18-FDG PET for large-vessel vasculitis diagnosis and follow-up

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ABSTRACT
Objective. Large-vessel vasculitis (LVV) are chronic inflammatory diseases that affect arteries. While a mere clinical-serological approach does not seem sensitive either in the initial evaluation nor in long-term monitoring, 18-FDG positron emission tomography (18-FDG PET) is currently considered a useful assessment tool in LVV. We aimed at exploring the utility of 18-FDG, compared with traditional assessments, in the short- and long-term follow-up of patients with LVV. In addition, we compared patterns of vascular involvement in patients with Takayasu's arteritis (TAK) and giant cell arteritis (GCA).
Method. We retrospectively analysed 47 patients affected by LVV, evaluating clinics, blood chemistry and 18-FDG PET results, at two time points, short-term (average 8 months after diagnosis) and long-term (average 29 months).
Results. 18-FDG PET uptake, expressed as mean value of SUV max, decreased significantly during follow-up in all the patients. A low concordance between 18-FDG PET and acute phase reactants levels was observed, but also a good sensitivity in detecting the response to treatment.
Conclusion. The results confirm the role of 18-FDG PET as a powerful tool in the evaluation of LVV, both at the time of diagnosis and during monitoring. Furthermore, the data confirm that GCA and TAK are part of the same disease spectrum.

Introduction
According to the Chapel Hill Consensus Conference of 2012 (1), large-vessel vasculitis (LVV) are defined as inflammatory diseases that affect arteries. Two main variants are distinguished: Takayasu's arteritis (TAK) and giant cell arteritis (GCA). Both of them are the most common causes of aortitis (2). Concerning the disease classification of LVV, some issues are still debated, namely whether they represent two distinct nosological entities or rather belong to the same spectrum of disorders, as suggested by striking similarities in the distribution of arterial lesions (3).

Aortitis can have extremely variable and often non-specific symptoms and signs, therefore the index of suspicion of the evaluating clinician must be high to establish an accurate diagnosis in a timely fashion (2, 4). Diagnosis should be placed as soon as possible both for the risk of potential life-threatening complications, such as aortic aneurysm, dissection, occlusion (thrombosis and stenosis), and for the need of an early disease-specific treatment (5, 6).

Clinical examination, inflammatory markers and imaging are all critical components of vasculitis assessment in every stage of the disease, but none of these items, used individually, is sufficient to adequately evaluate the activity of LVV (7).

The gold standard for diagnosis remains the biopsy, however angiography, CT, MRI and positron emission tomography with 18-F-Fluorodeoxyglucose (18-FDG PET) are widely accepted as complementary tools to assess vascular involvement at first diagnosis. More controversial, instead, is how to deal with disease monitoring, to detect during the follow-up LVV relapses and damage.

Not every patient with systemic symptoms suggestive of exacerbations presents an anatomical progression of the vascular involvement (8). On the other hand, it is well known that disease activity is particularly difficult to ascertain, and post-mortem histological studies have shown a significant rate of vascular inflammation even in patients with vasculitis considered inactive (9). In fact, active vascular inflammation could be detected in the absence of clinical or biological signs of activity (10-17). Relying on these markers during asymptomatic periods can potentially lead to the false assumption that

the disease is in remission, while there is ongoing active inflammation with fibrosis and progressive occlusion (18). Traditional inflammatory markers (*i.e.* ESR and CRP) have non-optimal sensitivity (19) and low specificity (13, 18, 20) and thus are not reliable for predicting recurrences or disease progression (7). This limit is particularly critical in patients treated with IL-6 inhibitors (16, 21), being this cytokine implicated in hepatic CRP synthesis (20).

