Do statins decrease vascular inflammation in patients at risk for large-vessel vasculitis? A retrospective observational study with FDG-PET/CT in polymyalgia rheumatica, giant cell arteritis and fever of unknown origin

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Abstract

Objective

[18F] Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) can detect the presence of large-vessel vasculitis (LVV) in patients with polymyalgia rheumatica (PMR), giant cell arteritis (GCA) and fever of unknown origin (FUO). The aim of this study was to evaluate whether statins could reduce FDG-PET/CT-assessed vascular inflammation in this group of patients.

Methods

Clinical, demographic, laboratory data, current pharmacological treatments, and cardiovascular risk factors of patients with PMR, GCA and FUO, who underwent FDG-PET/CT, were recorded. FDG uptake was measured at prespecified arterial sites with the mean standardised uptake value (SUV), and with a qualitative visual score, summed up to obtain a total vascular score (TVS). LVV was diagnosed if arterial FDG visual uptake was equal or higher of liver uptake.

Results

129 patients were included (96 with PMR, 16 with GCA, 13 with both PMR and GCA, and 4 with FUO), of whom 75 (58.1%) showed LVV. Twenty out of 129 (15.5%) patients were taking statins. TVS was significantly lower in patients treated with statins (p=0.02), especially in the aorta (p=0.023) and femoral arteries (p=0.027).

Conclusion

Our preliminary results suggest that statins may exert a potential protective role on vascular inflammation in patients with PMR and GCA. Statin use could spuriously decrease FDG uptake of the vessel walls.

Key words

polymyalgia rheumatica, giant cell arteritis, large-vessel vasculitis, positron emission tomography, statins

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Introduction

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are closely related inflammatory disorders of the elderly (1, 2). PMR causes pain and stiffness in the neck, shoulders and in the pelvic girdle (3). It is commonly accompanied by systemic inflammatory signs such as fever, malaise, weight loss, and increased inflammatory indexes (4). GCA is the most frequent large-vessel vasculitis in the adult (5). It is characterised by a granulomatous inflammation of the aorta and its main branches. The extra-cranial branches of the carotid arteries, like the temporal arteries, are frequently involved with headache, local pain, and, possibly, sight loss (6).

PMR features are seen in up to 40–60% of newly diagnosed GCA and up to 16–21% of PMR patients may develop GCA, especially if they are inadequately treated (6-8). The association between these two conditions has been studied also by imaging techniques, such as [^{18}F]fluorodeoxyglucose positron emission tomography/computerised tomography (FDG PET/CT) (9). Large-vessel vasculitis (LVV) has been documented as an increased FDG uptake in up to 30% of PMR patients (10-12) and in up to 83% of GCA patients (13-16).

In the late 1990s, increased large-vessel FDG-uptake was shown also in patients with fever of unknown origin (FUO), a condition defined as fever higher than 38.3°C, which persists for at least 3 weeks without a known cause despite clinical tests and hospital admission of at least one week duration (17). PET/CT can ascertain the most frequent causes underlying FUO *i.e.* neoplasms, infections, and inflammatory diseases (18, 19). Recently, in a cohort of 240 patients with FUO, a final diagnosis of PMR and LVV was made in 21% suggesting that the sole manifestation of these conditions can be long-standing fever and systemic inflammatory signs (20).

The association between large-vessel vasculitis and atherosclerosis is less clear (21). Endothelial dysfunction may be present in patients with active vasculitis responding to steroid treatment (22, 23), a finding observed especially in Takayasu arteritis (24). Another study suggested that carotid intima-media thickness (IMT) might be reduced in patients with GCA compared to age-matched healthy controls (25). Carotid IMT may decrease during GC treatment despite the persistence of endothelial disfunction (26). However, IMT may not be an ideal proxy for cardiovascular risk in patients with GCA since it can be influenced by the presence of chronic vasculitic lesions, especially in the axillary arteries (27). Mortality for ischaemic heart disease is the same in GCA patients as in the general population (28). However, another study (29) has reported an increased risk for cardiovascular diseases in a large cohort of 809 GCA patients compared with age-sex matched healthy controls. Conversely, venous thromboembolic events and cerebrovascular events occur apparently with a similar incidence in GCA patients and controls (30).

Despite these contrasting clinical observations, chronic inflammation is a common feature of both atherosclerosis and vasculitis. In these conditions, macrophages play a crucial role because they promote release of cytokines, enzymes, reactive species of oxygen, facilitate antigen presentation, and stimulate secretion of tissue modelling factors (31).

