Università degli Studi di Padova

Dipartimento di MEDICINA - DIMED

CORSO DI DOTTORATO DI RICERCA IN SCIENZE CLINICHE E SPERIMENTALI
CURRICOLO IN SCIENZE REUMATOLOGICHE E LABORATORISTICHE
XXIV CICLO

Experimental thesis

The role of hybrid ^{18}F-FDG PET/MR in the diagnosis and management of large vessel vasculitis

Coordinatore: Ch.mo Prof. Paolo Angeli
Supervisore: Ch.mo Prof. Luca Iaccarino

Dottorando : Roberto Padoan

Table of Contents

List of paper discussed in the thesis

Paper I

Fully integrated 18F-FDG PET/MR in large vessel vasculitis.

Padoan R, Crimì F, Felicetti M, Padovano F, Lacognata C, Stramare R, Quaia E, Cecchin D, Bui F, Zucchetta P, Schiavon F.

Q J Nucl Med Mol Imaging. 2019 Oct 9.

Paper II (unpublished)

Persistent low-grade FDG-PET vascular inflammation in remitted LV-GCA patients is associated to a significant high risk of relapse.

Padoan R, Tomelleri A, Campochiaro C, Baldissera E, Crimì F, Zucchetta P, Cecchin D, Picchio M, Dagna L, Doria A, Schiavon F.

Manuscript in submission

Congress abstracts on the topic

- ArLAR21 e-Congress Jordan - March 2021. Oral presentation: "*Persistent low-grade vascular inflammation in remitted large vessel vasculitis patients is associated with an increased risk of relapse. A longitudinal study using fully integrated 18F-FDG PET/MR*." **R Padoan**, M Felicetti, F Crimì, C Lacognata, D Cecchin, P Zucchetta, F Schiavon

- 21th EULAR Congress, June 2020. Poster: *"Persistent low-grade FDG-PET vascular inflammation in remitted LVV-GCA patients is associated to a significant high risk of relapse"* **R Padoan**, A Tomelleri, M Felicetti, C Campochiaro, E Baldissera, F Crimì, P Zucchetta, D Cecchin, M Picchio, L Dagna, A Doria, F Schiavon

- 56th SIR (Italian Society of Rheumatology) Congress, Rimini 27-30 November 2019. Oral Presentation: " *Persistent low-grade vascular inflammation in remitted large*

vessel vasculitis patients is associated with an increased risk of relapse. A longitudinal study using fully integrated 18F-FDG PET/MR." **Padoan R**, Felicetti M, Crimì F, Lacognata C, Cecchin D, Zucchetta P, Schiavon F.

- 20th EULAR Congress, Madrid 12-15 June 2019. Poster: *"Persistent low-grade vascular inflammation in large vessel vasculits: a longitudinal study using fully integrated 18F-FDG PET/MR"* **Padoan R**, Felicetti M, Crimì F, Padovano F, Lacognata C, Cecchin D, Zucchetta P, Schiavon F.

- 19th International Vasculitis & ANCA Workshop, Philadelphia 7-10 April 2019. Oral Presentation: "*Fully integrated 18f-fdg pet/mr in large vessel vasculitis*." **Padoan R**, Crimì F, Felicetti M, Punzi L, Lacoganta C, Stramare R, Cecchin D, Bui F, Zucchetta P, Schiavon F.

- 19th EULAR Congress, Amsterdam 13-16 June 2018. Poster: "*Fully integrated 18f-fdg pet/mr in large vessel vasculitis*." **Padoan R**, Crimì F, Felicetti M, Padovano F, Punzi L, Lacoganta C, Stramare R, Cecchin D, Bui F, Zucchetta P, Schiavon F.

- 18th International Vasculitis & ANCA Workshop, Tokyo 25-28 March 2017. Poster: "*The feasibility of hybrid PET/MRI in large vessels vasculitis"* **Padoan R**, Felicetti M, Crimì F, Lacognata C, Stramare R, Cecchin D, Bui F, Zucchetta P, Punzi L, Schiavon F.

Summary

Background: Imaging role in large vessel vasculitis (LVV) has tremendously increased during the last decade because of technique improvement. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become a tool for the diagnosis and disease activity assessment in LVV with a variable reported sensitivity and specificity of approximately 70% and 77% in Takayasu arteritis (TAK) and 80% and 89% in giant cell arteritis (GCA). Recently, a novel imaging technique, hybrid ^{18}F-FDG PET/MR, has been developed. The aim of the whole PhD project was to evaluate the feasibility of hybrid ^{18}F-FDG PET/MR in patients with LVV and to better characterize its role in monitor disease activity over time, and predict clinical outcomes.

Methods: The overall project comprised two experimental phases.

The first one, the feasibility study, was conducted on consecutive inpatients and outpatients affected with or with the suspect of LVV that were studied with a ^{18}F-FDG PET/MR scan, along with a comparator group consisting of patients with non-metastatic malignancies. For each PET scan, a qualitative analysis and a semi-quantitative measure using the maximum of the standardized uptake value (SUV_{max}) were performed. SUV_{max} measurements normalized to the liver uptake were categorized using the Meller's grading scale. Vessel's wall thickness (WT) was measured at five fixed points. A comparison of characteristics of FDG-PET and vessel's wall thickening in patients with clinically active LVV versus clinical remission was conducted.

The second one, the follow-up study, was conducted on consecutive patients classified as GCA with LVV involvement (LV-GCA), with a minimum disease duration of 12 months and clinically remitted, who underwent to at least one PET/MR scan between January 2015 and January 2020. For each scan a qualitative summary score (PETVAS) based on global arterial FDG uptake was assessed, along with the Meller's grading scale. Frequency and characteristics

of LV-GCA patients with low-grade inflammation were studied. Predictive value of PET scan was finally evaluated.

Results: A total of 55 PET/MR scans were conducted, of which 32 performed in 23 LVV patients (from a minimum of 1 to a maximum of 3 examinations/patient) and 23 in controls. All LVV patients were Caucasian, 82% were female, median age at PET examination was 63 [53-65] years and median BMI was 26.2 [21.8-27.3]. We found higher SUV_{max} compared to controls, in all examined sites, irrespective of clinical disease activity. As expected, when considering only the LVV group, the SUV_{max} of patients with a qualitatively active disease was significantly higher when compared to qualitatively inactive disease, in all aortic levels considered, except for the max wall thickness (WT) level. In patients with a clinically active disease, the SUV_{max} was still higher than in patients with a clinical inactive disease for every anatomical level considered, however without reaching a significant value. Mean WT resulted higher in patients than in controls. Unlike metabolic activity, the mean WT did not significantly differ between clinically active or inactive patients in all aortic levels considered. Mean WT positively correlated with age in both cohorts, negatively correlated to disease duration, while no correlation with SUV_{max} was observed.

For the follow-up study, 88 PET scans were performed in 54 LVV-GCA patients, predominantly female (77.8%), aged 68[7,8] years, with a regular BMI (23.9[2.8]) and with a long-standing disease (27[32.6] months). A subsequent PET/MR scan was available in 34 patients (median time between the two scans 9[6.3] months). At first PET examination, low-grade metabolic activity was reported in 68.5% of the cases. LV-GCA patients that showed absence of inflammation had longer disease duration ($p=0.034$), lower CRP levels ($p=0.056$) and lower daily prednisone dosage ($p=0.029$). Change of treatment was more frequent in the high activity group ($p<0.001$), while worsening of subsequent PET (or PETVAS score) was more frequent in the low activity group ($p=0.003$). In the low grade inflammation group,

treatment tapering was significantly associated with subsequent PET worsening (OR 12 [1.2-154], p=0.040). In a multivariable model, change of treatment was independently associated with reduced odds of worsening of the subsequent PET scan (OR 0.26 [0.00-0-95], p=0.047).

Conclusions: ^{18}F-PET/MR appears to be able to determine the presence of large vessels inflammation, similar to PET/CT (but with low radiological exposure). Vascular wall thickness progressively increases with age, significantly higher in patients than controls, but in subjects with long-standing disease it could represent a damage rather than disease activity. Low-grade metabolic activity is a common feature in remitted in LV-GCA patients with a long-standing disease, being present in almost 70% of the cases. In such patients, treatment tapering is significantly associated with subsequent PET worsening. This study provides novel, prospective evidence about the potential value of FDG-PET scans in patients with LVV who are assessed months to years into the course of disease. FDG-PET performed in patients with LVV during established clinical remission can identify subsets of patients at risk for future clinical relapse.

Introduction

Large vessels vasculitis (LVV) are characterized by the inflammation of large and medium-size arteries and occur in two main separate conditions: giant cells arteritis (GCA) and Takayasu's arteritis (TAK). GCA was traditionally thought to be confined to the cranial arteries; however, many patients with GCA also have evidence of large-vessel involvement [1,2]. Patients with large-vessel involvement often present with different clinical features than patients with cranial GCA, but the extent to which patients have overlapping versus distinct cranial and extra-cranial disease is not well characterized [3–5]. A substantial percentage of patients with GCA, with and without a positive temporal artery biopsy, have large-vessel involvement with estimates ranging from 20-80% detected by conventional imaging [1,2,6].

The diagnosis of LVV could be particularly complicated when systemic constitutional signs or unexplained inflammatory syndromes are the only clinical manifestations. Imaging role has tremendously increased during the last decade because of technique improvement. Ultrasonography has been demonstrated to be useful for GCA diagnosis [7,8], but it cannot provide information about the thoracic aorta. Both computer tomography (CT) and computer tomography angiography (CTA) are useful in measuring aortic diameter, detecting mural calcification, wall thickening, contrast enhancement and late complications (aneurysms and stenosis) [9]. However, ionizing radiations can arise concern when repetitive explorations are necessary. Magnetic resonance (MR) and magnetic resonance angiography have remarkable spatial resolution and are able to depict wall abnormalities before luminal changes occur [10,11]. It is still debated if vessels' wall thickness correlate or not with therapy response in both GCA and TAK [12,13]. Positron emission tomography (PET) is a non-invasive imaging method that detects ^{18}F-fluorodeoxyglucose (FDG) uptake in vessel walls. It has become a tool for the diagnosis and disease activity assessment in LVV with a variable reported sensitivity and specificity of approximately 70% and 77% in TAK [14] and 80% and 89% in GCA [15].