Regarding the role of imaging, CT, US and angiography mostly allow to evaluate the progression or the appearance of new arterial lesions, but poorly correlate to the vascular inflammation (22-24). This latter is instead correlated with the progression of the disease and the development of stenosis and thrombosis (24). On the contrary, positron emission tomography with ^{18}F-Fluorodeoxyglucose (^{18}-FDG PET) is a very sensitive functional imaging technique for the diagnosis of inflammatory changes in vessels with a diameter greater than 4 mm (25)and thus has proved to be extremely useful in the management of large-vessel vasculitis (26-42).

^{18}-FDG PET can facilitate an early diagnosis due to the fact that the increased metabolic activity caused by the inflammation of the vascular wall precedes the morphological changes in the arterial wall (28, 36, 37).Often FDG absorption correlates with the presence of increased inflammation markers (24), but moderate absorption is also present in patients with inactive vasculitis and no sign of systemic inflammation. It is still unclear whether this reflects a subclinical inflammation and predict arterial progression and vascular complications (24).

In addition, ^{18}-FDG PET findings of inflammation normalise after treatment with immunosuppressants, mirroring clinical improvement(29). Thus, 18-FDG PET can be considered a reliable indicator of disease activity (38).

A prospective study was recently published in which ^{18}-FDG PET scan was performed in patients with LVV, other pathologies mimicking LVV (*i.e.* hyperlipidaemia) and in healthy controls. ^{18}-FDG PET showed a sensitivity of 85% and a specificity of 83% in distinguish-

ing a clinically active LVV from other control diseases. In this study, an uptake was interpreted as an active vasculitis in the majority of LVV patients considered in remission from a clinical point of view (41 out of 71 patients) (39).

Despite the high sensitivity and specificity of ^{18}-FDG PET for the diagnosis of LVV, it is still debated whether it might be useful to monitor disease activity after therapy. More specifically, data on the correlation between ^{18}-FDG PET scores and inflammation markers are relatively scarce.

The aim of this work is to evaluate the concordance of ^{18}F-fluorode-oxyglucose-positron emission tomography computed tomography (^{18}-FDG PET) imaging with the laboratory tests and the clinical judgment, in order to explore the utility of ^{18}-FDG PET with respect to traditional assessments in the follow-up of patients with large-vessel vasculitis (LVV).

Patients and methods

We retrospectively evaluated a population of 47 patients affected by LVV fulfilling the 1990 American College of Rheumatology (ACR) classification criteria for GCA and TAK, referred to our unit from November 2012 to June 2018 (total follow-up period: 15 years). To assess the disease activity, clinical condition and inflammation markers were evaluated at two time points, short-term (average 8 months after diagnosis) and long-term (average 29 months); the mean time interval between the two evaluations was 24 months.

Among inflammatory markers we considered erythrocyte sedimentation rate (ESR, normal values 0–30 mm/h), C-reactive protein (CRP, normal values 0-0.5 mg/dL) and fibrinogen (normal values 200–400 mg/dl), when measured no more than 2 weeks before ^{18}-FDG PET.

Demographic and clinical data included age, sex, disease signs and symptoms (*i.e.* fever, headache, arthromyalgia, jaw claudication, abdomen claudication, limbs claudication, hyposphygmia of peripheral pulses, ischaemic heart disease, visual loss and cerebrovascular manifestations), date of diagnosis and disease duration. For GCA patients, we

recorded the histopathology of temporal artery biopsy (TAB) when available. Therapy was also recorded.

In parallel, we took into account two consecutive ^{18}-FDG PETs performed by patients during follow-up, one in the "short-term" (T0) and the other in the "long-term" (T1).

Of each ^{18}-FDG PET examination we considered the overall outcome, "active" or "non-active" vasculitis as resulting from the radiologist judgement, the value of SUV max, the distribution of the uptake in the vascular districts (*e.g.* ascending aorta, arch, descending aorta, abdominal aorta, iliac arteries, lower limbs, succlavia and carotids) and the target-to-background ratio (TBR) values in different districts: thoracic aorta - cava (AOThorcava), abdominal aorta - cava (AOAbdcava), thoracic aorta - liver (AOThorliver), abdominal aorta - liver (AOAbdliver), hot vessel - cava (Hotvescava), hot vessel - liver (Hotvesliver). The study received the local ethics committee approval (protocol 14914) and was conducted according to the Declaration of Helsinki.