Statins, blood cholesterol lowering agents, are commonly used in clinical practice to prevent cardiovascular events by improving the lipidic profile and consequently contrast formation of atherosclerotic plaques. There is increasing evidence that these molecules have also anti-inflammatory properties through different mechanisms, (a) up-regulation of endothelial nitric oxide synthase (32) which is reduced in endothelial dysfunction; (b) reduction of C-reactive protein (CRP) concentrations (33); (c) reduction of neutrophil-recruiting chemokines (MCP-1, IL-8, RANTES), pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-12, TNF-α) (34) and of INF-γ-mediated induction of MHC-II molecules in endothelial cells (35) (Fig. 1).

FDG PET/CT is a valid technique to evaluate vascular atherosclerosis. Indeed, FDG uptake can target plaque macrophage glucose utilisation and inflammation. Vascular plaque FDG

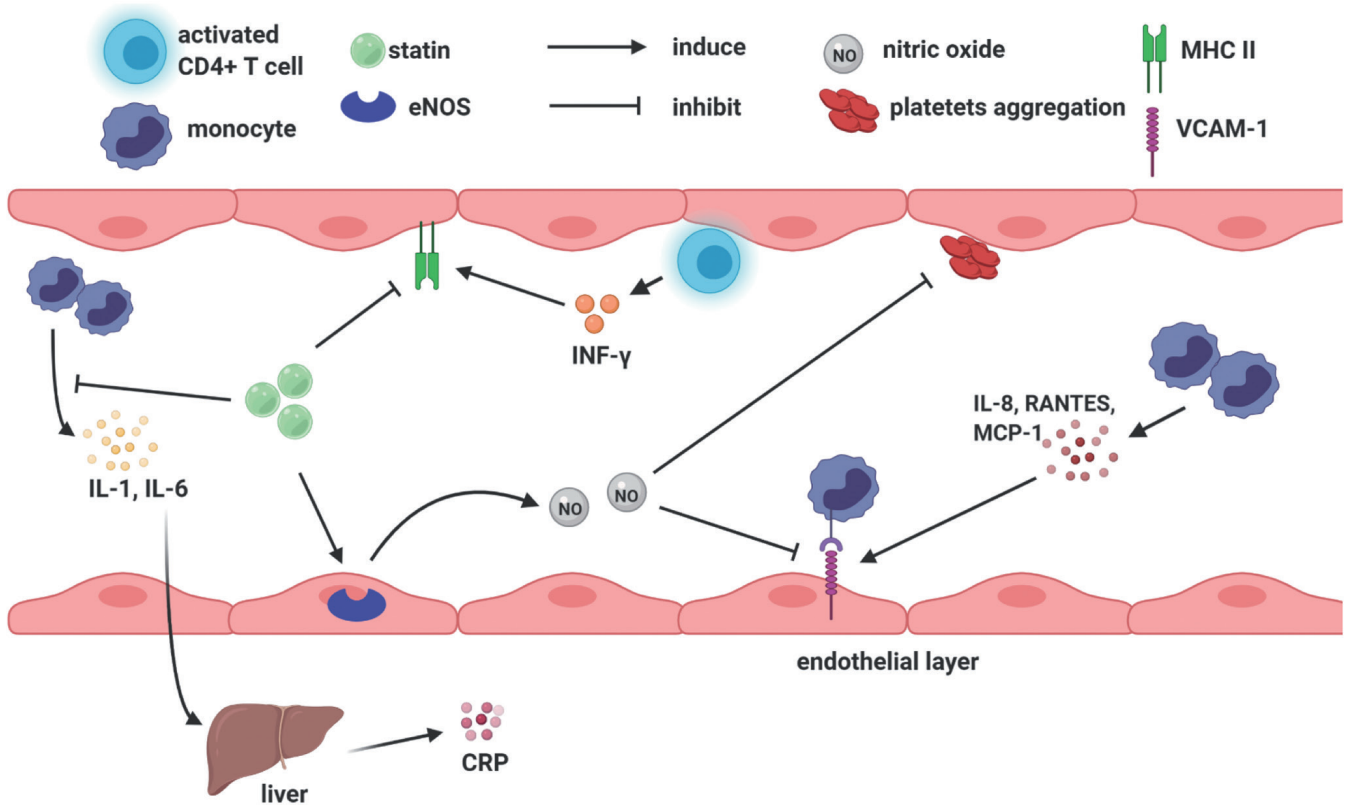

Fig. 1. Potential anti-inflammatory mechanisms of statins in large-vessel vasculitis
IL: interleukin; eNOS: endothelial nitric oxide synthase; MHC II: major histocompatibility complex II; IFN-γ: interpheron-gamma; VCAM-1: vascular cell adhesion protein 1; RANTES: regulated on activation normal T cell expressed and secreted; MCP-1: macrophage chemotactic protein-1; CRP: C-reactive protein. Created with www.biorender.com.

