Diagnosis of Giant Cell Arteritis by 18 F-fdg Pet/ct in Patients on Glucocorticoid Therapy: Importance of Delayed Imaging

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Research Article

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Abstract

Objective

The aim of this study is to analyse the diagnostic value of positron emission tomography (PET) in patients with giant cell arteritis (GCA) despite glucocorticoid (GC) therapy before PET acquisition.

Materials and methods

Consecutive patients with strongly suspected GCA according to 2022 EULAR/ACR criteria were included. Physician diagnosis of GCA after 6 months of follow-up was the gold standard. PET was performed at baseline and 6 months later. In patients with negative results at 60 min, delayed imaging was performed at 180 min.

Results

Twenty-six patients were included with a median (IQR) age of 70.5 (57–88) years. Baseline PET was positive in all but one: 18 patients at 60 min and 7 patients after delayed imaging at 180 min. The median (IQR) GC dose at the time of baseline PET was 45 mg/d (26.2–45) of prednisone equivalent with a median exposure of 14 days (7-76.2). At 6 months of follow-up, PET was performed in 22 patients, with positive results in 16. Delayed imaging was performed in 6 patients due to negative PET at 60 min, with positive results in all cases, despite treatment with GC and/or biological therapy.

Conclusion

In patients on GC therapy, delayed imaging protocols applying procedural recommendations for vascular quantification could improve diagnostic accuracy. Therefore, we suggest performing imaging only at 180 min in patients who have been on GCs for more than 3 days as well as in those with highly suspected GCA but negative findings in baseline PET at 60 min.

Introduction

Giant cell arteritis (GCA) is the most common type of vasculitis in Caucasian (European and North American) patients over 50 years of age and is characterized by granulomatous inflammation in the walls of medium and large arteries [1–3]. Until a few years ago, GCA was studied as a vasculitis mostly affecting cranial arteries. Recently, however, with the development of new imaging techniques [4], it has been found that in a subgroup of patients with GCA, the vasculitis involves cranial and extracranial vessels at the same time, or even only extracranial vessels, the aorta and its main branches [5].
Regarding the use of imaging in GCA patients, the European League Against Rheumatism (EULAR) recommends ultrasound (US) as the first-line imaging modality [6]. Nonetheless, for extracranial arteritis, especially in cases of aortic involvement, other imaging techniques may be useful [6]. In line with this, in 2022, the EULAR/American College of Rheumatology (ACR) classification criteria for GCA for the first time included imaging techniques for classifying these patients, with particular emphasis on both ultrasound and positron emission tomography (PET) [7].

One of the technical limitations of PET is related to the history of glucocorticoid (GC) use (both duration and dose) before performing the imaging study. Slart et al. suggest withdrawal or delay of GC therapy until after performing the PET scan, but fluorine-18-fluorodeoxyglucose (FDG) PET within 3 days after starting of GC as a possible alternative [8]. Similarly, Nielsen et al. indicate that there is a window of opportunity within the first 3 days of treatment, observing a reduction in sensitivity after 10 days [9].

Seeking to enhance the performance of PET, delayed imaging could be useful. Although the procedure has yet to be properly standardised and research is ongoing (there being no clinical criteria for the systematic indication of this type of imaging), in patients with a high likelihood of the diagnosis and those who have been treated with GC for > 3 days, delayed acquisition -at 180 min after tracer injection for FDG PET/CT- may identify sites of active disease in patients with arteritis [10]. The clinical utility of semiquantitative parameters such as standard uptake values (SUVs) or target-to-background ratios (TBRs) for the initial diagnosis of GCA is as yet unknown, and their use is not recommended. Nevertheless, they may be of interest not only in diagnosis but also for follow-up [7].

The purpose of the present study is to provide evidence on the potential contribution of delayed PET imaging in patients with strong suspicion of GCA and negative 60-minute standard PET scan, due to limited acquisition accuracy in relation to previous GC therapy, either due to the duration of therapy or the dose used.

Materials and Methods

Patients

Inclusion criteria for this prospective, observational, longitudinal study were the presence of features of GCA according to 2022 EULAR/ACR criteria [7] in patients referred to the Rheumatology Department at Hospital Universitario de Navarra (HUN) between 2020 and 2023. Patients were excluded if on biological disease modifying antirheumatic drug (bDMARD) or targeted synthetic disease modifying antirheumatic drug (tsDMARD) therapy at the baseline visit. We collected data on demographic, clinical and therapeutic characteristics, as well as comorbidities documented in patient electronic health records.