Statistical analysis

Data were expressed as mean values (± standard deviation) or median values (25th-75th percentiles) for continuous variables and as absolute frequencies and percentages for nominal variables. Patients with missing data were excluded from the analysis. Patients who developed CV events were compared to those who did not, using t-test or Mann-Whitney U-test for continuous variables and Fisher's exact test for the nominal valuables. Prism 4 for Windows (GraphPad Software Inc.) was used for the analysis. Concordance was analysed by means of the Cohen K coefficient (0.21–0.40 indicates modest concordance; 0.41–0.60 indicates moderate concordance, 0.61–0.80 indicates substantial concordance). The analyses were performed using IBM-SPSS, v. 20, package for Mac Os X.

Results

Patients characteristics

The total group of patients consists of 47 subjects, 10 men and 37 women, with a diagnosis of arteritis. The mean

Table I. Demographic and clinical characteristics of patients at baseline.

	Total (n=47)	GCA (n=35)	TAK (n=12)
Age (years), median (IQR)	60 (53-61)	65 (57-71)	36 (27-51)
Sex, M/F	10/37	9/26	1/11
ESR (mm/h), median (IQR)	79 (33-107.5)	69 (33-106.5)	98.5 (39.75-117.3)
CRP (mg/dl), median (IQR)	4.21 (1.3-8.36)	3.7 (1.47-8.32)	6.7 (0.43-10.43)
Fibrinogen (mg/dl), median (IQR)	640 (471-880)	640 (471-880)	668 (397.3-890.8)
Steroid (pulse), n (%)	16 (34)	8 (23)	8 (67)
Steroid (maintenance), n (%)	34 (72)	28 (80)	6 (50)
MTX, n (%)	17 (36)	12 (34)	5 (42)
AZA, n (%)	1 (2)	1 (2)	0 (0)
CFX, n (%)	20 (43)	16 (46)	4 (33)
MMF, n (%)	1 (2)	1 (2)	0 (0)
Latency before diagnosis (months), median (IQR)	3 (0-8)	2 (0-8)	3 (0-13)

M: male; F: female; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; MTX: methotrexate; AZA: azathioprine; CFX: cyclophosphamide; MMF: mycophenolate mofetil.

Table II. SUVmax and TBR values in different vascular districts in the short (T0) and long-term (T1) follow-up.

		n	Mean value ± SD	T0 *vs.* T1 (*p*-value)
18-FDG PET SUVmax	T0	42	3.99 ± 1.85	< 0.0001
	T1	42	2.21 ± 0.92	
TBRCavaAOThor	T0	31	2.148 ± 0.94	< 0.0001
	T1	31	1.54 ± 0.35	
TBRCavaAOAbd	T0	31	2.15 ± 0.65	< 0.0001
	T1	31	1.56 ± 0.40	
TBRLiverAOThor	T0	31	1.71 ± 0.67	< 0.0001
	T1	31	1.21 ± 0.26	
TBRLiverAOAbd	T0	31	1.75 ± 0.64	< 0.0001
	T1	31	1.22 ± 0.25	
TBRCavaHotVessel	T0	14	2.76 ± 0.97	0.0078
	T1	14	1.45 ± 0.65	
TBRLiverHotVessel	T0	13	2.28 ± 0.79	0.0039
	T1	13	1.21 ± 0.41	

18-FDG PET: 18F-fluorode-oxyglucose-positron emission tomography; TBR: target to background ratio; AO: aorta, Thor: thoracic; Abd: abdominal.