However, vascular uptake on PET could be not specific for vasculitis and discriminating atherosclerotic alterations may be challenging. Another limitation is the lack of a standardized definition of vascular inflammation based on the intensity of ^{18}F-FDG uptake and the absence of a standard methodological assessment [16]. Its combination with CT improves anatomic localization and detects vessels wall changes [6,17–20]. Therefore, the combination of ^{18}F-FDG PET and MR would theoretically offer not only a more detailed morphological analysis of the vessels but also a reduction of the radiation exposition compared to PET/CT. Indeed, according to Melsaether et al, the reduction in the dose administered by a PET/MR as compared to PET/CT ranges from 18.9% to 64.3% (mean dose reduction from 7.40 to 9.16 mSv) [21].

Up to now, only one preliminary report has been performed with the combined use of PET and MR in LVV patients [22].

Recent EULAR recommendations for imaging modalities in LVV included FDG-PET to diagnose LVV [23]. However, beside its diagnostic role, PET might also be of value to refine prognosis; however, data on this hypothesis are still scant. The identification of potential predictors of relapse, in the context of LVV, would be clinically useful, considering that there are no accepted predictive models. Some risk factors of relapse have been proposed: high glucocorticoid requirements, fever at onset and severity of vessel inflammatory infiltrate at temporal artery biopsy [24]; male gender and body mass index (BMI) [25,26]; short duration of glucocorticoid administration [27]; large vessel involvement [28].

Low-grade vascular inflammation at PET examination is a common feature in remitted LVV patients [6], irrespective of clinical manifestation, highlighting potential discordance between clinical and imaging assessments at later stages of disease. Persistent low-grade vascular inflammation in remitted patients, could represent the expression of persistent subclinical disease activity or post-inflammatory vascular remodeling.

Objectives

The aim of the whole PhD project was to evaluate the feasibility of a novel imaging technique, namely hybrid ^{18}F-FDG PET/MR, in patients with LVV and to better characterize its role in monitor disease activity over time, and predict clinical outcomes.

Specific aims were:

- To evaluate the usefulness of ^{18}F-FDG PET/MR in a series of LVV patients in the clinical setting (**Paper I**)
- To define the relationship between the metabolic activity and vessel's wall thickening (**Paper I**)
- To evaluate the frequency of low-grade vascular inflammation at PET/MR examination in clinical remitted GCA patients (**Paper II**)
- To determine how such low disease activity may predict subsequent clinical or imaging worsening in GCA patients (**Paper II**)

Methods

FEASIBILITY STUDY (Paper I)

Patient population

For the feasibility study, we assessed consecutive inpatients and outpatients affected with or with the suspect of LVV, satisfying the American College of Rheumatology (ACR) criteria [29,30], who were referred to our Rheumatology Unit, a tertiary vasculitis referral centre, between 2015 and 2018. Both patients with the suspicion of active LVV (new onset or relapse) and patients in remission routinely followed by our center were included in the study.

An age-, sex- and race-matched control group, affected by different non-metastatic malignancies at diagnosis and never treated (mouth, gastrointestinal or skin) was selected and scored for vascular uptake and wall thickness to obtain reference values.

Patients were excluded in case of pregnancy, presence of pacemakers or other non-MR compatible medical devices, metallic implants and severe claustrophobia.

All data were entered into a computerized data bank. The study was carried out in accordance with the principles of the Declaration of Helsinki. All potential participants were informed about the procedure and were asked to sign an informed consent form.

Patient assessment

Each patient was clinically evaluated prior to every PET examination, as regular clinical practice. Basic demographic information, acute phase reactants, clinical manifestations, treatments and sequelae were assessed.

Symptoms suspicious for active LVV were fatigue, unexplained fever or otherwise unexplained weight loss in combination with myalgia, polymyalgia rheumatica, carotidynia, headache, jaw claudication, sight loss, temporal artery abnormalities, pulse deficit or vascular bruits. Additionally, elevation of the acute phase reactants, including C-reactive protein (CRP), unrelated to other conditions was also regarded suspicious for active vasculitis.

Relapses were defined as the recurrence, worsening, or newly developed clinical and laboratory findings of vasculitis, leading to one of the following: an increase in the glucocorticoid dose to more than 5 mg per day of prednisolone (or equivalent), an initiation of or increase in immunosuppressive therapy, or hospitalization [31].

PET/MR imaging

Images were acquired with an integrated PET/MR scanner (Siemens Biograph mMR), which allows simultaneous acquisition of PET and MR data (An example of PET/MR in a LVV patient is shown in **Figure 1**).

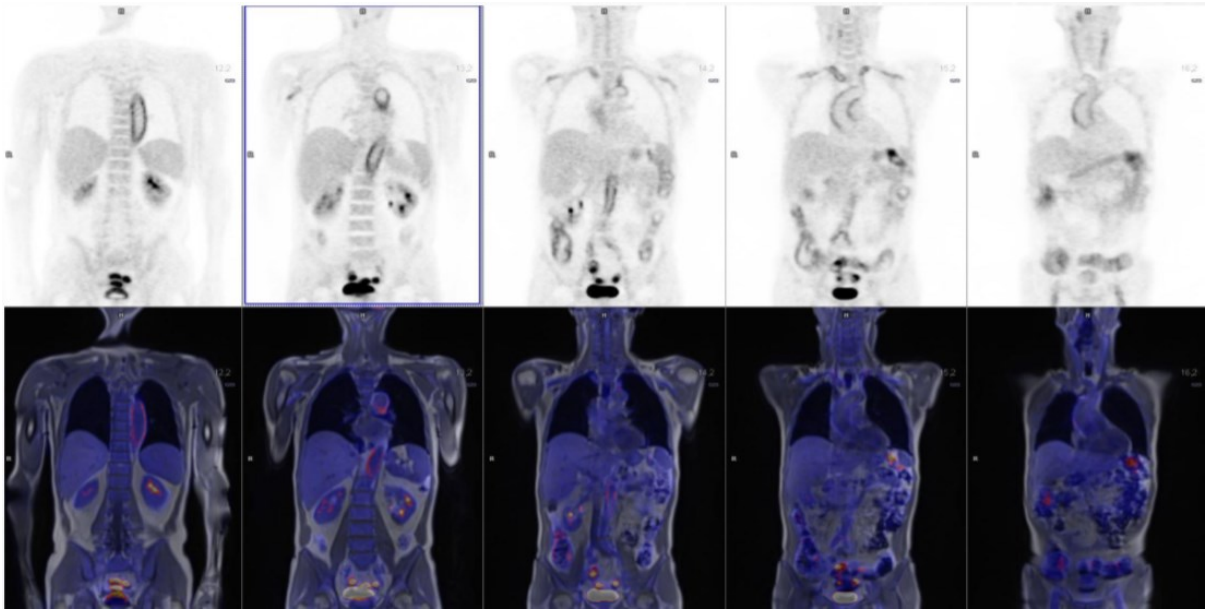

Figure 1. *^{18}F-FDG PET/MR (Siemens Biograph mMR) of a qualitatively positive LVV patient showing (upper row) high uptake at the thoracic and abdominal walls of the aorta. Lower row shows fused PET an MR data.*

All sequences were acquired in axial plane and no contrast agents were used during MR examination. The MR images were acquired including DIXON sequence for the correction of attenuation and anatomical localization, T1 TURBO SPIN ECHO sequences (coronal breath-holding), T1 VIBE FAT SAT sequences (transaxial breath-holding) and T2 TURBO SPIN ECHO (transaxial free breathing), as described in **Table 1**.

The correction for the attenuation of the PET images was obtained by interpolating the data acquired with the DIXON sequence, allowing the images to be segmented into four different tissue components (water, fat, air and lung tissue). The four measurements were used to generate a densitometric map (μ-map), which is needed to make the correction for attenuation of the raw PET data.

Table 1. Protocol for MR imaging acquisition.

Sequences	*TR*	*TE*	*Thickness*	*Time acquisition*
T1w - SE	463 ms	8.6 ms	5 mm	
T2w - TSE fat sat	4000 ms	82 ms	4 mm	
VIBE	4.3 ms	1.91 ms	3 mm	
PET				5 min (bed)

PET = Positron emission tomography; MR = magnetic resonance; TR = repetition time; TE = echo time; T1w = T1 weighted; SE = spin echo; T2w = T2 weighted TSE = turbo-spin echo; VIBE = volume interpolated breath-old examination.

For PET imaging, patients were kept fast for at least 6 hours before intravenous injection of 3 MBq/kg of ^{18}F-FDG (maximum blood-glucose levels 180 mg/dl); the scanning was initiated from 60 to 90 minutes after tracer injection, images were acquired from vertex to thighs.

Images were analyzed and post-processed on a dedicated workstation, using the SyngoVia software (Siemens Healthineers).

Two experienced readers (P.Z., C.L.) evaluated patient's images, in consensus, blinded to clinical situation.

For each PET scan, a qualitative analysis was performed to diagnose or rule out the presence of vasculitis, based on the presence or absence of metabolic activity in the vessels' wall. A smooth linear or long segmental pattern of ^{18}F-FDG uptake in the aorta and its main branches, with an intensity higher than the liver uptake, was regarded as findings highly suggestive for LVV.