The maintenance of the GCA diagnosis after at least 6 months of follow-up was considered the gold standard. Remission was defined according to treat-to-target recommendations for GCA and polymyalgia rheumatica (PMR) [11]. The study was approved by the local ethics committee (CEIm -Nr. PL_2018/62) and patients gave written informed consent before starting the study.
Measures for assessing disease activity

Together with clinical manifestations characteristic of GCA or PMR, acute phase reactants, erythrocyte sedimentation rate (ESR, mm/h) and plasma C-reactive protein (CRP, mg/l), were used to assess and monitor disease activity. ESR values of < 20 and < 25 mm/h in men and women, respectively, and CRP of < 5 mg/l were considered normal. Further, all patients underwent an FDG PET/CT scan in the PET Unit at Clínica Universidad de Navarra (CUN) at baseline to evaluate GCA disease activity and again at 6 months to assess treatment response.

FDG PET/CT imaging protocol

FDG was synthesized in-house with an 18 MeV cyclotron (Cyclone 18/9, IBA Radio pharma Solutions, Louvain-la-Neuve, Belgium). PET/CT was performed on a PET/CT scanner (Siemens Biograph mCT 64, Siemens, Knoxville, TX, USA). Patients fasted for at least 6 hours before FDG intravenous administration (3 to 5 MBq/kg). Blood glucose levels were required to be below 126 mg/dL [12]; otherwise, patients were treated with insulin to bring the levels below this threshold before imaging. No adverse effects associated with radiotracer injection were observed [12]. PET/CT images were acquired after 60 min (early) and 180 min (delayed), using non-contrast-enhanced CT performed with a 120 kV CARE Dose4D system and an image quality reference of 80 mAs, from head to knee. Consecutively, PET emission data were acquired in 3D mode with an emission time of 2–3 min per bed position. Reconstruction was optimized for quantification in compliance with EARL (time-of-flight ordered-subsets expectation maximization method, with 3 iterations, 21 subsets, and a 5-mm Gaussian filter).

FDG PET/CT imaging assessment

After anonymization, FDG PET/CT images were visually and semi-quantitatively analysed by two blinded PET nuclear medicine physicians, one junior (MVB) and the other with more than 20 years of experience (MJGV), on a dedicated workstation with Syngo.via (Siemens) PET software following the joint procedural recommendations proposed by Slart et al. [8]. Disagreements were resolved by consensus between the two readers.

For qualitative assessment, a 4-point visual grading system was applied, with standardized interpretation criteria, grades 2 and 3 being defined as positive for active GCA [8, 13]. A total vascular score (TVS) was calculated in 7 arterial territories (thoracic aorta, abdominal aorta, subclavian, axillary, carotid, iliac, and femoral), and reported as grade 0 (no uptake), 1 (less than liver), 2 (same as liver), or 3 (greater than liver). PET was considered positive for active GCA when the grade was ≥ 2 in one of the arterial regions (Fig. 1). TVS ranged from 0 (no vascular FDG uptake in any of the 7 vascular regions) to 21 (grade 3 vascular FDG uptake in all regions).

For semi-quantitative analysis, volumes of interest were drawn in the arterial wall and lumen blood pool. The maximum standardized uptake values (SUVmax) of the arterial wall and lumen, and the arterial wall-to-lumen ratio (TBR) were measured from early and delayed images, defining a cut-off for positivity of ≥ 1.34 [14, 15].
Statistical analysis

