), especially when integrated with computed tomography (CT), is taking hold as a useful diagnostic technique to examine the aorta and the other large vessels in giant cell arteritis (GCA) with concomitant large vessel involvement (LV-GCA). In this paper we examined the progresses performed in this field in the last twenty years and the evidence available so far according to two different points of view (‘pros’ and ‘cons’), in order to give a comprehensive answer to a still open question about the role of PET/CT in the diagnosis and follow-up of GCA.

© 2017 Elsevier B.V. All rights reserved.

\textbf{Keywords:}

Giant cell arteritis (GCA)
Temporal artery
Large vessel vasculitis
Fluorodeoxyglucose
18F-FDG
Positron emission tomography
PET
Computed tomography
CT
Imaging

\textbf{Contents}

1. Introduction .............................................................. 1125
2. Is 18F-FDG-PET essential in the diagnosis and follow-up of temporal arteritis? Pros ...................................................... 1126
   2.1. Large vessel giant cell arteritis (LV-GCA) .............................................. 1126
   2.2. Diagnostic modalities for LV-GCA .................................................. 1126
   2.3. 18F-FDG-PET in GCA: qualitative or semiquantitative scoring methods? .............................................................. 1126
   2.4. Is 18F-FDG-PET useful for the diagnosis of polymyalgia rheumatica (PMR) .................................................. 1127
   2.5. Is 18F-FDG-PET useful in the follow-up of LV-GCA and in predicting aortic complications? .............................................................. 1128
   2.6. Conclusions ............................................................. 1128
3. Is PET/CT essential in the diagnosis and follow-up of temporal arteritis? Cons ...................................................... 1128
   3.1. Value of 18F-FDG-PET in the diagnosis and follow-up of GCA .............................................................. 1128
   3.2. Can 18F-FDG-PET scan predict which patients are prone to aortic complications? .............................................................. 1129
   3.3. Conclusions ............................................................. 1129
4. Final general considerations ................................................. 1129
   Disclosures ........................................................................ 1130
   Take home messages ...................................................... 1130
   References ................................................................. 1130

1. Introduction

Temporal arteritis, also known as giant cell arteritis (GCA), is a granulomatous vasculitis affecting large arteries. Its exact pathogenesis is
not fully understood, yet major progress has been achieved in recent years, leading to new therapeutic targets like inhibition of the IL-6 pathway or the modulation of immune checkpoints [1].

Recent evidence suggests that there is heterogeneity of histological lesions in GCA that are correlated with different immunological Th9 and Th17 signature. The recent demonstration that varicella zoster virus (VZV) antigen is present in the 64% of GCA-negative temporal artery biopsies (TAB) and in the 73% of GCA-positive TAB could represent an important point of arrival in the search for a causative agent in the pathogenesis of a metanomic disease such as GCA [2].

Novel genes differentially expressed between TAB positive-GCA and GCA control vascular smooth muscle cells may be involved in proliferation. Endothelin-1 was identified as a link between genes of interest. It is not surprising that proliferation was reduced by endothelia antagonist [3].

Therefore, still debate exists about the role of disease-modifying anti-rheumatic drugs (DMARDs) [4], vs. the biotherapies [5].

Despite all these novel aspects of GCA, diagnostic dilemmas exist [6] and an unusual presentation of the inflammation may pose diagnostic difficulties [7].

All the above raised the controversy in the 4th CORA (Controversies in Rheumatology in Autoimmunity) meeting in Bologna 2016, particularly whether PET/CT can add a value for the diagnosis and moreover in the follow-up of these patients.

There were no better candidates to discuss this dilemma than Prof. Carlo Salvarani from Italy (pros) and Prof. Daniel Blockmans (cons).

2.1 Is 18F-FDG-PET essential in the diagnosis and follow-up of temporal arteritis? Pros

The increasing availability and improvement of imaging techniques are making a deep impact in the evaluation of patients with vasculitis, particularly for those with large vessel vasculitis (LVV). Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) is taking hold as a diagnostic tool to examine the aorta and the other large vessels in large vessel (LV-)GCA [8]. In this debate I will demonstrate that 18F-FDG-PET is a useful imaging technique for diagnosing LV-GCA and may also have a role in monitoring the disease course.