The images obtained were initially evaluated qualitatively, comparing the uptake of the vessels' walls with the surrounding tissues and the hepatic parenchyma, applying the four-point scale

proposed by Meller [20] and validated by Walter [18] (*Grade 0*: absence of significant uptake, *grade 1*: slight uptake definitely lower than the liver, *grade 2*: moderate uptake equal to the liver parenchyma, *grade 3*: high grade pathological uptake superior to the liver).

A semi-quantitative assessment using the maximum (SUV_{max}) and the mean (SUV_{Mean}) value of the standardized uptake was obtained with a circular ROI, manually drawn in the area with an increased metabolic activity. Subsequently, liver SUV_{max} and SUV_{mean} were evaluated with a circular ROI (fixed 5 cm diameter) drawn in the right lobe avoiding the biliary tree. A vessel-to-liver ratio was then calculated, as proposed by Hautzel et al [19].

For each scan, we also evaluated the abdominal aorta wall thickness (WT, in mm) through MR imaging. Ascending aorta, aortic arch and its main branches were excluded because of cardiac pulsation artefacts and because of acquisition planes not perpendicular to vessels' lumen. The WT values were recorded at four different fixed vascular levels (at the inferior margin of T5, T9, T12 thoracic vertebrae and L3 lumbar vertebra) and at the thickest vessel wall (max WT) level. Four standard positions of measurement with calipers were set for each slice, perpendicularly to aorta lumen: 12, 3, 6 and 9 o'clock, and the mean value of the measurements for each slide was calculated, as shown in **Figure 2**.

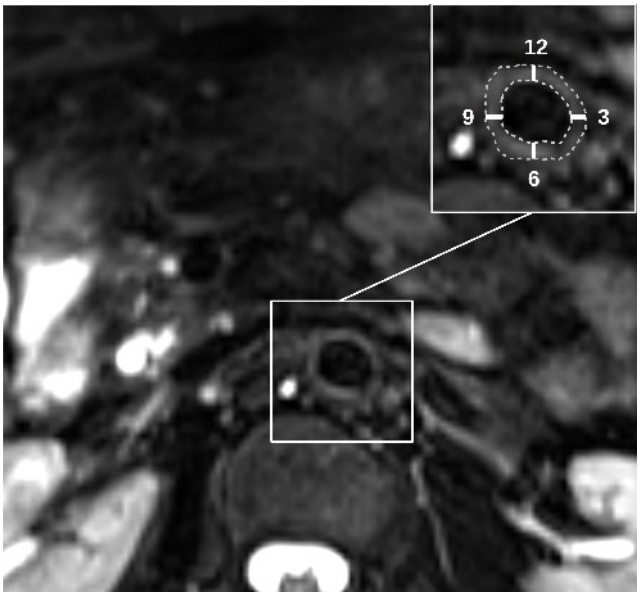

Figure 2. *The four standard positions of vessel's wall thickness measurement for each slice. The mean value of the measurements at 12, 3, 6 and 9 o'clock for each slide was calculated*.

Mean aorta WT measurements were considered as normal with a WT < 3 mm, according to previously reported data [32,33].

The SUV_{max}, SUV_{mean} and the corresponding SUV normalized to liver were evaluated at the same four levels (T5, T9, T12, L3) and at the level of max WT.

FOLLOW-UP STUDY (Paper II)

Patient population

For the follow-up study, we included all consecutive patients classified as GCA [29] with LVV involvement (LV-GCA), recruited from an ongoing prospective, observational cohort. All the patients were referred to our Rheumatology Unit or to the Unit of Immunology, Rheumatology, Allergy and Rare Diseases of the IRCCS San Raffaele Hospital.

We included all the LV-GCA patients with a minimum disease duration of 12 months and clinically remitted, who underwent to at least one PET/MR scan between January 2015 and January 2020.

If available, a subsequent visit and PET/MR scan at scheduled 6-month intervals (minimum of 4 months and maximum of 12 months) has also been considered and assessed.

All patients provided written informed consent, and the study was carried out in accordance with the principles of the Declaration of Helsinki.

Patient assessment

At each visit, patients underwent a detailed clinical evaluation, imaging assessment, and laboratory investigations. Clinically active disease was defined by the presence of at least one clinical symptom directly attributed to ongoing vasculitis and increase in acute phase reactants. Chronic fatigue or elevated acute phase reactants in the absence of clinical symptoms were not considered evidence of active disease. Remission was defined as the absence of any clinical symptoms directly attributable to vasculitis. A disease relapse was defined as a recurrence of clinical disease activity after a period of remission necessitating an increase in prednisone dose of ≥ 10mg per day and/or addition of a glucocorticoid-sparing therapy.

Clinical assessments and treatment decisions were made blinded to imaging data.

Treatment status between visits was categorized as increased/changed or tapered/withdrawn. Treatment change was defined as change in daily prednisone dose by ≥5 mg at the time of the follow-up visit relative to the baseline visit or an addition/50% dose change of a DMARD or biologic therapy at least 3 months prior to the follow-up visit.

PET/RM imaging assessment

Images were acquired with an integrated PET/MR scanner (Siemens Biograph mMR), available in both centres (University of Padova and IRCCS San Raffaele Hospital). Briefly, all patients underwent a whole body scan, acquired 60 to 90 minutes after injection of 3 MBq/kg of ^{18}F-FDG, with the same parameters than those used in **Paper I**. Degree of arterial FDG uptake was assessed relative to the liver in 9 arterial territories (ascending aorta, aortic arch, descending thoracic aorta, abdominal aorta, right carotid artery, left carotid artery, innominate

artery, right subclavian artery and left subclavian artery). Each area was scored from 0 to 3, according to Meller et al [20] (0 = no FDG uptake; 1 = FDG uptake less than liver; 2 = FDG uptake equal to liver; 3 = FDG uptake more than liver). Low-grade inflammation was defined as Meller 1 and 2 (inferior or equal to liver).

A global summary score (Positron Emission Tomography Vascular Activity Score, PETVAS, **Table 2**) was calculated by summing the amount of arterial FDG uptake in the 9 territories, with scores ranging from 0-27, as previously reported [34]. Changes in PETVAS were assessed over visit intervals.

Table 2. Calculation of the PET Vascular Activity Score (PETVAS) of Arterial FDG Uptake, as proposed by Grayson et al [34]. PETVAS range = 0 to 27.

Arterial territory	Qualitative score
Ascending aorta	0,1,2,3
Aortic arch	0,1,2,3
Descending thoracic aorta	0,1,2,3
Abdominal aorta	0,1,2,3
Right carotid artery	0,1,2,3
Left carotid artery	0,1,2,3
Innominate artery	0,1,2,3
Right subclavian artery	0,1,2,3
Left subclavian artery	0,1,2,3

Statistical analysis

An overview of analyses presented in this study is as follows: 1) calculation of performance characteristics of FDG-PET/MR in patients with LVV versus comparators; 2) comparison of characteristics of FDG-PET and vessel's wall thickening in patients with clinically active LVV versus clinical remission; 3) assessment of frequency of low-metabolic activity in remitted LV-GCA patients; 4) determination of clinical variables associated with PET low-metabolic activity; 5) assessment of impact on disease activity of changes in treatment in LV-GCA patients; 6) analysis to determine if PET scans performed during clinical remission predict subsequent PET worsening or clinical relapses.

Data are expressed as median and interquartile ranges for continuous variables while categorical data are expressed as numbers and percentages. Shapiro-Wilk test was performed to test normality. Mann-Whitney U-test was used to compare the differences between non-parametric variables and Kruskal-Wallis test was used when more than two groups were considered. A post-hoc analysis with Bonferroni's test was performed in presence of significant results. Chi-squared test or Fisher's exact test were used to compare differences in proportions, as appropriate. Spearman's correlation was used to evaluate strength and direction of correlation between two ranked nonparametric variables.

Logistic regression analysis was performed to study the associations between nuclear medicine interpretation of active vasculitis on the PET scan (outcome measure) and the following predictor variables: low-metabolic activity, disease duration since the diagnosis, PETVAS score, diagnostic latency intended as time between initial symptom onset and diagnosis, body mass index, age at diagnosis, sex, current use of glucocorticoid-sparing therapy, daily prednisone dose, change of treatment since the first PET, sex, erythrocyte sedimentation rate, and C-reactive protein. Only variables with $p<0.2$ in univariable analyses were included in the multivariable model.

A two-tailed p-value ≤ 0.05 was considered statistically significant.

Data were analysed using SPSS software version 20.0 (SPSS, Chicago IL, USA).

Results

In the following sections results of the different papers are summarized, representing a progressive step-forward process.

Paper I

Demographic and clinical features of LVV patients

A total of 64 PET/MR scans have been retrieved; 9 were not suitable for MR vessel wall analysis, due to respiratory movement artefacts or poor examination quality, and thus excluded. We therefore considered 32 scans, performed in 23 LVV patients (from a minimum of 1 to a maximum of 3 examinations/patient) and 23 PET/MR in controls (**Figure 3**).

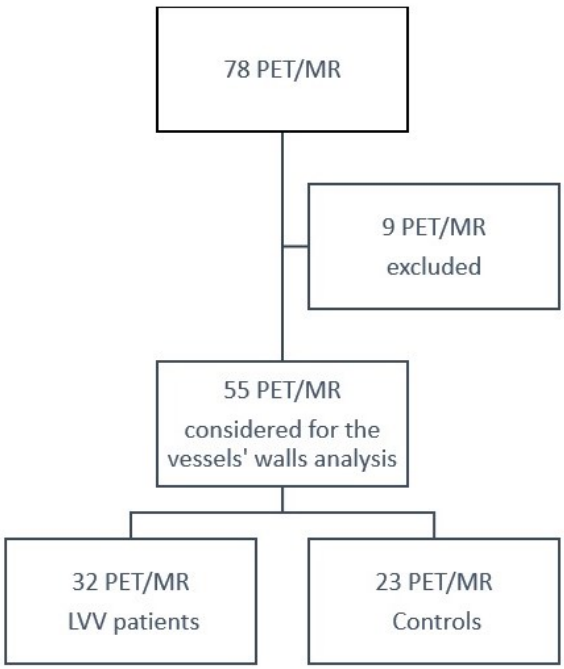

Figure 3. *Flow-chart of patients and PET/MR selection process*.