age at diagnosis is 58.43 years (range 21–80, SD 15.75).
The GCA group consists of 35 subjects, 26 women (74%) and 9 men (26%), with an average age of 64.97 years. The TA group consists of 12 subjects, 11 women (92%) and one man (8%), with an average age of 39.33 years.
The two groups show significant differences in age (GCA 64.97 *vs.* TAK 39.33, *p*=0.01), in line with the epidemiological characteristics of GCA and TAK, but not in the mean value of the laboratory parameters. Patient characteristics are shown in Table I.
Following the diagnosis, 34% of patients were treated with steroid pulses and 43% with cyclophosphamide (CFX), in most cases IV, up to the to-

tal dose of 7 g. Thirty-six percent of patients were treated with methotrexate (MTX) (26% GCA, 11% TAK). No patient who received CFX had already been treated with MTX; 19% of patients performed both steroid bolus and CFX. Mycophenolate (MMF) was used in 2% of patients (all GCA) and azathioprine (AZA) in 2% (all GCA).
At the time T1, 6% of patients needed to repeat steroid pulses and 2% were still under treatment with CFX. 83% of patients continue low-dose steroid therapy (6-methylprednisolone 4-8 mg/day); 55% used MTX as steroid-sparing agent, 11% AZA, 8% anti-TNF-α and 6% tocilizumab (TCZ).
The first 18-FDG PET was performed 12 months as average after onset of symp-

toms, and 7 months after the diagnosis of arteritis. The second 18-FDG PET was performed 29 months as average after the diagnosis. The average interval between first and second 18-FDG PET was 28 months.

Comparison of 18-FDG PET uptake and TBR between short and long-term follow-up in all patients
According to the radiologist's judgement, of the 38 positive 18-FDG PETs at short-term evaluation, only 15 remained positive, while 23 became negative and one that was negative, became positive. The mean value of SUV max at short-term follow-up in all patients is 4.09 (SD±2.13), while at long-term follow-up is 2.23 (SD±1.13). 18-FDG PET uptake, expressed as mean value of SUV max, decreased significantly (*p*<0.001) during follow-up in all the patients (Table II).
In the comparison between short and long term, all TBR districts analysed changed significantly (*p*<0.001). Values for each district are shown in Table II.

Distribution of fluorodeoxyglucose and difference in TBR in GCA and TAK
Analysing the uptake of FDG in the various vascular districts and comparing this data between GCA and TAK patients, exclusively the aortic arch uptake appears to be significantly different. In particular, the aortic arch is more involved in TAK patients compared to the GCA (TAK 80% *vs.* GCA 43%, *p*=0.04). Analysing the values of the different TBRs at short-term follow-up and comparing these data between GCA and TAK patients, exclusively AOAbdcava TBR appears to be significantly different between GCA and TAK (*p*=0.024). Images of two different patterns of vascular involvement detected with 18-FDG PET are shown in Figures 1 and 2.