The demographic and clinical characteristics of participants, as well as the variables associated with delayed imaging, were described using measures of central tendency and dispersion, namely, mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and frequencies and percentages for categorical variables. Statistical analysis was performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 26 consecutive patients with a predominantly cranial phenotype of GCA were included (Table 1). Their baseline clinical characteristics and laboratory results over the course of the study are summarised in Tables 1 and 2 respectively. Six months after diagnosis, all but one patient were in remission.
### Table 1
Characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis, years, mean (IQR)</strong></td>
<td>70.5 (57–88)</td>
</tr>
<tr>
<td>Sex, woman, n (%)</td>
<td>18 (69.2)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
</tr>
<tr>
<td>- Hypertension</td>
<td>12 (46.1)</td>
</tr>
<tr>
<td>- Diabetes</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>- Dyslipidaemia</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td>- Hypothyroidism</td>
<td>5 (18.2)</td>
</tr>
<tr>
<td>- Hyperuricaemia</td>
<td>7 (7.7)</td>
</tr>
<tr>
<td>- Smoker/ex-smoker</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td>Days between symptom onset and giant cell arteritis diagnosis, mean (IQR)</td>
<td>148.0 (30.2-487.5)</td>
</tr>
<tr>
<td>Signs and symptoms, n (%)</td>
<td>17 (65.4)</td>
</tr>
<tr>
<td>- Headache</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>- Polymyalgia rheumatica</td>
<td>9 (34.6)</td>
</tr>
<tr>
<td>- Jaw claudication</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>- General malaise</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>- Scalp tenderness</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>- Neck pain</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>- Visual impairment</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>- Cerebrovascular accident</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>- Aneurysms</td>
<td></td>
</tr>
</tbody>
</table>

IQR: interquartile range
Table 2
Laboratory results of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>22</td>
<td>18</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>- n</td>
<td>63.5 (6-120)</td>
<td>10.5 (2–29)</td>
<td>3 (2–18)</td>
<td>2 (2–31)</td>
</tr>
<tr>
<td>- value, mm/1 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>26</td>
<td>22</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>- n</td>
<td>45.5 (2.5–296)</td>
<td>2.6 (0.2–59.9)</td>
<td>1.5 (0.1–16.9)</td>
<td>0.7 (0.1–11.9)</td>
</tr>
<tr>
<td>- value, mg/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone equivalent</td>
<td>26</td>
<td>26</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>- n</td>
<td>45 (0–60)</td>
<td>35 (0–50)</td>
<td>10 (0–30)</td>
<td>5 (0–15)</td>
</tr>
<tr>
<td>- dose, mg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range).

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

**PET results**

All 26 patients underwent a baseline PET scan. The mean glucose level at the time of this scan was 101 mg/dl (SD 21). The median (IQR) time between diagnosis and PET was 4.5 days (0-20.8) and a median (IQR) of 270 days (182–327) elapsed between the baseline and follow-up PET scans. The median GC dose at the time of the baseline PET was 45 mg/d (26.2–45) of prednisone equivalent with a median exposure of 14 days (7-76.2). Four patients had been given boluses of 6-methylprednisolone before the first PET: two having received 3 boluses of 125 mg/d, one 3 boluses of 500 mg/d and one 3 boluses of 1000 mg/d.

At baseline, PET findings were positive in 25 patients (Table 3). We implemented delayed imaging at 180 min in 8 patients at this stage due to negative findings in the 60-min PET images, with positive results in 7 patients (Table 4). Two of these patients had received GC boluses (at a dose of 125 mg in one case and 500 mg in the other), and despite this, the delayed imaging yielded positive findings (Fig. 2).
Table 3
Baseline positron emission tomography results and glucocorticoid (GC) dose stratified by duration of GC therapy.

<table>
<thead>
<tr>
<th>Days on GCs (patients with delayed images)</th>
<th>N</th>
<th>GC dose (mg/d), median (IQR)</th>
<th>PET 60-min TVS, median (IQR)</th>
<th>PET 60-min TBR, mean</th>
<th>PET 180-min TBR, mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 (0)</td>
<td>3</td>
<td>15 (0–45)</td>
<td>9 (3–19)</td>
<td>1.73 ± 0.73</td>
<td></td>
</tr>
<tr>
<td>4-10 (3)</td>
<td>9</td>
<td>45 (30–45)</td>
<td>7 (2–18)</td>
<td>1.45 ± 0.30</td>
<td>1.78 ± 0.63</td>
</tr>
<tr>
<td>&gt;10 (5)</td>
<td>14</td>
<td>35 (10–45)</td>
<td>8 (0–19)</td>
<td>1.43 ± 0.39</td>
<td>1.82 ± 0.38</td>
</tr>
</tbody>
</table>

PET: positron emission tomography; GC: glucocorticoid; TVS: total vascular score; TBR: target-to-background ratio; IQR: interquartile range