uptake has been linked to cardiovascular events such as myocardial infarction and stroke (36, 37). A systematic review showed that FDG uptake in the carotid arteries is associated with age, male gender, and body mass index in healthy subject, as well as arterial hypertension, hypercholesterolaemia, and diabetes mellitus (38). In patients with a cerebrovascular event, FDG uptake was higher in the involved carotid artery than in the contralateral one.

The aim of this paper is to ascertain if statins could affect inflammation in LVV, as shown by FDG-PET/CT.

Materials and methods

Consecutive patients seen between January 2009 and April 2016 were retrospectively studied. PMR patients were identified according to Bird *et al*. criteria (39); GCA patients were identified according to the ACR criteria (40); and FUO patients were identified according to Durack's criteria (41). All patients who underwent FDG-PET/CT are routinely asked informed consent for the retrospective utilisation of their anonymised images for research purposes, as approved by the local ethical committee (CONSAZQA_0001).

Every patient underwent standard clinical examination including an accurate history of all drug treatments. The following parameters were recorded: disease duration, morning stiffness, fever, weight loss, headache, jaw claudication, visual disturbances, girdles and spine pain and previous treatment with glucocorticoids (GC). Physical examination included the evaluation of pain at pressure on biceps long head, subacromial area, ischiatic and trochanteric bursae, sacro-iliac joints and pain during the mobilisation of the shoulder or pelvic girdles (each of these parameters were recorded in a dichotomic way as "present" or "absent"), elevation grade in the upper limbs, presence of peripheral arthritis, anomalies of the temporal artery, presence of vascular bruits and claudicatio of the extremities.

CRP (ELISA), erythrocyte sedimentation rate (ESR), total, HDL (colorimetric enzymatic method), and LDL cholesterol (Martin equation), and white blood cell count (WBC) were evaluated. Hypercholesterolaemia was defined as serum total cholesterol higher than 220 mg/dl or ongoing treatment with statins. In patients with fever of unknown origin (FUO), a diagnostic work-up (*i.e*. haemocultures, echocardiogram, screening for neoplastic diseases) was performed. Treatment with statins was defined as assumption of any type of statin at the recommended dosages for at least 6 months.

Every patient underwent FDG PET/CT. After a minimum time of 6-h fasting, a dose of 4.8-5.2 Mbq of F18-FDG/kg was injected through a peripheral venous catheter. Patients were set in a silent room and were invited not to move. Data acquisition began 60 minutes after the administration of ^{18}F-FDG. Patients simultaneously underwent FDG-PET with CT from the skull base to the thighs by using an integrated FDG-PET/CT scanner (Hirez; Siemens Medical Solutions, Knoxville TN, USA). In

Table I. Median values (range) of PET vascular inflammation evaluated with the visual method (Total Vascular Score) and vascular SUV in the whole cohort of patients comparing patients with and without LVV, as well as statins-users with non-users.

	Total patients (n=129)	Statin-users (n=20)	Statin-non-users (n=109)	*p*	LVV patients (n=75)	Statin-users (n=8)	Statin non-users (n=67)	*p*	Patients without LVV (n=54)	Statin users (n=12)	Statin non-users (n=42)	*p*
TVS	11 (0-42)	8 (1-27)	12 (0-42)	**0.02**	20 (4-42)	15 (7-27)	20.5 (4-42)	0.15	6 (0-14)	5.33 (1-12)	6.5 (0-14)	0.31
Vascular SUV	0.75 (0.36-2.08)	0.71 (0.48-0.97)	0.82 (0.36-2.08)	0.45	0.83 (0.39-1.97)	0.76 (0.62-0.96)	0.83 (0.39-1.97)	0.22	1.57 (0.38-0.77)	1.46 (0.92- 2.2)	1.6 (0.77-2.45)	0.26

several patients, the scan included also the legs and feet, if these were clinically involved. PET raw data were reconstructed with OSEM e FBP algorithms included in the reconstruction software and the whole CT dataset was merged with PET tridimensional data through a integrating software (Syngo Image Fusion; Siemens Erlangen, Germany) which created anatomical images overlapped with FDG uptake.