Concordance between clinical disease activity and biomarker values at short-term evaluation
We assessed the concordance between the clinical evaluation of disease activity and the inflammatory markers (*i.e.* ESR, CRP). The disease was considered "active" in the presence of at least one clinical symptom (*i.e.* fever, headache, arthromyalgia, jaw claudication,
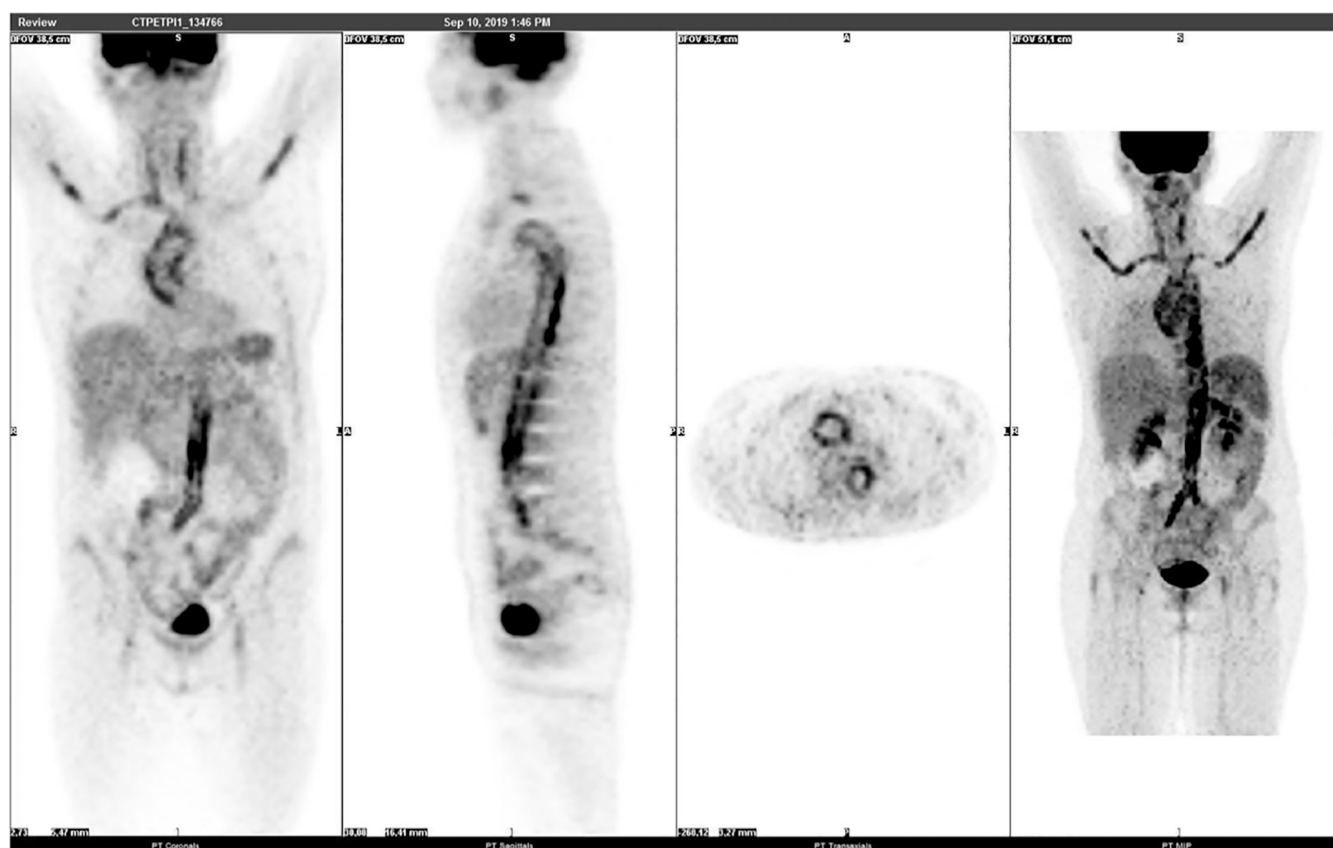
Fig. 1. 18F-FDG 18-FDG PET/CT scans of aortitis.

abdomen claudication, limbs claudication, hyposphygmia of peripheral pulses, ischaemic heart disease, visual loss and cerebrovascular manifestations).
Regarding the relationship between clinical judgement and CRP, these parameters agree in 73% out of cases. Normal CRP serum levels were detected in 11% of patients with clinically active disease, while 16% of patients with no symptoms of vasculitis has elevated CRP levels. Thus, a low concordance is detected between clinical evaluation of disease activity and CRP ($\kappa=0.206$).
Taking into account ESR, the concordant cases are 97%. No patient without symptoms has a high ESR and only 1 patient with clinically active disease has normal ESR. These data show a tendency of these two parameters to agree ($\kappa=0.93$).