Table 4
Delayed F-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging results.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female (%)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Age in years, median (IQR)</td>
<td>70.5 (66-81.8)</td>
</tr>
<tr>
<td>Temporal artery biopsy positive, n (%)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Magnetic resonance angiography positive, n (%)</td>
<td>5 (60)</td>
</tr>
<tr>
<td>Computed tomography angiography positive, n (%)</td>
<td>5 (60)</td>
</tr>
<tr>
<td>Ultrasound positive, n (%)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Delayed-PET positive, n (%)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Glucocorticoid dose (mg/d), median (IQR)</td>
<td>45 (40–45)</td>
</tr>
<tr>
<td>Days of delay, median (IQR)</td>
<td>19.5 (13–22)</td>
</tr>
<tr>
<td>60-min TBR, mean (SD)</td>
<td>1.17 ± 0.09</td>
</tr>
<tr>
<td>180-min TBR, mean (SD)</td>
<td>1.81 ± 0.40</td>
</tr>
</tbody>
</table>

IQR: interquartile range; PET: positron emission tomography; SD: standard deviation; TBR: target-to-background ratio.

After 6 months of follow-up, PET was performed on 22 patients; and findings were positive in 16, although metabolic activity had decreased in all cases. We completed delayed imaging in six patients, as they had had negative findings in PET imaging at 60 min; and findings at 180 min were positive in all cases. Notably, 14 patients were being treated with tocilizumab (TCZ) and 2 with 15 mg/week of methotrexate subcutaneously. The median time between diagnosis of GCA and initiation of TCZ
treatment was 81.5 days (40.5-183.2). Ten patients were given TCZ intravenously and the other four subcutaneously.

Four patients died before the 6-month follow-up PET: two due to pneumonia, one due to abdominal aortic aneurysm rupture, and another for unknown reasons.

**Discussion**

GCA can manifest in three different ways, namely, with cranial, extracranial or mixed manifestations. Without delayed PET imaging, we would not have detected extracranial involvement in around 30% of patients. Notably, in delayed imaging, all but one of these patients showed extracranial involvement, this underlining the high prevalence of extracranial manifestations in this condition, which are usually underdiagnosed, and the high sensitivity of delayed PET imaging.

An interesting finding of this study is that in patients who are PET positive at baseline, it does not appear to be worthwhile to perform a 6 to 10 month follow-up PET scan, given the high positivity rate: all patients except one were in clinical remission. Early diagnosis and/or suspicion of GCA is essential to avoid complications or irreversible sequelae, such as loss of vision and blindness. In addition, it is also a key factor to achieve good performance in diagnostic tests. In line with this, and in accordance with EULAR and ACR recommendations, treatment should be started immediately if there is a strong suspicion of GCA [6, 7]. However, the rapid introduction of the treatment may alter the results of diagnostic tests, so our aim was to analyse this possibility and explore ways to improve the procedure.

It is known that temporal artery biopsy (TAB) can give positive results after 2–6 weeks of GC therapy [16, 17], but it is advisable to perform it within the first 7 days after treatment initiation to maximise its sensitivity [18]. According to Papadakos et al, having been on GC therapy for > 7 days was independently linked to lower rates of positive TAB (67% lower probability of a positive TAB) [18]. Other studies have demonstrated that histological evidence of arteritis persists despite 2 weeks of GC therapy [19, 20], although its sensitivity decreases from 78–40% over this time [18]. Similarly, in the case of PET, there seems to be a window of opportunity to optimise its performance and utility that varies between 0 and 10 days [8, 9]. GCs can rapidly induce clinical remission, but often there is a lack of consistency between clinical characteristics and histopathological findings, which may remain positive up to 1 year after starting therapy [21]. Various imaging techniques such as ultrasound are affected by GC therapy and PET is no exception [22–24], although it is not clear whether this translates to higher rates of relapse or treatment failure [24]. In line with Narvaez et al. [25], our study has demonstrated that PET can be useful after more than 2 weeks of GC therapy and even a relatively high GC mean dose. In relation to this, standardised delayed imaging in patients with strongly suspected GCA but in whom PET results are negative (grade 1), especially after prolonged treatment with high doses of GCs [25], may improve the utility of this technique. In this study, delayed imaging was positive in all but one of the patients after more than 2 weeks of treatment with high GC doses, using a TBR cut-off ≥ 1.34 (comparing to blood pool activity) [14, 15], yielding a specificity of 96.1%.
Notably, the GC dose seems to be less relevant than the time on this type of therapy. In our study, delayed PET imaging was performed more in the group with a longer history of GC therapy (> 10 days) despite the high doses used in both groups (Table 3). This finding could be explained by the fact that the long-treatment group contained more patients with PMR who had received long-term GC therapy.