2.1. Large vessel giant cell arteritis (LV-GCA)

Evidence of LVV at conventional angiography occurs in GCA in over a quarter of patients [9]. Stenosis of the superior branches of the aortic arch occurs in 10−15% of patients. In 2 retrospective studies, 9.5% to 18% of patients developed aortic aneurysm or dissection [10,11], while in a prospective study, 22.2% of patients had aortic aneurysm/dilatation after a median follow-up of 5.4 years [12]. Cranial manifestations (in particular headache and jaw claudication) and vision loss are frequent in patients with LV-GCA [13]. Constitutional symptoms occur in 35% of patients. Temporal artery biopsy is positive in only ~50% of patients [14]. American College of Rheumatology (ACR) classification criteria for GCA are satisfied in only 39% of patients [14,15].

The prevalence of LVV in newly diagnosed GCA is related to the ability of the imaging techniques to detect early vascular inflammation. By using ultrasonography, 29–54% of patients had a positive ‘halo sign’ in at least one artery (especially carotid, subclavian and axillary arteries) [16–18]. This sign is considered highly specific for vasculitis. CT studies reveal aortic thickening (presumed aorticitis) in 45–65% of patients with GCA at diagnosis [19,20], while by using 18F-FDG-PET, increased FDG uptake in the large vessels (especially in subclavian arteries) was observed in 83% of 35 GCA patients at diagnosis [21]. Therefore 18F-FDG-PET seems to be the most sensitive imaging modality for detecting LV inflammation in GCA.

2.2. Diagnostic modalities for LV-GCA

Temporal artery biopsy (TAB) is the gold standard for the diagnosis of GCA [9]. However, a negative TAB doses not rule out GCA, and diagnosis of biopsy negative GCA was reported in up to 40% of patients [22]. A high proportion of negative TAB (~40%) has been reported in patients with radiographic evidence of LV-GCA [14,15]. Furthermore, our group clearly demonstrated that the histologic features of negative TABs do not allow for the differentiation between GCA and non-GCA patients [22]. In the absence of an inflammatory infiltrate, other histologic changes of the temporal artery wall are not specific for GCA. ACR 1990 classification criteria for GCA were designed to differentiate this vasculitis from other vasculitides [23], and are not useful for making the diagnosis in individual patients [9]. Furthermore, no imaging modalities are included in these criteria. Therefore, imaging techniques are indispensable for diagnosing and monitoring patients with LV-GCA.

Finally, about 15% of GCA patients have elevated fever as the only presenting manifestation [24]. These patients frequently associate LV involvement. Imaging studies may also have an important diagnostic role in this subgroup of patients.

2.3. 18F-FDG-PET in GCA: qualitative or semiquantitative scoring methods?

18F-FDG is taken up by metabolically active cells and is not highly metabolized, which makes it possible to identify the focus of inflammation. The accumulation of radiolabeled 18F-FDG delineates arterial wall inflammation. The co-registered images of combined 18F-FDG-PET/computer tomography (CT) scanners allow a more precise anatomic location of metabolic activity compared to single 18F-FDG-PET. In addition, because arterial wall infiltration by inflammatory cells is thought to be the first step occurring in LVV, 18F-FDG-PET may be positive early on in the disease course and thus be helpful in making an early diagnosis [25]. In contrast, the diagnostic performance of 18F-FDG-PET declines by nearly 50% shortly after the onset of corticosteroid and other immunosuppressive treatment [26].

18F-FDG-PET also shows the extent of vascular involvement, although some arteries, such as the renal arteries and temporal arteries, cannot be visualized [8].

18F-FDG-PET is minimally invasive and involves a very small dose of radiation. Most authors use a qualitative analysis of 18F-FDG uptake for assessing the presence of vasculitis. Meller et al. [25] in 2003 compared vascular uptake and liver uptake, using a 4-point scale: grade 0: no uptake; grade 1: uptake lower than liver; grade 2: similar to liver; grade 3: higher than liver. In untreated patients, grades 2–3 were considered relatively specific for vasculitis, while grade 1 (rarely 2) were observed in atherosclerotic vessels. Fig. 1 shows 18F-FDG-PET/CT scan of a patient with large vessel GCA showing grade 3 vascular uptake. Discriminating between atherosclerotic and vasculitic lesions is important, particularly in elderly patients such as those with GCA. Vasculitic lesions are usually characterized by a more intense 18F-FDG uptake; further clues pointing to vasculitis are the involvement of arteries usually spared by atherosclerosis and a linear pattern of 18F-FDG uptake over long vascular segments (in contrast to the irregular and patchy 18F-FDG uptake usually seen in atherosclerosis) [27].