The control group was composed by age-, sex-, race- and BMI-matched patients, affected by mixed non-metastatic malignancies (mouth, gastrointestinal or skin).

All scans were well tolerated and conducted without adverse reactions.

All LVV patients were Caucasian (100%), mostly females (82%) M/F ratio of 4:19, with median age at PET examination of 63 [53-65] years and a median BMI of 26.2 [21.8-27.3]. Patients in the control group were Caucasian (100%), predominantly female (78%) M/F ratio of 5:18, with median age at PET examination of 61 [50-67] years and a median BMI of 23.8 [21.8-27.6]. There were no significant differences in the demographic variables between the two groups.

Among LVV patients, 56.5% were classified as GCA, 34.8% as TAK and 8.7% as isolated aortitis. No significant differences were observed between LVV patients, with the exception of age at diagnosis that resulted significantly lower in TAK patients (43.5 vs 68 years, p=0.003). Furthermore, no statistically significant differences were observed between GCA and TAK patients at the time of PET/MR examinations, both in terms of diagnostic latency and acute phase reactants. Particularly, in the whole group of LVV patients, the median erythrocyte sedimentation rate (ESR) value at PET examination was 49 [38-68] mm/h, while CRP was 4.5 [2.6-8.9] mg/L. Median disease duration at examination was 27 months, without any significant difference between GCA and TAK patients.

Analysis of metabolic activity

Comparing LVV patients to controls, no significant differences were observed between the liver SUV_{mean} (median 1.8 and 1.9 respectively) and the liver SUV_{max} (2.7 and 2.8 respectively).

In LVV patients, the median SUV_{max} at the site of highest vessel metabolic activity was 3.0 [2.5-4.8]. There were no significant differences in FDG uptake between patients with fasting glucose levels < 110 mg/dL and those with 110-180 mg/dL, in all selected sections.

When comparing patients to controls, the SUV_{max} evaluated at the pre-defined levels (T5, T9, T12, L3 and max WT) resulted higher in LVV patients as compared to controls, as reported in **Figure 4A**.

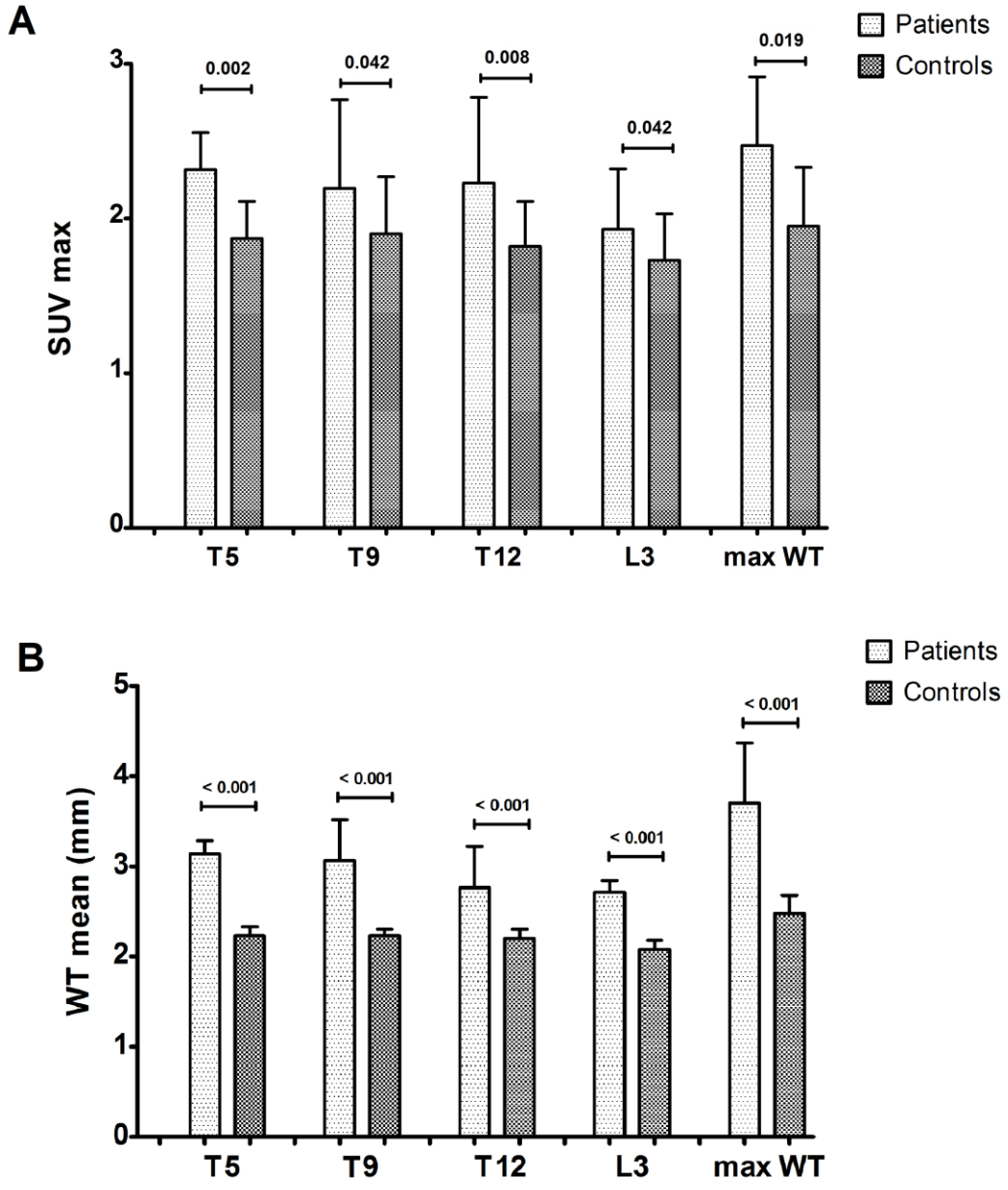

Figure 4. ***A)*** *Comparison of* SUV_{max} *between LVV patients and controls;* ***B)*** *comparison of WT mean (in mm) between LVV patients and controls*.

When considering only the LVV group, as expected the SUV_{max} of PET in patients with a qualitatively active disease was significantly higher when compared to qualitatively inactive

disease (**Figure 5A**) in all aortic levels considered, except for the max WT level. While, in patients with a clinically active disease, the SUV_{max} was still higher than in patients with a clinical remitted disease for every anatomical level considered, however without reaching a significant value, as shown in **Figure 5B.**

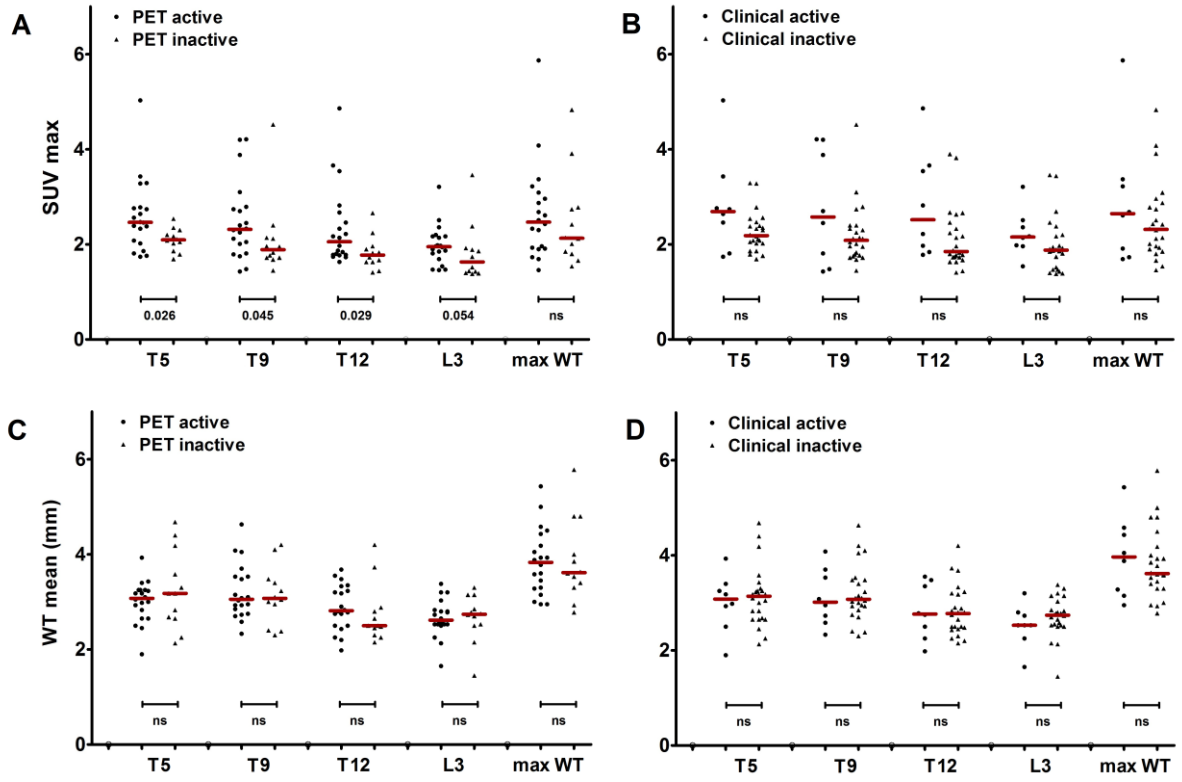

Figure 5. ***A)*** *Comparison of* SUV_{max} *between qualitatively positive (PET active) and negative (PET inactive) patients;* ***B)*** *comparison of* SUV_{max} *between clinically active and remitted patients;* ***C)*** *comparison of WT mean (in mm) between qualitatively positive (PET active) and negative (PET inactive) patients;* ***D)*** *comparison of WT mean (in mm) between clinically active and remitted patient.*

Analysis of wall thickening

The median WT resulted always significantly higher in LVV patients in every examined slice, when compared to controls irrespective of clinical active or inactive disease. The median value

ranged from 2.7 to 3.7 mm in LVV patients, while from 2.1 to 2.5 mm in the controls ($p < 0.001$), **Figure 4B**.