Concordance between clinical disease activity and biomarker values at long-term evaluation
We similarly assessed the concordance between the clinical evaluation of disease activity and the inflammatory

markers (*i.e.* ESR, CRP, fibrinogen) also at long-term follow-up.
Elevated CRP (that is >0.5 mg/dl) and clinical disease activity show a low concordance since these parameters agree in only 67% of cases. In particular, CRP was negative in 5% of patients with clinical disease activity, while in 22% with no symptoms of vasculitis CRP was elevated ($\kappa=0.405$).
A fair agreement is observed between fibrinogen and clinical disease activity, since data are concordant in 76% of cases ($\kappa=0.521$).
In the case of ESR, no discordant cases are observed, leading to a high degree of agreement between the clinical activity of the disease and the ESR value ($\kappa=1.00$).

Comparison between the clinical evaluation of disease activity and the result of 18-FDG PET
We compared the clinician assessment of the disease activity with the outcome of 18-FDG PET at short- and long-term follow-up.
At short-term assessment, based on

clinical manifestations and inflammatory markers, 33 out of 42 patients (78.57%) showed an active disease. Among these patients, 18-FDG PET examination was positive in 28 subjects (66.67%). In 9 patients the disease was considered inactive by the clinician (21.43%), but in these ones 18-FDG PET was negative only in 1 subject (2%); 8 of 9 patients have a positive result at 18-FDG PET examination (19.05%).
At long-term assessment, the disease is considered inactive in 30 of 40 patients (75%); 18-FDG PET is concordant (*i.e.* negative for active vasculitis) in 18 subjects (45%) while 12 subjects (30%) are positive at 18-FDG PET examination. On the other hand, in 10 patients the disease is considered active by the clinician (25%) and among these 18-FDG PET is positive in 4 subjects (10%), and negative in 6 (15%).
Thus, these data show no concordance between 18-FDG PET and clinical evaluation of disease activity because of the 18 discordant cases ($\kappa=-0.046$ for short-term follow-up and $\kappa=0.000$ for long-term).
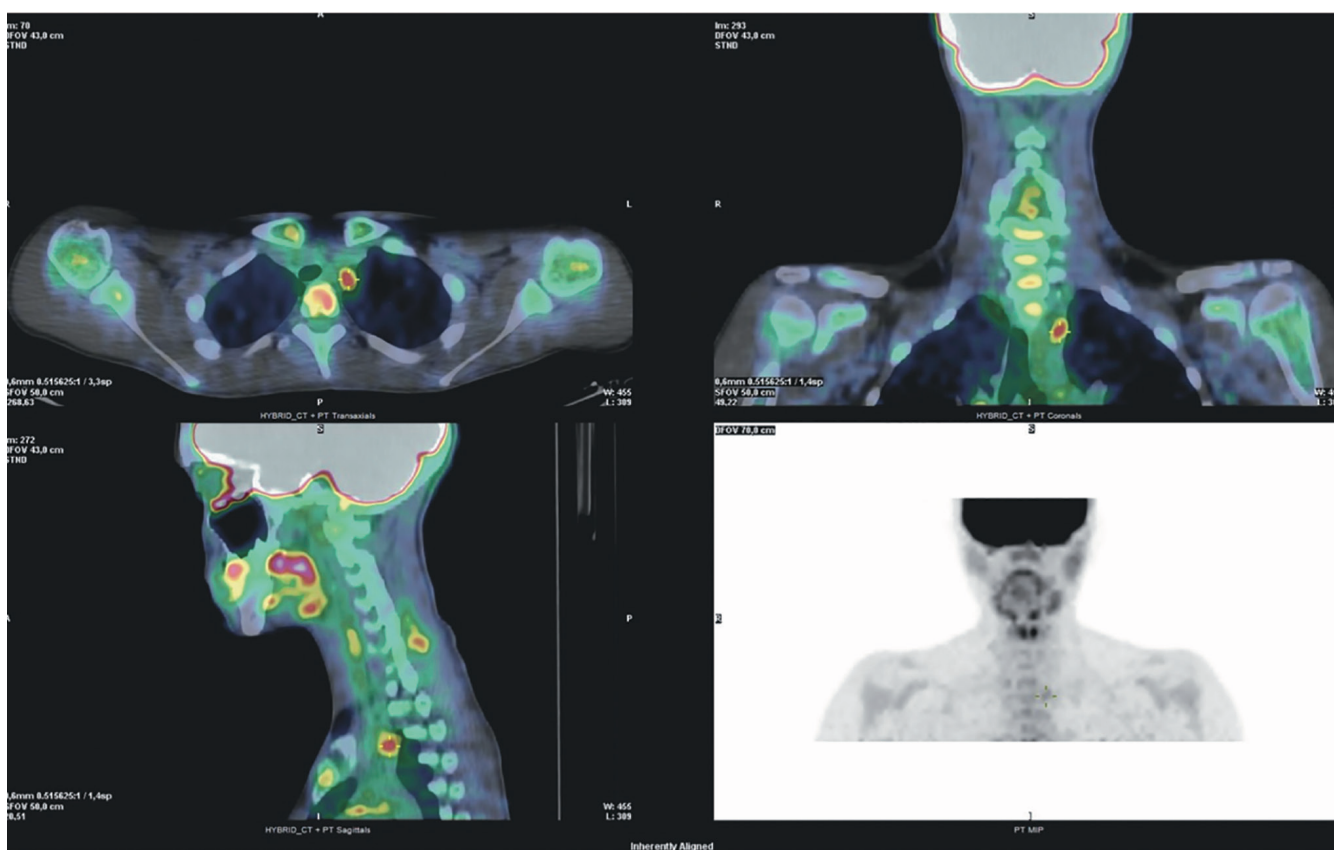
Fig. 2. ^{18}F-FDG [18]FDG PET/CT scans of focal vasculitis of the left carotid emergence.