An alternative approach for reading 18F-FDG-PET scans is to determine the maximum standardized uptake value (max SUV) of the arterial wall relative to that of a reference organ (usually the liver) and to define a cut-off value diagnostic for vasculitis; however, at present there is no established optimal cut-off value [28].

In 2015 Stellingwerff et al. [29] defined the optimal 18F-FDG-PET/CT scoring method for GCA diagnosis using TAB and clinical diagnosis as the reference method. In this retrospective study, 18F-FDG-PET/CT scans of GCA patients (12 steroid-naïve and 6 on steroid therapy) and 3 control groups (inflammatory, atherosclerotic, and normal) were evaluated. Two quantitative visual methods (first impression and vascular uptake versus liver uptake) and 4 semi-quantitative methods (SUVmax}
aorta, SUVmax aorta-to-liver ratio, SUVmax aorta-to-superior-caval-vein ratio, and SUVmax aorta-to-inferior-caval-vein ratio) were compared to evaluate the diagnostic accuracy. \(^{18}\)F-FDG uptake pattern (diffuse or focal) and presence of arterial calcifications were also scored. The presence of calcifications in the arterial wall is indeed considered as a specific sign of atherosclerosis. Visual vascular uptake higher than liver uptake resulted in the highest diagnostic accuracy (sensitivity 83%, specificity 91%) for the detection of GCA, especially in combination with a diffuse \(^{18}\)F-FDG uptake pattern [29]. Sensitivity increased to 92% when patients on glucocorticoids were excluded by the analysis. Regarding the semiquantitative methods, the aorta-to-liver SUVmax ratio (cutoff point: 1.03) had the highest diagnostic accuracy, with a sensitivity and specificity of 69% and 92%, respectively. Sensitivity increased to 90% when patients on glucocorticoids were excluded. The authors outlined the importance to score the pattern of \(^{18}\)F-FDG uptake (local vs. diffuse) and to correct for the presence of atherosclerosis [29].

Besson et al. [28] conducted a systematic review and performed a meta-analysis on the diagnostic performances of \(^{18}\)F-FDG-PET for GCA, with or without polymyalgia rheumatica (PMR). The meta-analysis of six selected studies found a sensitivity of 80% and a specificity of 89%. GCA ACR 1990 criteria were used as reference standard for the diagnosis of GCA [23]. Overall the diagnostic performance of \(^{18}\)F-FDG-PET against GCA ACR criteria was good. A smooth linear or long segmental pattern of \(^{18}\)F-FDG uptake in the aorta and its main branches was a characteristic imaging technique for LVV, especially with other available diagnostic modalities, the addition of \(^{18}\)F-FDG-PET increased the clinical diagnostic accuracy from 54% to 70% (\(p = 0.04\)). The addition of \(^{18}\)F-FDG-PET changed the treatment recommendation in 27% of patients not receiving immunosuppressive drugs and in 23% receiving immunosuppressants. This study confirmed that \(^{18}\)F-FDG-PET is a sensitive and specific imaging technique for LVV, especially when performed in patients not receiving immunosuppressive drugs. It increases the overall diagnostic accuracy and has an impact on the clinical management in a significant proportion of patients.

Therefore \(^{18}\)F-FDG PET is a useful technique for diagnosing GCA. \(^{18}\)F-FDG-PET is particularly valuable in patients presenting with less typical manifestations, such as fever of unknown origin, or when other diagnostic tests are inconclusive, in particular when temporal artery biopsy is negative for GCA. Visual grading method with an arterial \(^{18}\)F-FDG uptake superior to liver uptake is an efficient marker for vasculitis.