Image analysis

Vascular uptake was evaluated with a visual score and a semi-quantitative method. Volumetric regions of interests (VOIs) were localised on CT anatomical regions to identify four aortic segments (ascending, arch, descending, abdominal), subclavian arteries, common carotid arteries, iliac and femoral arteries; VOIs were drawn on a theoretical vessel's wall to exclude the uptake of blood from the vascular lumen. A further region was drawn within the left ventricular chamber using the PET image to estimate the tracer concentration in the arterial blood (blood-pool, BP).

The arterial uptake of FDG was quantified through the calculation of the mean standardised uptake values (SUV) within each VOI. The average of mean SUV within each VOI was calculated and normalised for the blood's FDG content (BP), thus defined as target-to-background ratio (TBR), which should measure the real metabolic activity of the arterial wall.

In order to evaluate the presence and extension of atherosclerosis, total arterial calcium load (ACL) was also estimated by CT in the same arterial segments. Calcium density was classified upon a semi-quantitative scale of 5 points based on the percentage of calcification of the arterial ring documented through trans-axial CT projection: 0= no calcifications, 1=0-25%, 2=25-50%, 3=50-75%, 4=75-100%, with a possible variation in the score between 0 and 48. Arterial uptake suggesting LVV was visually ascertained when it was diffused and not focal, and classified on a 4-point scale, as proposed by Walter et al (42): 0 = no uptake; 1 = presence of uptake lower than that of the liver; 2 = uptake similar to that of the liver; 3 = uptake higher than that of the liver. The reading operator was blind for the type of disease and of treatment, and for the results of laboratory examinations. To determine the frequency of each value, these scores were further classified as "negative" (0 and 1) and "positive" (2 and 3). For each patient the sum of the four points from the vascular uptake was indicated as total vascular score (TVS) with a maximum value of 36.

Statistical analysis

Means were compared by the Student's t test or by one way analysis of variance if their distribution was normal and by the Kruskall Wallis test when it was non parametrical. Frequencies were compared by the chi square test. Correlations were analysed through the Spearman's rho test. Multiple regression was calculated including as dependent variable statin assumption in a dichotomous way (yes/no) and as independent variables sex, age, diagnosis, GC consumption and vasculitis/aortitis at PET/CT. *p*-values less than 0.05 were considered significant. All the calculations were performed using Medcalc® v. 19.2.1 (Belgium) as statistical software.

Results

A total of 129 patients were included (87 women, 67.4%) with a median age of 74 years (range 50–92 years). Of these, 96 had a diagnosis of PMR, 16 of GCA, 13 of PMR associated with GCA and 4 of FUO. The median interval between the onset of symptoms and PET/CT was 85 days (range 4–1957 days).

LVV was seen in 75 patients by PET/CT (58.1%): it was present in 48/96 PMR cases (50%), in 12/16 GCA patients (75%), in 11/13 (84%) patients with overlapping PMR and GCA and in 4/4 patients with FUO (100%). Of all patients, 43 (33.3%) patients showed grade-2 LVV and 32 (24.8%) patients grade-3 LVV. Grade-2 aortitis was present in 39 patients (30.2%) and grade 3 aortitis in 27 patients (20.9%). The patients with aortitis had either an isolated aortic involvement or the combination of peripheral and aortic vasculitis. A peripheral grade-2 LVV without aortic involvement was detected in 9 patients whereas a pure peripheral grade-3 LVV was not observed in any subject. Of all patients, 32 (28.7%) were treated with GC at the time of PET/TC.

Median BMI was 24.9 (range 17.3–35.6), 24.9 (range 17.3–33.2) in women and 25.5 (range 20.9–35.6) in men. Hypercholesterolaemia was observed in 34/129 patients (26.4%). Median values of total and fractional cholesterol are shown in Supplementary Table 1 (S1). Forty-four patients (34.1%) had a history of hypertension, 13 (10.1%) of type 2 diabetes mellitus, 10 (7.8%) of myocardial infarction, 8 (6.2%) of stroke, and one (0.8%) of peripheral arterial occlusive disease. Both diabetes mellitus and history of myocardial infarction were more frequent in men (p=0.02 and 0.013, respectively). Statins were assumed by 20 patients (15.5%), 11 women (12.6%) and 9 men (21.4%) (ns). They were rosuvastatin in eleven patients (55%), atorvastatin in three

Table II. Median values (range) of vascular inflammation evaluated by the visual method (TVS=Total Vascular Score) and by the calculation of vascular SUV in patients with statins treatment compared with those without, divided according to the investigated vessel. The SUV was not calculated for the axillary arteries because of technical reasons, including the arterial diameter and impossibility of obtaining sections perpendicular to the arterial lumen.