Unlike metabolic activity (intended as SUV_{max}), the WT values resulted not significantly different between clinically active or inactive patients in all aortic levels considered, as shown in **Figure 5C**. Similarly, WT values did not significantly differed between patients with a qualitatively positive PET or qualitatively negative PET (**Figure 5D**).

Median WT values in patient's cohort resulted positively correlated with age at PET examination, in all the considered levels (**Figure 6**). The same results were observed in the control group.

Conversely, in LVV patients, WT values resulted inversely correlated with disease duration at PET examination (**Figure 7**).

Finally, we did not observe a significant correlation between SUV_{max} and WT values in all examined levels, regardless of clinical disease activity, in both patients and controls.

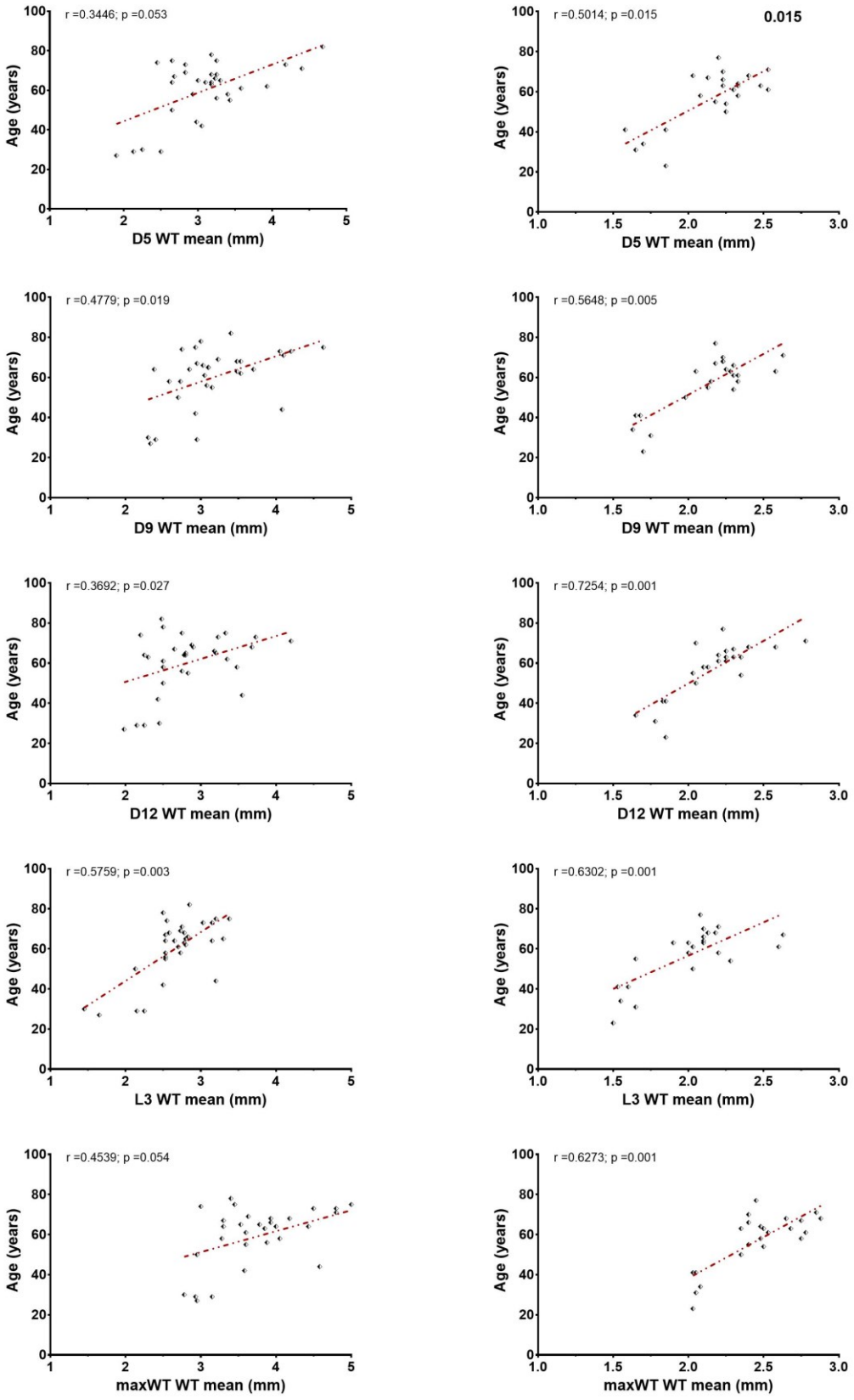

Figure 6. *Correlations between age at PET examination and vessel's wall thickness (WT), for every section considered, in LVV patients (left) and controls (right).*

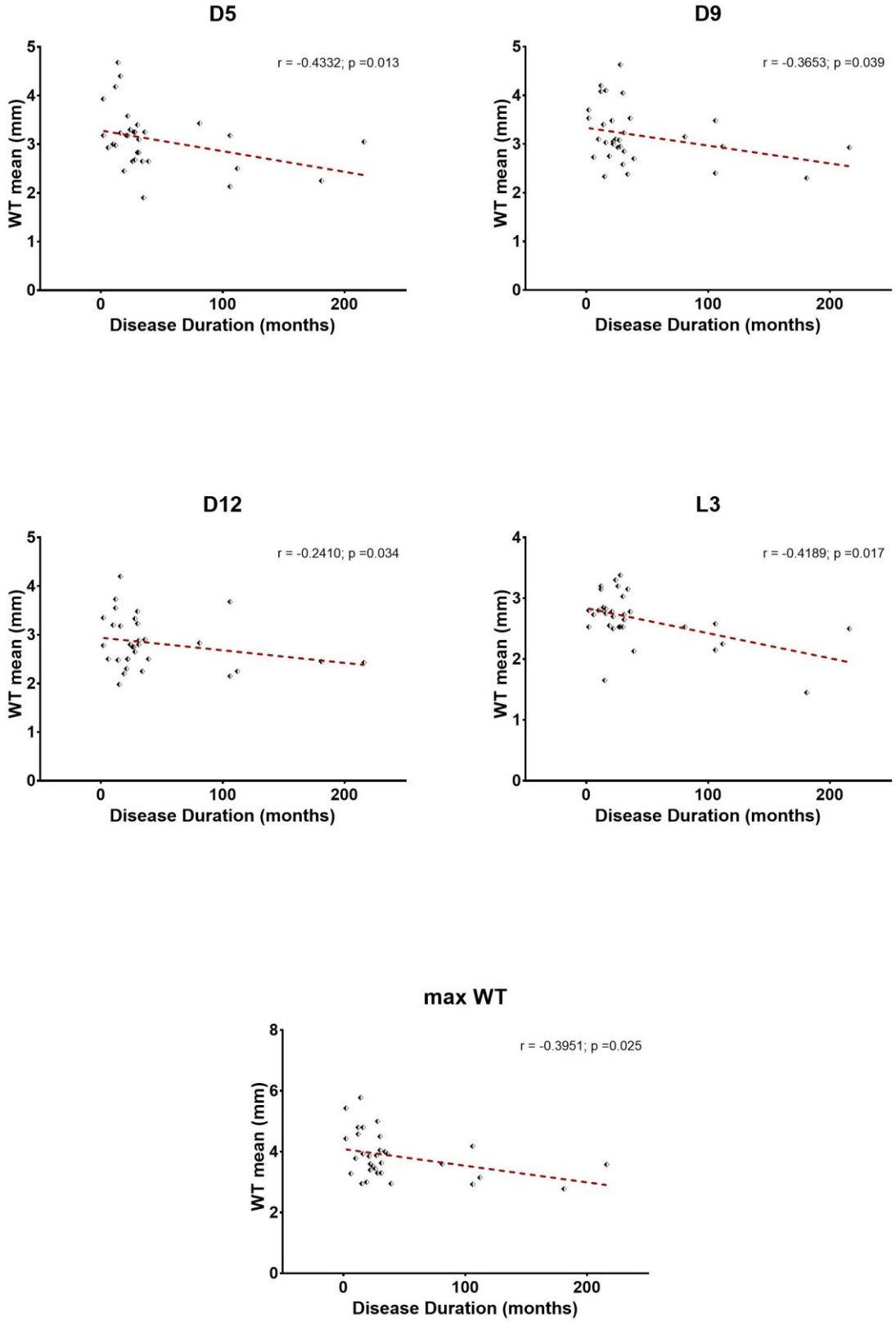

Figure 7. *Correlations between disease duration (months) at PET examination and vessel's wall thickness (WT), for every section considered*.

Association between FDG-PET activity and clinical remission

Twelve (50%) of our clinically remitted LVV patients had a positive qualitative and semi-quantitative PET/MR. On the contrary, all patient with active disease at clinical examination (n=8) had also a highly pathologic PET/MR (Meller 3).