Concordance between [18]FDG PET and acute phase reactants at short- and long-term evaluation

We evaluated the concordance between [18]FDG PET outcome and ESR, PCR and fibrinogen at the short and long-term follow-up. The results indicate a poor concordance of acute phase reactants and [18]FDG PET, both in the short and long term (data not shown).

Concordance between [18]FDG PET and treatment response

By evaluating the result of [18]-FDG PET in patients treated with steroid pulses and in patients treated with cyclophosphamide, an agreement was observed between the negativity of [18]FDG PET and therapy (κ=0.027 for CS, κ=0.152 for CFX).

Discussion

The data presented in this paper indicate that [18]FDG PET represents a valid and powerful tool for the evaluation of patients affected by large-vessel vasculitis, both at the time of diagnosis and during monitoring. [18]FDG PET allows to increase diagnostic sensitivity and to observe both the response to treatment and its maintenance over time. In fact, [18]FDG PET improve in all the patients: comparing short and long-term evaluation, a statistically significant reduction in the average value of SUVmax is observed, as well as a reduction of TBR values in all the districts considered.

These conclusions are based on real life data, obtained in large cohort of patients evaluated homogeneously in a single centre and subjected to standardised screening procedures that include a large number of [18]FDG PET.

Furthermore, our data show a very similar vascular involvement in both arteritis. The only significant difference that has emerged is the involvement of the aortic arch, more frequently affected in TAK. Comparing the values of the different TBRs in the two arteritis, only the TBR calculated between vena cava and abdominal aorta appears to be significantly different between GCA and TAK. Taken together, these data suggest that GCA and TAK are not two different conditions but part of the same disease spectrum.

Recently Salvarani *et al.*, using [18]FDG PET/CT, published data that support this conclusion. These authors detected similar distribution pattern of the arterial lesions in GCA and TA, although some subtle differences were reported. They also observed the tendency of arterial lesions to be contiguous in the aorta and symmetric in branch vessels, as previously noted in angiographic studies, and showed a symmetric extension of the lesions in paired vascular beds at carotid, axillary, subclavian, iliac and femoral arteries level, clustering with the contralateral counterpart, not only in TAK but also in GCA population (43-45).