	TVS (n=129)	TVS in statin-users (n=20)	TVS in statin-non-users (n=109)	*p*	Vascular SUV (n=129)	Vascular SUV in statin-users (n=20)	Vascular SUV in statin-non-users (n=109)	*p*
Aortic arch	1 (0-3)	1 (0-3)	2 (0-3)	**0.023**	0.83 (0.43-2.25)	0.77 (0.56-1.56)	0.83 (0.43-2.25)	0.34
Ascending aorta	1 (0-3)	1 (0-3)	2 (0-3)	**0.017**	0.78 (0.42-1.80)	0.74 (0.43-1.23)	0.78 (0.42-1.80)	0.34
Descending aorta	1 (0-3)	1 (0-3)	1 (0-3)	0.065	0.93 (0.38-2.50)	0.90 (0.57-1.54)	0.94 (0.38-2.50)	0.43
Abdominal aorta	0 (0-3)	0 (0-2)	1 (0-3)	0.082	0.86 (0.35-2.50)	0.82 (0.59-1.38)	0.89 (0.35-2.50)	0.36
Right carotid artery	0 (0-3)	0 (0-3)	0 (0-3)	0.202	0.82 (0.31-2.17)	0.77 (0.48-1.58)	0.83 (0.31-2.17)	0.49
Left carotid artery	0 (0-3)	0 (0-3)	0 (0-3)	0.227	0.75 (0.10-1.80)	0.79 (0.33-1.10)	0.74 (0.10-1.80)	0.89
Right subclavian artery	1 (0-3)	1 (0-3)	1 (0-3)	0.084	0.73 (0.30-2.42)	0.69 (0.52-1.17)	0.74 (0.30-2.42)	0.30
Left subclavian artery	1 (0-3)	1 (0-3)	1 (0-3)	0.093	0.79 (0.31-2.50)	0.73 (0.47-1.00)	0.79 (0.31-2.50)	0.26
Right axillary artery	0 (0-3)	0 (0-2)	0 (0-3)	0.181	Not performed	Not performed	Not performed	-
Left axillary artery	0 (0-3)	0 (0-2)	0 (0-3)	0.181	Not performed	Not performed	Not performed	-
Right iliac artery	0 (0-3)	0 (0-1)	0 (0-3)	0.095	0.72 (0.29-2.00)	0.66 (0.33-1.07)	0.73 (0.29-2.00)	0.17
Left iliac artery	0 (0-3)	0 (0-1)	0 (0-3)	0.082	0.75 (0.27-1.83)	0.68 (0.41-1.25)	0.77 (0.27-1.83)	0.42
Right femoral artery	1 (0-3)	1 (0-2)	1 (0-3)	**0.023**	0.44 (0.21-1.42)	0.44 (0.22-0.85)	0.45 (0.21-1.42)	0.74
Left femoral artery	1 (0-3)	1 (0-2)	1 (0-3)	**0.027**	0.50 (0.22-1.43)	0.52 (0.22-0.92)	0.50 (0.22-1.43)	0.66

patients (15%), simvastatin in two patients (10%), atorvastatin in two patients (10%), pravastatin in one patient (5%) and fluvastatin in another one (5%).

Statin assumption was independent from the presence of vasculitis at FDG PET/TC; the group with grade 3 vasculitis assumed them less frequently than the remaining patients (1/31 *vs*. 19/78, p=0.051). Likewise, statin assumption was not associated with the presence of aortitis. GC and statin treatments there not correlated with each other (p=0.80). Furthermore, there was no correlation between the presence of vasculitis and total ACL.