When comparing clinically remitted LVV patients with a positive PET to those with a completely negative PET, they resulted significantly older (64[12] vs 57[33] years, p=0.005) and with a lower disease duration (26.5[21.4] vs 52.5[34.8] months, p=0.001).

We did not find any significant correlation between SUV_{max} and acute phase reactants (both CRP and ESR).

Paper II

In this paper we started from the results of **Paper I**, where we described a discrepancy between the vessel's wall inflammation detected by FDG-PET/MR and clinical symptoms, as well as wall thickening. A proportion of clinical inactive patients still have a certain degree of metabolic activity over time. Moreover, we analyzed a small group of GCA patients prospectively followed over time, from diagnosis up to 5 years, and routinely assessed with PET/MR every 12 months. We noted a significant ($p<0.001$) decrease in whole body metabolic activity, measured with the PETVAS score [34], only from the baseline to the first year, thereafter no significant variations were registered (**Figure 8**).

Therefore, we decided to investigate and better characterize this persistent low-grade inflammation in remitted GCA patients and whether it may have a prognostic role for subsequent relapses.

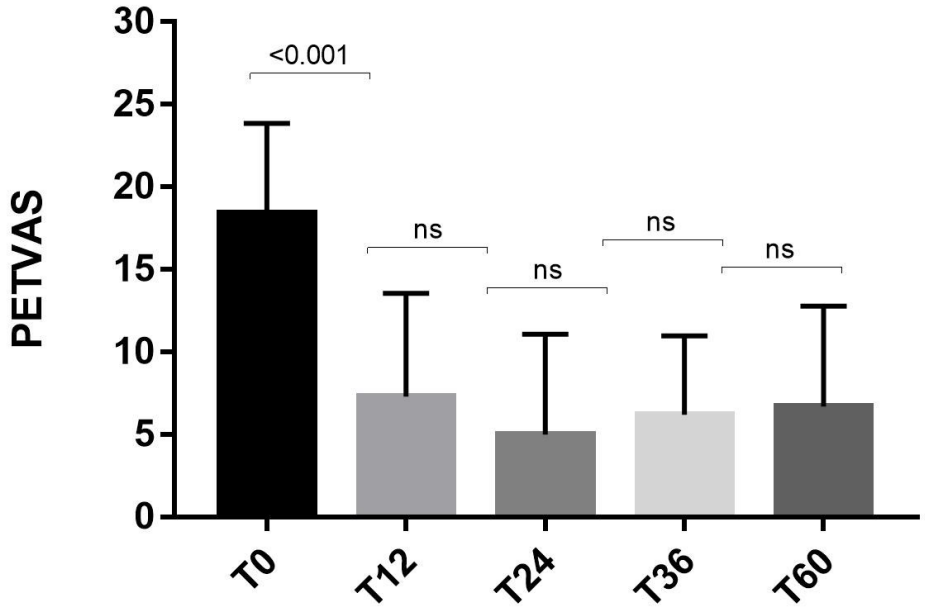

Figure 8. *Modification of the PETVAS over time in a small (n=14) group of GCA patients, prospectively followed for 60 months. A significant reduction in PETVAS score was observed only from baseline to 12 months. Thereafter no significant differences were noted, with PETVAS remaining almost unchanged over time.*

Study population

From January 2015 to January 2020, a total of 54 LV-GCA patients were recruited, 48 followed-up at Padova University, while 6 at IRCCS San Raffaele Hospital. A total of 88 PET/MR scans were performed. A subsequent visit and PET/MR scan were available in 34 patients (median time between the two scans 9 [6.3] months).

LV-GCA patients were predominantly female (77.8%), aged 68 [7.8] years, with a regular BMI (23.9 [2.8]) and with a long-standing disease (27 [32.6] months). At recruitment, 88.9% of the patients were currently receiving a treatment for the vasculitis: 47.9% were treated only with low-dose glucocorticoids (4.9±5.3 mg/day of prednisone), while 52.1% with a combination of

glucocorticoids and immunosuppressive agents (12% Azathioprine, 52% Methotrexate, 36% Tocilizumab).

Qualitative assessment of PET/MR in remitted LV-GCA patients

At first PET examination, low-grade metabolic activity (Meller 1 or 2) was reported in 68.5% of the cases, while complete remission in 15% and high metabolic activity in 25%. Comparing patients with absence of inflammation, to those with low-grade vascular inflammation and to those with high metabolic activity, we found that LV-GCA patients that showed absence of inflammation had longer disease duration (p=0.034), lower CRP levels (p=0.056) and lower daily prednisone dosage (p=0.029). While no significant differences were noted in age, sex, BMI, and type of immunosuppressive agents. Clinical features of the three groups are listed in **Table 3**.

Total PETVAS score resulted, as expected, significantly lower in patients with absence of inflammation, compared to those with low-grade inflammation and those with high-grade inflammation (**Figure 9**).

Table 3. Clinical features of the LV-GCA cohort, according to the grade of PET inflammation, as proposed by Meller et al [20].

	Absence of activity (n=5)	**Low metabolic activity (n=37)**	**High metabolic activity (n=12)**	***p* value**
Sex (female)	3 (60)	31 (83.8)	8 (66.7)	0.351
BMI (kg/m^2)	26.1±1.5	24.6±3.0	22.4±1.2	0.439
Age at diagnosis (y)	60±13	66±8	66±7	0.492
Diagnostic latency (m)	3.2±2.9	4.7±8.8	5.3±9.9	0.776
Age at PET examination (y)	65±9	68±8	68.7	0.885
Disease duration at PET examination (m)	75±69	33±26	29±20	**0.034**
ESR (mm/h)	12±7	19±12	23.5±12.7	0.365
CRP (mg/dL)	3.5±2.3	5.2±3.9	9.2±7.3	**0.056**
Ongoing treatment	3 (60)	33 (89.2)	12 (100)	0.125
Prednisone (mg/d)	1±2.2	4.6±3.7	8.9±8.8	**0.029**
Immunosuppressant	3 (60)	17 (45.9)	5 (41.7)	0.870
PETVAS	0±0	4.9±3.4	14.0±5.9	**<0.001**

BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PET: Positron emission tomography; PETVAS: Positron Emission Tomography Vascular Activity Score.

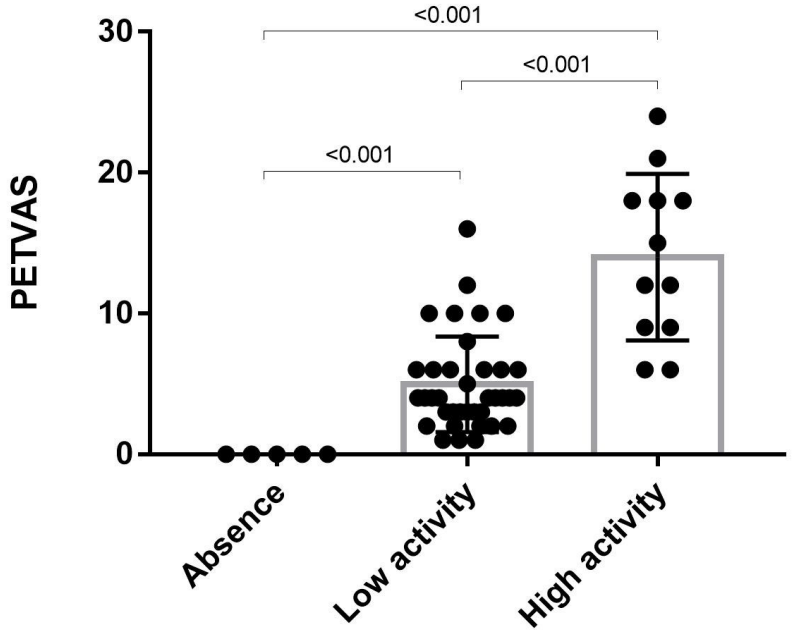

Figure 9. *PETVAS score of the LV-GCA patients (n=54) included, according to the grade of metabolic activity.*

Effect of treatment on imaging and clinical assessment

Simultaneous increase in glucocorticoids and other immunosuppressive drugs occurred during 17 of 54 (31.5%) visit intervals. Over 3 visit intervals, there was increase in glucocorticoids only, whereas over 14 visit intervals, there was increase in dosage/addition of DMARD and/or biologic agent. Change of treatment (blinded from PET results) was significantly more frequent in the high activity group ($p<0.001$).

Decreased treatment was noted over 37 (68.5%) visit intervals.

At the subsequent PET examination, a worsening of metabolic activity (increase in Meller grading) and PETVAS score was observed more frequently in those patients with low-grade inflammation ($p=0.003$). Although not statistically significant, only 4 clinical flare were registered, but all of them in the group of patients with low-grade inflammation.

Effect of treatment on imaging and clinical outcome is reported in **Table 4**.

Table 4. Effect of treatment on imaging and clinical outcome, according to the grade of vessel's inflammation.

	Absence of activity (n=5)	Low metabolic activity (n=37)	High metabolic activity (n=12)	*p* value
Change of treatment	0 (0)	7 (18.9)	10 (83.3)	**<0.001**
Worsening of subsequent PET	2 (100) *data on 2 pts	16 (66.7) *data on 24 pts	0 (0) *data on 8 pts	**0.003**
Worsening of subsequent PETVAS	2 (100) *data on 2 pts	16 (66.7) *data on 24 pts	0 (0) *data on 8 pts	**0.003**
Subsequent clinical flare	0 (0) *data on 2 pts	4 (16.7) *data on 24 pts	0 (0) *data on 8 pts	0.453

PET: Positron emission tomography; PETVAS: Positron Emission Tomography Vascular Activity Score.

In the low-grade inflammation group, treatment tapering was significantly associated with subsequent PET worsening, with an Odds Ratio of 12 [1.2-154] (p=0.040), **figure 10**.