In an interesting study, Fuchs and coworkers [26] assessed the impact of \(^{18}\)F-FDG-PET on the management of patients with LVV. The patients with vasculitis included in the study (\(n = 30\)) were mainly patients with LV-GCA; 31 controls were also included. An international expert panel determined diagnoses and clinical management, with and without the results of \(^{18}\)F-FDG-PET. \(^{18}\)F-FDG-PET alone had an overall sensitivity of 73% and a specificity of 84% for diagnosing LVV. The diagnostic accuracy of \(^{18}\)F-FDG-PET was higher in patients not receiving immunosuppressive drugs (93% vs 64%, \(p = 0.006\)). Taken in contest with other available diagnostic modalities, the addition of \(^{18}\)F-FDG-PET increased the clinical diagnostic accuracy from 54% to 70% (\(p = 0.04\)). The addition of \(^{18}\)F-FDG-PET changed the treatment recommendation in 27% of patients not receiving immunosuppressive drugs and in 23% receiving immunosuppressants. This study confirmed that \(^{18}\)F-FDG-PET is a sensitive and specific imaging technique for LVV, especially when performed in patients not receiving immunosuppressive drugs. It increases the overall diagnostic accuracy and has an impact on the clinical management in a significant proportion of patients.

Therefore \(^{18}\)F-FDG PET is a useful technique for diagnosing GCA. \(^{18}\)F-FDG-PET is particularly valuable in patients presenting with less typical manifestations, such as fever of unknown origin, or when other diagnostic tests are inconclusive, in particular when temporal artery biopsy is negative for GCA. Visual grading method with an arterial \(^{18}\)F-FDG uptake superior to liver uptake is an efficient marker for vasculitis.

### 2.4. Is \(^{18}\)F-FDG-PET useful for the diagnosis of polymyalgia rheumatica (PMR)?

\(^{18}\)F-FDG-PET may also be useful in the diagnosis of PMR, a condition strictly associated to GCA. A French study showed that ischiatic and interspinous bursae uptake on \(^{18}\)F-FDG-PET are suggestive of PMR [30]. A Japanese study used \(^{18}\)F-FDG-PET/CT to investigate FDG accumulation in large joints, bursas, and large vessels in 14 untreated patients with PMR, 11 controls with rheumatoid arthritis and 6 controls with other active rheumatic diseases [31]. PMR patients showed increased FDG uptake in ischial tuberosities, greater trochanters, and lumbar spinous processes. Positive results at 2 or more of these sites showed high sensitivity (86%) and specificity (88%) for the diagnosis of PMR. High FDG uptake was also found in the aorta and subclavarian arteries in two patients with isolated PMR without cranial manifestations, confirming the data of Blockmans et al. [32]. These authors demonstrated the presence of vascular uptake in 31% of 35 patients with isolated PMR who performed \(^{18}\)F-FDG-PET. Therefore, imaging pattern of inflammation at \(^{18}\)F-FDG-PET may help in diagnosing PMR and in identifying an associated occult LVV. However, the diagnosis of PMR is mainly based on clinical and laboratory (inflammatory markers)
parameters and there is no indication to perform $^{18}$F-FDG-PET in each patient with PMR unless LV-GCA is suspected.

2.5. Is $^{18}$F-FDG-PET useful in the follow-up of LV-GCA and in predicting aortic complications?

The role of $^{18}$F-FDG-PET is less well established in predicting the course of the disease and its complications. In patients with GCA, baseline FDG uptake has been shown not to be correlated with the risk of subsequent relapse [21]. No differences in the decrease of total vascular score were observed in repeated PET scans between patients with and without disease flares [21]. After effective treatment, vascular FDG uptake decreases or normalizes, often in parallel with a reduction in serum inflammatory markers [8]. However, low-grade vascular FDG uptake may persist in a sizeable number of patients. It is currently unclear whether persistent low-grade vascular FDG uptake is due to smoldering vasculitis or vascular remodeling [8]. Some data have been provided that a positive $^{18}$F-FDG-PET in GCA may be associated with a higher risk to develop aortic complications in the long-term. In one study, the patients with an increased FDG uptake in the aorta at GCA diagnosis, had a significantly larger diameter of the ascending aorta ($p = 0.025$) and descending aorta ($p = 0.04$) and a significantly larger volume of the thoracic aorta ($p = 0.03$) [32]. All these patients underwent $^{18}$F-FDG-PET during the acute phase of GCA and CT scan of the aorta at late follow-up. In a more recent retrospective multicenter study, all 9 patients who developed aortic complications (dilation in all and dissection in 1 at a median time of 33 months after the GCA diagnosis) had LV inflammation on previous $^{18}$F-FDG-PET performed at diagnosis or during the follow-up [33]. A positive $^{18}$F-FDG-PET was significantly associated with a higher risk of aortic complications ($p = 0.004$). Therefore, some preliminary data seem to indicate a possible role for $^{18}$F-FDG-PET in predicting vascular complications in GCA. However, these data must be confirmed, in particular there is the need of long-term studies evaluating if the subgroup of patients with persistent FDG uptake are really at increased risk of developing vascular complications.