One of the potential limitations of this study is related to the TBR cutoff used for the images taken at both 60 and 180 min (TBR ≥ 1.34 normalised to blood pool activity). Martínez-Rodríguez et al. [14, 15] classified control patients with TBR < 1.25 ± 0.16 as negative and those with values ≥ 1.34 as positive, and when we applied the cutoff established by these authors as positive for vasculitis (TBR ≥ 1.34) [15] to our series, only one patient was not classified as having GCA based on their baseline PET (TBR = 1.28, unpublished data). Further, we should interpret our results with caution given the relatively small sample size in this series, and the lack of a control group.

Nonetheless, a strength of the study is its prospective observational nature, a design that is associated with a lower risk of bias. Moreover, to our knowledge, this is the first study showing the potential of delayed PET imaging in patients with GCA on long-term high-dose GC therapy, following procedural recommendations for vascular quantification.

Notably, patients with negative 60-min PET findings showed vessel wall activity on delayed images (at 180 min). We therefore suggest that, given the nature of histological findings in GCA, where monocytes and macrophages are dominant and behave as tumoral cells in terms of $^{18}$F-FDG uptake [26], only one acquisition at 180 min would probably be sufficient to diagnose patients with GCA.

**Conclusions**

PET imaging beyond 3–10 days after GC initiation still has a high rate of positive diagnosis in patients with high suspicion of GCA. In addition, the use of delayed PET imaging (at 180 min) using procedural recommendations for vascular scoring achieves a sensitivity of 96% in the diagnosis of GCA, even in patients on long-term high-dose GC therapy. In fact, GC dose seems to be less relevant than the time on treatment. Based on these preliminary results, we suggest performing imaging only at 180 min in patients who have been on GCs for more than 3 days as well as in those with highly suspected GCA but negative findings in baseline PET at 60 min.

**Abbreviations**

PET: positron emission tomography

GCA: giant cell arteritis

GC: glucocorticoid

EULAR: European League Against Rheumatism
Declarations

Funding

VA was awarded a grant from the Spanish Rheumatology Society for performing the PET scans at the CUN.

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Ethical approval

The Navarra University Hospital's Ethics Committee approved this study (CEIm -Nr. PL_2018/62). All patients provided written informed consent for inclusion. The study was performed in accordance with the Declaration of Helsinki.

Conflict of interests

The authors have no conflicts of interest to declare.

Third party material and consent for publication

The manuscript contains third party material and obtained permissions are available on request by the Publisher.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Open Access

No

References


8. Slart RHJA; Writing group; Reviewer group; Members of EANM Cardiovascular; Members of EANM Infection & Inflammation; Members of Committees, SNMMI Cardiovascular; Members of Council, PET Interest Group; Members of ASNC; EANM Committee Coordinator. FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET Interest Group (PIG), and endorsed by the ASNC. Eur J Nucl Med Mol Imaging. 2018 Jul;45(7):1250-1269. doi: 10.1007/s00259-018-3973-8.


60 min (early) and 180 min (delayed) acquisition in a control population: a visual and semiquantitative comparative analysis. Nucl Med Commun. 2013 Sep;34(9):926-30. doi: 10.1097/MNM.0b013e32836370fb.


Figures
Figure 1. Qualitative assessment of FDG uptake at 60 min (total vascular score, TVS).

See image above for figure legend.

Grade 0: no uptake; Grade 1: less than liver; Grade 2: same as liver; Grade 3: greater than liver. Negative: grade 0, 1 or 2. Positive: grade 2 or 3.
Figure 2

Uptake in early (upper) and delayed (lower) images (target-to-background ratio [TBR]: blood pool/aortic wall) in a patient who had received glucocorticoid boluses.

Early (60-min) and delayed (180-min) imaging target-to-background ratio (TBR): blood SUVmax/wall SUVmax; TBR positive ≥ 1.34