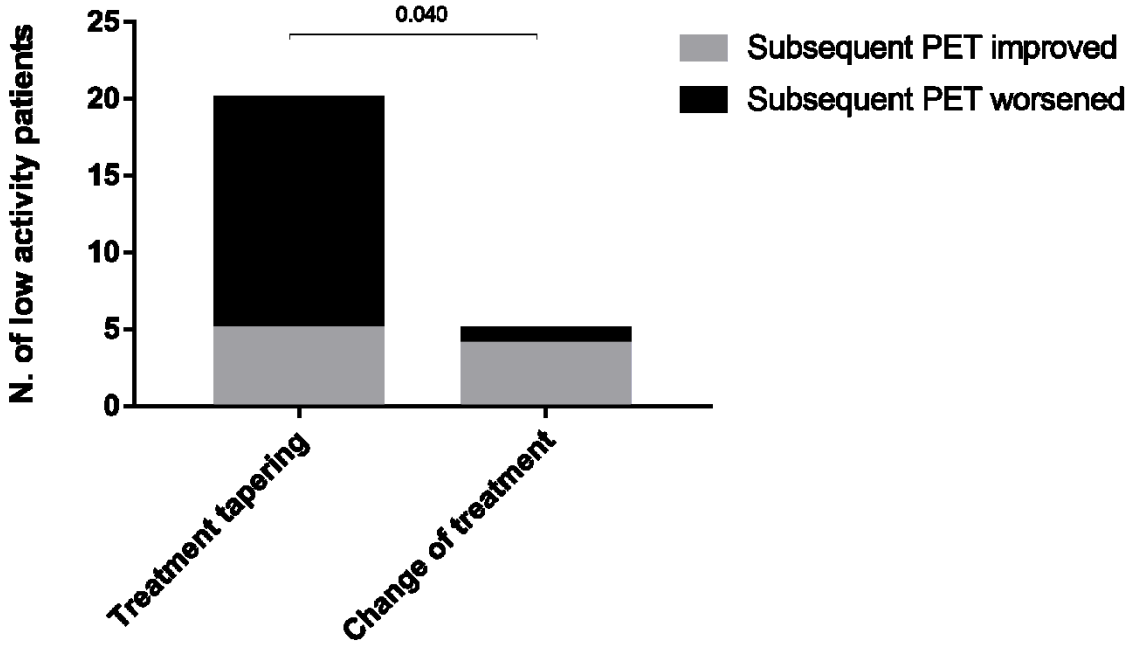

Figure 10. *Imaging outcome at subsequent PET/MR evaluation, according to the change or tapering of current treatment, in the group of patients with low-grade inflammation*.

Predictive value of FDG-PET/MR

The value of PET scan findings to predict future clinical events was assessed. Due to limited events (n=4 clinical relapses), we focused on potential predictors of subsequent PET worsening, intended as increasing in PETVAS score.

At univariable analysis low metabolic activity (OR 8 [1.37-46.81], p=0.021) resulted significantly associated with increased odds of subsequent PET worsening, while change of treatment (OR 0.03 [0.00-0.26], p=0.002) and PETVAS score (OR 0.77 [0.62-0.96], p=0.021) resulted significantly associated with reduced odds of subsequent PET worsening.

In a multivariable model, only change of treatment was independently associated with decreased odds of subsequent PET worsening (OR 0.26 [0.00-0.95], p=0.047).

Results of univariable and multivariable analysis are reported in **Table 5**.

Table 5. Univariable and multivariable logistic regression for subsequent PET worsening.

	Univariable		Multivariable	
	OR (95%CI)	***p* value**	**OR (95%CI)**	***p* value**
Low metabolic activity	**8.00 (1.37-46.81)**	**0.021**	1.39 (0.10-18.76)	0.807
Change of treatment (yes vs no)	**0.03 (0.00-0.26)**	**0.002**	**0.26 (0.00-0.95)**	**0.047**
PETVAS	**0.77 (0.62-0.96)**	**0.021**	1.03 (0.74-1.44)	0.855
Sex (male vs female)	0.71 (0.10-4.93)	0.733	Non included in the multivariable analysis	
BMI (kg/m^2)	1.23 (0.90-1.67)	0.190		
Age at diagnosis (y)	0.99 (0.90-1.09)	0.833		
Diagnostic latency (m)	0.96 (0.89-1.04)	0.348		
Disease duration (m)	1.01 (0.99-1.04)	0.304		
Prednisone (mg/d)	0.89 (0.75-1.08)	0.248		
Immunosuppressant (yes vs no)	2.57 (0.64-10.34)	0.183		
ESR (mm/h)	0.95 (0.89-1.02)	0.132		
CRP (mg/dL)	0.92 (0.77-1.09)	0.338		

BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PETVAS: Positron Emission Tomography Vascular Activity Score

Discussion

Our study represents the first clinical application of PET/MR use in patients with LVV after the pilot study of Einspieler et al [22], but on a significantly larger patient population. The preliminary results confirm that PET/MR appears to be able to determine the presence of large vessels inflammation similarly to PET/CT. The qualitative assessment of the uptake, using the Meller grading [20], can be usefully integrated into the clinical practice, counting the affected segments and providing a measure of the extension of the inflammation. The low radiological exposure represents a valid alternative for disease monitoring, especially in young women. Vascular WT progressively increases with age both in patients and in controls, probably due to a progressive atherosclerotic process, as previously reported by Li et al [32]; it is significantly higher in patients than controls, but in subjects with long-standing disease it could most likely represent a previous damage, which led to fibrosis and vascular remodeling. Indeed, even considering the thickest area (max WT), in subjects with both clinically and metabolically active disease, no significant differences were noted when compared to clinically and metabolically inactive patients, suggesting that such a site is not the major point of disease activity. Accordingly, Scheel did not find any significant changes in MR imaging after steroid treatment in 8 patients with LVV in 2004 [35], and more recently Spira et al reported the absence of wall thickness decrease, evaluated with MR, in 3 of 12 LVV patients treated with biological therapy [36].

Both in patients and in controls, we did not find any correlation between SUV_{max} and mean WT, at all aortic levels considered. This is in accordance with the observations of Both et al who compared the efficacy of MR with PET in 25 patients with GCA in immunosuppressive therapy, concluding that MR did not allow a follow-up evaluation [37].

The majority of clinically active patients presented a positive PET and the SUV_{max} was associated with the clinical data as reported in several publications [38–40]. Less significant in

our study appears the correlation with acute phase reactants, according to previously reported data [6,17,37]. Indeed, the relationship between PET activity and serologic inflammatory markers remains unclear, as Treglia et al points out in a systematic review of the PET role in LVV patients in evaluating therapy response [41]. However, in our population the lack of correlation between SUV and acute phase reactants is probably due to a higher number of patients in whom the examination was performed during clinical remission.

The fact that some of our clinically inactive patients had a positive qualitative and semi-quantitative PET could be related to subclinical atherosclerosis or post-inflammatory vascular remodeling or persistent disease activity.

Arnaud et al demonstrated no correlations between clinical manifestations, serological biomarkers and PET metabolic activity in a study of 28 TAK patients [42]. Blockmans, in a prospective study on the role of FDG-PET in diagnosis and follow-up of GCA patients, observed a reduction of FDG uptake after 3 months of steroid therapy compared to the baseline, which remained stable even at 6 months, despite clinical remission [6].

As limitations, it has to be pointed out that due to the low number of patients, we were not able to compare GCA to TAK patients. Despite the apparent similar involvement at PET imaging, these two diseases are distinct illnesses in both pathogenesis and clinical evolution. Furthermore, thoracic aorta vessel walls were not examined because both of the need of axial oblique images acquisition and cardiac contraction artifacts. Finally, the use of a contrast agent and cardiac gating to evaluate the thoracic aorta could permit a more reliable anatomical assessment of the thoracic aorta.

FDG PET/CT imaging has been shown to be useful in assessing disease activity and monitoring response to therapy in various inflammatory disorders, such as sarcoidosis [43]. In an in vitro model of temporal arteritis, glucocorticoid therapy was shown to gradually reduce macrophage infiltration and inflammation over the course of 12 months [44], suggesting that FDG PET/CT

could be useful to monitor therapeutic efficacy in vasculitis. Several small studies support this hypothesis by demonstrating decreased FDG uptake following successful immunosuppressive therapy [6,34,45]. In a prospective study evaluating the effect of high-dose glucocorticoid therapy, the sensitivity of FDG PET remained unchanged after 3 days of prednisolone 60 mg, with all patients demonstrating persistent increased FDG uptake [46]. However, after 10 days of therapy, 64% of patients had visual normalization on PET imaging. On semi-quantitative analyses, the FDG uptake intensity decreased by 10 to 15% after 3 days and by 30 to 40% after 10 days of high-dose glucocorticoid therapy.

While most patients with clinically active vasculitis had FDG-PET scan findings that demonstrate vascular inflammation, low-grade uptake may persist several months following successful therapy. There is minimal data on FDG-PET findings during clinical remission in GCA, with one study noting increased arterial uptake in more than 80% of patients during clinical remission [47], consistent with also our findings.

Despite the lack of histologic confirmation, results from the present study strongly suggest that subclinical vascular inflammation is likely a major contributor to the varying degree of arterial FDG uptake observed during clinical remission. Patients with LV-GCA who had a persistent low-grade uptake during clinical remission were at risk for subsequent PET worsening and future clinical relapse, in line with the results of Grayson et al [34].

The exact nature of this persistent faint uptake is unclear, and it has been suggested that it could hence represent subclinical vasculitis [34,48]. Alternatively, increase in PET activity with reduction in treatment could be related to increased metabolic activity from vascular repair or a secondary cause such as worsening atherosclerosis [49].