2.6. Conclusions

$^{18}$F-FDG-PET should be considered the investigation of choice for the diagnosis of extracranial vascular involvement in patients with GCA. $^{18}$F-FDG PET may be helpful in making an early diagnosis in untreated patients. However, its diagnostic performance declines after starting corticosteroid treatment. A smooth linear or long segmental pattern of FDG uptake in the aorta and its main branches is a characteristic pattern of LV-GCA. Visual grading method with an arterial FDG uptake superior to liver uptake is an efficient marker for vasculitis. $^{18}$F-FDG-PET, more recently integrated with CT scan, should be performed in the following cases when there is a high clinical suspicion of GCA: 1) in patients with negative TAB, 2) in patients presenting with less typical manifestations of GCA, in particular fever of unknown origin, and 3) in patients with isolated clinical PMR symptoms. $^{18}$F-FDG-PET is useful in showing the extent and amount of inflammation, however PET does not convey information regarding wall structure or luminal flow. $^{18}$F-FDG-PET can also be performed after GCA diagnosis and used to vary the treatment in accordance to its results. However, the role of $^{18}$F-FDG-PET for long-term monitoring disease activity in GCA is not well established and more data are needed. $^{18}$F-FDG-PET results should always be interpreted in association to the clinical findings, laboratory results and evaluation of disease progression according to the other imaging techniques.

3. Is PET/CT essential in the diagnosis and follow-up of temporal arteritis? Cons

In 1999, our group published a first article on the use of $^{18}$F-FDG-PET in the diagnosis of GCA [34]. Since then, we published several prospective studies in GCA and PMR, confirming our initial findings that vascular FDG-uptake in the large thoracic vessels is a very specific sign for large vessel vasculitidis [21,35,36]. Hence, I may seem not to be the right person to defend the thesis that $^{18}$F-FDG-PET/CT is not essential in the diagnosis and follow-up of GCA, but I accepted this challenge since I indeed realize that $^{18}$F-FDG-PET/CT is not necessary in every patient with GCA. When a TAB is unmistakably positive, and ACR criteria are met, then the diagnosis of GCA can be made, with the very rare exceptions of ANCA-positive vasculitides involving the temporal artery [37].

Although costs of $^{18}$F-FDG-PET/CT are high and the apparatus is not available everywhere and in short notice, this technique has conquered its place in the diagnostic armamentarium for GCA, alongside the biopsy, ultrasound and MRI. In the recently published GIACTA trial, in which placebo-controlled treatment with tocilizumab, an interleukin-6 monoclonal antibody, was investigated (in combination with steroids), almost half of patients were not included on the basis of a positive temporal artery biopsy, but based on a positive PET scan [38].

3.1. Value of $^{18}$F-FDG-PET in the diagnosis and follow-up of GCA

In 1999, when our first article on the use of PET scan in large vessel vasculitis (LVV) was published [34], it was not yet widely known that GCA can involve the aorta and its proximal branches. In fact, it was in that same year 1999 that Cornelia Weyand’s group published a cardinal article on the existence of two subtypes of GCA: a cranial form and a large vessel form [14]. In the absence of cranial symptoms and with a negative temporal artery biopsy, we considered these patients with large vessel FDG-uptake as ‘PMR patients’, since they were too old to be categorized as Takayasu patients. This explains the erroneous content of this first article title: ‘New arguments for a vasculitic nature of polymyalgia rheumatica using positron emission tomography’. We now know that these patients most probably were in fact GCA patients suffering from the large vessel form of this disease (LV-GCA). In that same article, we described the disappearance of FDG-uptake under steroid treatment in three patients who were scanned twice, which opened perspectives as to the use of $^{18}$F-FDG-PET in the follow-up of these patients. In more recent publications, we published other striking examples of strongly positive PET scans, becoming less and less positive when the patients were treated with longer periods of steroids [39].