A key issue addressed in this paper is the reliability of evaluation of disease activity based exclusively on clinical symptoms and inflammatory markers. We observed that the presence of suspicious symptoms has a low concordance with CRP both in the short and long-term follow-up, while ESR appears to be a more reliable index. Due to the scarcity of data related to fibrinogen at short-term assessment, this

was analysed only in the long-term, and showed a modest correlation with clinical symptoms.

Thus, our results are in agreement with published data that suggest the non-optimal sensitivity (19) and the low specificity (13, 18, 20) of traditional inflammatory markers.

Similarly, comparing the disease activity evaluated on a clinical basis with the outcome of [18]-FDG PET, we did not observe any concordance between these parameters, either in the short-term or in the long-term follow-up.

Thus, our data confirm the low sensitivity and specificity of clinical manifestations, and even more of inflammatory markers, in monitoring disease activity, in particular the possible minimal residual disease in vessel walls that could be the cause of damage progression.

Besides being useful for the diagnosis and monitoring of LVV, [18]-FDG PET allows the differential diagnosis from other possible causes of increase in inflammatory markers and non-specific or non-typical symptoms. A negative temporal artery biopsy, an ultrasonography without an arterial halo, or an MRI without aortic wall thickening or oedema do not exclude the presence of LVV, that should be explored by [18]-FDG PET/CT when clinical data are suggestive of LVV(33).

Another advantage of obtaining a baseline [18]-FDG PET is to get an initial semi-quantitative parameter (SUV), useful for the diagnosis of aortitis and also in follow up for monitoring the response to therapy; according to some studies, it may also have a prognostic value (in particular in TAK) (29, 33).

[18]-FDG PET currently has the limitation of not being able to discriminate vascular remodelling from inflammatory involvement of the arterial wall as cause of persistent low-grade absorption of vascular FDG in treated patients considered in remission. Well known drawbacks of [18]-FDG PET are represented by the lack of a uniform definition of vascular inflammation based on the absorption of FDG; the inability to provide information on the wall structure or luminal flow; the power of resolution limited to vessels

with a diameter greater than 4 mm; the use of large amounts of ionising radiation (generally 15¬20 mSv per scan); the high costs and limited access (38, 40, 41).

A further aspect to take into account is that the presence of atherosclerosis and the increase in the rate of vascular uptake with age, that might overestimate the degree of vascular inflammation in older patients (42), even if the distribution of FDG uptake is usually different (*i.e.* circumferential in LVV, limited in atherosclerotic lesion)(42).

Nevertheless, [18]-FDG PET has enabled in our cohort the identification of a great number of patients with active disease, that the mere clinical-serological assessment had not recognised. Thus, [18]-FDG PET was a key tool for the assessment of disease activity, allowing also a better evaluation of the response to therapy, that possibly leads to a lower incidence of complications.

In conclusion, we suggest that a multi-parametric evaluation, based on clinical symptoms, inflammatory markers and imaging, is necessary to obtain a better diagnosis and monitoring of LVV. At present, [18]-FDG PET is the most reliable method for diagnosis and monitoring of vascular inflammation in patients with LVV, and is a useful tool in the diagnosis of uncertain forms and in therapeutic monitoring. This critical role of [18]-FDG PET will be strengthened by an increase in its resolution, as will be probably obtained by [18]-FDG PET-MRI that should allow the precise identification of the arterial wall inflammation, combined with a sensitive demonstration of response to treatment (23).

Acknowledgements

Take home messages
- [18]-FDG PET scan is the most reliable method for diagnosing and monitoring LVVtherapies;
- A multi-parametric evaluation, based on clinical symptoms, inflammatory markers and imaging, is necessary for a correct diagnosis and follow-up of LVV.

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