In conclusion, findings from this study demonstrate that advanced imaging techniques provide information about disease activity that is complimentary to, and unique from, clinical assessment. This study provides novel, prospective evidence about the potential value of FDG-

PE/MR scans in patients with LVV who are assessed months to years into the course of disease. While serial monitoring of patients with FDG-PET may identify vascular abnormalities in patients with LVV otherwise in apparent clinical remission, use of FDG-PET to monitor vascular inflammation in routine clinical practice is not currently advisable. However, this study provides preliminary evidence that FDG-PET performed in patients with LVV during established clinical remission can identify subsets of patients at risk for future clinical relapse. These findings support a need to study FDG-PET as a potential outcome measure of vascular activity in clinical trials in LVV, however, standardization of visual and quantitative criteria is required to obtain uniform and reproducible interpretation of FDG PET.

References

[1] Nuenninghoff DM, Hunder GG, Christianson TJH, et al. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum 2003;48:3522–31.

[2] Prieto-González S, Arguis P, García-Martínez A, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. Ann Rheum Dis 2012;71:1170–6.

[3] Muratore F, Kermani TA, Crowson CS, et al. Large-vessel giant cell arteritis: A cohort study. Rheumatol (United Kingdom) 2015;54:463–470.

[4] de Boysson H, Liozon E, Lambert M, et al. Giant-Cell Arteritis: Do We Treat Patients with Large-Vessel Involvement Differently?. Am J Med 2017;130:992–995.

[5] de Boysson H, Liozon E, Espitia O, et al. Different patterns and specific outcomes of large-vessel involvements in giant cell arteritis. J Autoimmun 2019;103.

[6] Blockmans D, de Ceuninck L, Vanderschueren S, et al. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Rheum 2006;55:131–7.

[7] Karassa FB, Matsagas MI, Schmidt WA, et al. Meta-analysis: test performance of ultrasonography for giant-cell arteritis. Ann Intern Med 2005;142:359–69.

[8] Murgatroyd H, Nimmo M, Evans A, et al. The use of ultrasound as an aid in the diagnosis of giant cell arteritis: A pilot study comparing histological features with ultrasound findings. Eye 2003;17:415–419.

[9] Litmanovich DE, Yıldırım A, Bankier AA. Insights into imaging of aortitis. Insights Imaging 2012;3:545–60.

[10] Andrews J, Al-Nahhas A, Pennell DJ, et al. Non-invasive imaging in the diagnosis and

management of Takayasu's arteritis. Ann Rheum Dis 2004;63:995–1000.

[11] Kato Y, Terashima M, Ohigashi H, et al. Vessel Wall Inflammation of Takayasu Arteritis Detected by Contrast-Enhanced Magnetic Resonance Imaging: Association with Disease Distribution and Activity. PLoS One 2015;10:e0145855.

[12] Tso E, Flamm SD, White RD, et al. Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. Arthritis Rheum 2002;46:1634–42.

[13] Eshet Y, Pauzner R, Goitein O, et al. The limited role of MRI in long-term follow-up of patients with Takayasu's arteritis. Autoimmun Rev 2011;11:132–6.

[14] Cheng Y, Lv N, Wang Z, et al. 18-FDG-PET in assessing disease activity in Takayasu arteritis: a meta-analysis. Clin Exp Rheumatol 31:S22-7.

[15] Besson FL, Parienti J-J, Bienvenu B, et al. Diagnostic performance of 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 2011;38:1764–1772.

[16] Puppo C, Massollo M, Paparo F, et al. Giant Cell Arteritis: A Systematic Review of the Qualitative and Semiquantitative Methods to Assess Vasculitis with 18F-Fluorodeoxyglucose Positron Emission Tomography. Biomed Res Int 2014;2014:1–11.

[17] Blockmans D, Stroobants S, Maes A, et al. Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. Am J Med 2000;108:246–9.

[18] Walter MA, Melzer RA, Schindler C, et al. The value of [18F]FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease. Eur J Nucl Med Mol Imaging 2005;32:674–81.

[19] Hautzel H, Sander O, Heinzel A, et al. Assessment of Large-Vessel Involvement in

Giant Cell Arteritis with 18F-FDG PET: Introducing an ROC-Analysis-Based Cutoff Ratio. J Nucl Med 2008;49:1107–1113.

[20] Meller J, Strutz F, Siefker U, et al. Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI. Eur J Nucl Med Mol Imaging 2003;30:730–6.

[21] Melsaether AN, Raad RA, Pujara AC, et al. Comparison of Whole-Body (18)F FDG PET/MR Imaging and Whole-Body (18)F FDG PET/CT in Terms of Lesion Detection and Radiation Dose in Patients with Breast Cancer. Radiology 2016;281:193–202.

[22] Einspieler I, Thürmel K, Pyka T, et al. Imaging large vessel vasculitis with fully integrated PET/MRI: a pilot study. Eur J Nucl Med Mol Imaging 2015;42:1012–24.

[23] Dejaco C, Ramiro S, Duftner C, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis 2018;77:636–643.

[24] Restuccia G, Boiardi L, Cavazza A, et al. Flares in biopsy-proven giant cell arteritis in northern Italy characteristics and predictors in a long-term follow-up study. Med (United States) 2016;95:1–10.

[25] K M, Y K, T T. Body mass index associates with disease relapse in patients with giant cell arteritis. Int J Rheum Dis 2019;22:1782–1786.

[26] Bellan M, Puta E, Croce A, et al. Role of positron emission tomography in the assessment of disease burden and risk of relapse in patients affected by giant cell arteritis. Clin Rheumatol 2020;39:1277–1281.

[27] S M, A A, M S, et al. Prevalence of Giant Cell Arteritis Relapse in Patients Treated With Glucocorticoids: A Meta-Analysis. Arthritis Care Res (Hoboken) 2020;72:838–849.

[28] Dumont A, Parienti JJ, Delmas C, et al. Factors associated with relapse and dependence on glucocorticoids in giant cell arteritis. J Rheumatol 2020;47:108–116.

[29] Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122–8.

[30] Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129–34.

[31] Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med 2017;377:317–328.

[32] Li AE, Kamel I, Rando F, et al. Using MRI to Assess Aortic Wall Thickness in the Multiethnic Study of Atherosclerosis: Distribution by Race, Sex, and Age. Am J Roentgenol 2004;182:593–597.

[33] Sun Y, Ma L, Ji Z, et al. Value of whole-body contrast-enhanced magnetic resonance angiography with vessel wall imaging in quantitative assessment of disease activity and follow-up examination in Takayasu's arteritis. Clin Rheumatol 2016;35:685–693.

[34] Grayson PC, Alehashemi S, Bagheri AA, et al. 18F-Fluorodeoxyglucose–Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis. Arthritis Rheumatol 2018;70:439–449.

[35] Scheel AK, Meller J, Vosshenrich R, et al. Diagnosis and follow up of aortitis in the elderly. Ann Rheum Dis 2004;63:1507–1510.

[36] Spira D, Xenitidis T, Henes J, et al. MRI parametric monitoring of biological therapies in primary large vessel vasculitides: a pilot study. Br J Radiol 2016;89:20150892.

[37] Both M, Ahmadi-Simab K, Reuter M, et al. MRI and FDG-PET in the assessment of inflammatory aortic arch syndrome in complicated courses of giant cell arteritis. Ann Rheum Dis 2008;67:1030–3.

[38] Prieto-González S, Depetris M, García-Martínez A, et al. Positron emission tomography assessment of large vessel inflammation in patients with newly diagnosed, biopsy-proven giant cell arteritis: a prospective, case-control study. Ann Rheum Dis 2014;73:1388–92.

[39] Lee YH, Choi SJ, Ji JD, et al. Diagnostic accuracy of 18F-FDG PET or PET/CT for large vessel vasculitis. Z Rheumatol 2016;75:924–931.

[40] Muto G, Yamashita H, Takahashi Y, et al. Large vessel vasculitis in elderly patients: early diagnosis and steroid-response evaluation with FDG-PET/CT and contrast-enhanced CT. Rheumatol Int 2014;34:1545–54.

[41] Treglia G, Mattoli MV, Leccisotti L, et al. Usefulness of whole-body fluorine-18-fluorodeoxyglucose positron emission tomography in patients with large-vessel vasculitis: a systematic review. Clin Rheumatol 2011;30:1265–75.

[42] Arnaud L, Haroche J, Malek Z, et al. Is (18)F-fluorodeoxyglucose positron emission tomography scanning a reliable way to assess disease activity in Takayasu arteritis?. Arthritis Rheum 2009;60:1193–200.

[43] P M, M P-G, D J, et al. Imaging Cardiac Sarcoidosis With FLT-PET Compared With FDG/Perfusion-PET: A Prospective Pilot Study. JACC Cardiovasc Imaging 2019;12:2280–2281.

[44] M C-B, A G-M, E L, et al. Changes in biomarkers after therapeutic intervention in temporal arteries cultured in Matrigel: a new model for preclinical studies in giant-cell arteritis. Ann Rheum Dis 2014;73:616–623.

[45] F B, G B, F C, et al. Role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography for therapy evaluation of patients with large-vessel vasculitis. Jpn J Radiol 2010;28:199–204.

[46] Nielsen BD, Gormsen LC, Hansen IT, et al. Three days of high-dose glucocorticoid

treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. Eur J Nucl Med Mol Imaging 2018;45:1119–1128.

[47] de Boysson H, Aide N, Liozon E, et al. Repetitive 18F-FDG-PET/CT in patients with large-vessel giant-cell arteritis and controlled disease. Eur J Intern Med 2017;46:66–70.

[48] KA N, MA A, M H, et al. Diagnosis of Giant Cell Arteritis in an Asymptomatic Patient. Arthritis Rheumatol (Hoboken, NJ) 2016;68:1135.

[49] D R, A M, ZA F. Molecular imaging in atherosclerosis: FDG PET. Curr Atheroscler Rep 2012;14:429–437.