So far for the good news. As previously pointed out, due to their small caliber however and their superficial localization in the proximity of the FDG-consuming brain, the temporal arteries themselves cannot be judged on a PET-scan. Thus, in patients with sole involvement of the temporal arteries, PET-scan will be negative. This was clearly demonstrated in a study by Brodmann et al. [40] in which they compare color-coded duplex sonography to FDG-PET in 22 patients with GCA. In 11 of these patients, there was only involvement of the temporal arteries, which was detected in all by sonography but not with PET. In 5 patients, there was only involvement of the large arteries, which could be detected by both methods in all of them. In the 6 remaining patients, there was simultaneous involvement of large and temporal arteries. Both sites of involvement were detected by sonography while PET scan visualized only large artery involvement. Although it is not clear what they regarded as the gold standard for temporal or large artery vasculitic involvement and although I have my doubts on this unrealistic high performance of sonography for large thoracic vessel involvement, the fact remains that PET scan will not detect GCA patients with pure temporal artery involvement.

In our prospective study with repeated PET-scans at 3 and 6 months during steroid treatment in 35 patients with biopsy-proven GCA, vascular FDG-uptake was noted in 29 patients (83%) at diagnosis, especially in the subclavian arteries and the aorta [21]. Some considerations have to be made on this high diagnostic performance. All these patients were prospectively gathered in our department of general internal medicine, where there may be a trend to have more patients with atypical clinical
presentations such as weight loss or fever. These patients probably have more large vessel involvement [35]. In patients presenting to the ophthalmology department for visual symptoms or to the neurology department for headache, PET may perform less well since these patients probably have more (sole) cranial arteries involvement.

The possible role of repetitive PET scanning during treatment was also investigated in the same study [21]. PET scans were repeated at 3 and 6 months, if the previous PET scans showed vascular FDG-uptake, and at relapse. All patients were treated with the same methylprednisolone taper scheme, with 32 mg/day as starting dose and end of treatment after 12 months. PET scans were scored at 7 different vascular areas (subclavian arteries, axillary arteries, carotid arteries, thoracic aorta, abdominal aorta, iliac arteries and femoral arteries) as negative (0) or positive (scored semi-quantitatively as 1, 2 or 3) and a Total vascular Score (TVS) was calculated, ranging from 0 to 21. There was a decrease of mean TVS from 7.9 ± 5.6 at baseline (diagnosis, before start of treatment) to 2.4 ± 3.5 at 3 month treatment (p < 0.0005), but no further decrease at 6 month treatment (mean TVS 3.8 ± 3.8). The patients who relapsed had similar TVS at baseline, 3 and 6 months and similar decreases of TVS at 3 and 6 months compared to those who did not relapse. Fourteen of the 18 patients who relapsed underwent a new FDG-PET scan before restarting or increasing methylprednisolone. Vascular FDG-uptake was detectable in 11 patients. The mean TVS was 2.5 ± 2.7 at relapse. However, GCA may relapse as PMR, and therefore, we cannot compare TVS at relapse directly with TVS at diagnosis (when all patients had active biopsy-proven GCA). Anyhow, all these data make PET scan less suitable to follow-up GCA: FDG-uptake not always predicted by the results of former PET scans. At relapse, vascular FDG-uptake seems to be less intense than at diagnosis, probably partly due to steroid intake (in those who relapsed while still taking methylprednisolone), partly because relapses in GCA patients may be in the form of isolated PMR. The exact nature of ongoing FDG-uptake in asymptomatic GCA patients taking steroids is not known: is it ongoing silent inflammation or is it due to vascular remodeling?

For all these reasons, I think there is no place for repetitive PET-scans during treatment of GCA. In patients under steroid treatment, interpretation of vascular FDG-uptake can be more difficult.

### 3.2. Can 18F-FDG-PET scan predict which patients are prone to aortic complications?

In 2008, we published the abovementioned study on the relationship between FDG uptake in the large vessels at diagnosis and late aortic diameter in GCA [32]. All patients with biopsy-proven GCA who underwent a FDG-PET scan in our center between 1996 and 2016 were asked to return and undergo a CT-scan of the aorta in the period from January to July 2006. The original FDG-PET scintigraphies were reread by two independent nuclear medicine specialists, who were unaware of CT-findings. Aortic FDG-uptake was reported as negative (score 0 or 1) or positive (score 2 or 3). The diameter of the aorta was measured at six different levels (ascending aorta, aortic arch, descending thoracic aorta, abdominal suprarenal, juxtarenal and infrarenal aorta) and the volume of the thoracic aorta and of the abdominal aorta were calculated. Twenty-four patients had no aortic FDG-uptake at diagnosis, 22 were FDG-uptake positive. The diameter of the ascending aorta was slightly larger in PET-positive patients than in PET-negative patients (40.4 ± 6.9 mm versus 37.0 ± 2.8 mm, p = 0.025). The same was true for the descending aorta (p = 0.044) and for the volume of the thoracic aorta (p = 0.029), but not for the diameter of the aortic arch (p = 0.281). In multivariate analysis, FDG-uptake at the thoracic aorta at diagnosis was the sole variable that corresponded with the volume of the thoracic aorta (p = 0.039), while gender, age, body length or the number of months elapsed since diagnosis were no independent variables [32].

Very recently, de Boysson et al. [33] published a retrospective study on 130 patients in which they investigated the relation between 18F-FDG-PET and the risk of subsequent aortic complications. Sixty-nine patients were PET positive, 61 PET negative. Nine patients – all PET positive – had experienced an aortic complication, 25 (6–54) months after a positive PET scan. In all but one patient, the location of the aortic complication (7/9 thoracic aorta dilatation, complicated with dissection in one; 1 abdominal aorta dilatation; 1 combination of thoracic and abdominal dilatation) corresponded with the positive vascular segments on PET. Again, in multivariate analysis, a positive PET was the only parameter which corresponded with the occurrence of aortic complications.

Do these two studies justify a PET scan in every GCA patient? We cannot rely solely on retrospective analyses. If these findings would be confirmed in a prospective study, then things might change and I would recommend to perform a PET scan in every GCA patient, to select those who may be at risk of aortic dilatation. Today, we do not know how we can prevent this late aortic dilatation. We even do not know if it is due to ongoing inflammation or to continuous shear stress on a weakened aortic wall. If it would be due to ongoing inflammation, can we stop it by longer treatment with steroids or with tocilizumab for instance? Nothing is known.

### 3.3. Conclusions

For all these reasons, I conclude that 18F-FDG-PET has shed a new light on an old disease, it has changed our way of viewing at it (from a localized disease of temporal arteries to a widespread inflammatory disorder of all large arteries), it has improved our diagnostic armamentarium, but in many patients one can still diagnose and treat GCA without PET. Temporal artery biopsy has lost its position as gold standard for the diagnosis of GCA ‘as a whole’, but remains the gold standard for cranial GCA. PET scan has never pretended to be a gold standard (since it will miss isolated cranial forms), but is the diagnostic technique of choice when LV-GCA is present.

### 4. Final general considerations

To conclude, the prevalence of LVV in newly diagnosed GCA is related to the ability of additional imaging techniques to detect early vascular inflammation.

In this regard, 18F-FDG-PET appeared so far to be the most sensitive imaging modality for detecting LV inflammation in GCA, exquisitely in the early phases of vasculitic process and in this specific subgroup of patients.

18F-FDG-PET appears a sufficiently sensitive and specific imaging technique for LV-GCA when performed in patients not receiving immunosuppressive drugs. It increases the overall diagnostic accuracy, with deep impact on the clinical management in a significant proportion of cases.

It should be valuable in patients presenting with less typical manifestations, such as fever of unknown origin, or when other diagnostic tests are inconclusive, in particular when TAB is negative for GCA; or finally, in patients with isolated PMR clinical symptoms (the latter appearing recurrent, steroid-resistant in some cases, or anyhow requiring unusually higher steroid doses) whose clinical suspicion of concomitant LV-GCA is quite high.

The role of 18F-FDG-PET is less well established in predicting the course of the disease, especially to predict the development of aortic complications.

Analogously, the exact nature of ongoing FDG-uptake in asymptomatic GCA patients taking immunosuppressive therapy and in general during the follow-up is not known: to define the presence of persistent smoldering vasculitic process or merely ‘vascular remodeling’ will be one of the challenges for the next future in this field.
Disclosures
The authors disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

Take home messages
• Increasing evidence support the need of additional imaging techniques to diagnose and monitor a specific subgroup of patients with GCA, such as LV-GCA ones.
• 18F-FDG-PET is a sensitive and specific imaging technique to diagnose LV-GCA in an early phase, especially when performed in untreated patients.
• 18F-FDG-PET may help in diagnosing PMR and in identifying an associated occult LVV.
• Prospective studies are needed to establish its exact role in monitoring the disease course and predicting the aortic complications.
• The influence of immunosuppressive therapy on the sensitivity and specificity of this technique during the follow-up remains to be established.

References