In all patients, the median TVS was significantly lower in patients assuming statins compared with statin-free subjects (p=0.02). No statistically significant difference was observed in the median SUV between statin-utilisers and statin-free patients. Considering both patients affected by LVV and those not affected, no statistically significant differences were observed between the median TVS and SUV in relation to the assumption of statins (Table I). The same variations have been evaluated in relation to the individual arterial locations: TVS was significantly lower in statin-treated patients at the aortic arch, ascending aorta and femoral arteries (Table II). In supplementary Table II, we have compared the TVS for the different vascular locations of patients with and without LVV, according to their statin treatment. Among statin-users with LVV, a tendency to a lower uptake was seen in the aortic arch and ascending aorta (p=0.07); among statin-users without LVV, a tendency to a lower uptake was seen in the femoral arteries (p=0.05).

Furthermore, it was evaluated if TVS could be influenced by patients' sex, since men were more frequently treated with statins: this association was absent (p=0.07). ACL was higher in patients taking statins [14 (range 2-35) *vs*. 8 (range 0–35); p=0.012]. It did not correlate with TVS (rho -0.09, p=0.28), but was inversely correlated with vascular SUV (rho -0.19, p=0.03). Lastly, patients treated with GC had a median TVS comparable with those not taking them.

Multiple regression analysis was performed by using as dependent variable statin assumption and as independent variables sex, age, diagnosis, GC use and vasculitis/aortitis at PET/CT. The only variable which influenced statin assumption was age (p=0.04), with older patients more likely to assume them. Age and TVS were not correlated (p=0.23).

The effect of statin consumption on clinical and laboratory parameters is shown in Table III. Fever was the sole clinical parameter that was seen more often in patients not assuming statins (p=0.03).

Discussion

Our clinical study retrospectively evaluated if the treatment with statins could affect vascular inflammation in a cohort of patients with PMR, GCA and FUO. Patients treated with statins showed a lower uptake of the radioactive tracer FDG especially in the aorta and in the femoral arteries. This difference was slightly more evident at the aorta in patients with LVV, and in the femoral arteries in patients without LVV. The non-significance of these differences could be due to the low number of patients on statin treatment. An additional observation is that vasculitis patients submitted to PET/CT should be investigated for statin use, because it could spuriously lower FGD uptake.

Statins were taken by 15.5% of 129 patients. This percentage is lower but comparable with the observed percentage in Italy (24%) in subjects with more than 45 years (43). This difference could be due to patients underreporting such treatment, to a lesser use of statins because of the older mean age of our patients, or, alternatively, to the fact that they might have a lower number of co-morbidities compared with the general population (44).

Table III. Laboratory parameters in statins-treated patients compared with those not treated with statins.

	Total (n=129)	Statin-users (n=20)	Statin-non-users (n=109)	*p*
Morning stiffness (min)	45 (0-480)	52.5 (0-300)	45 (0-480)	0.34
Fever	40/129 (31%)	2/20 (10%)	38/109 (34.9%)	0.03
Arthritis	39/129 (30.2%)	10/20 (50%)	29/109 (26.6%)	0.06
Weight loss	47/129 (36.4%)	10/20 (50%)	37/109 (33.9%)	0.21
Tenosynovitis	20/129 (15.5%)	5/20 (25%)	15/109 (11.6%)	0.20
White blood cells (n/μl)	8.4 (4.3-15)	8.2 (6-12.5)	8.5 (4.3-15)	0.99
Haemoglobin (g/dL)	12.6 (8.2-16.8)	12.5 (10.5-16.8)	12.6 (8.2-16.7)	0.55
Platelets (n/μl)	317 (108-643)	292 (175-465)	322 (108-643)	0.28
ESR (mm/h)	59 (8-140)	43 (8-120)	60 (9-140)	0.16
CRP (mg/L)	35 (0.4-162)	23.5 (1.5-106)	36.1 (0.4-162)	0.13
Total cholesterol (mg/dL)	200 (78-388)	194.5 (137-251)	200 (78-388)	0.94
HDL cholesterol (mg/dL)	62 (21-105)	55 (34-97)	63 (21-105)	0.77
LDL cholesterol (mg/dL)	114.1 (50-222)	112 (868-162)	114.1 (50-222)	0.40

The difference between statin-assuming and statin-naive patients was demonstrated when vessel inflammation at PET/CT was assessed by direct image analysis, but not when the automatic reading of the SUV in vessel VOIs was used. The second method, being independent from the operator's judgement if not for VOI's positioning, should be theoretically more objective. In our study, the nuclear medicine specialist who scored the images was unaware of the clinical diagnosis, laboratory results and ongoing treatment. A possible explanation of the discrepancy between the two measurement modalities derives from the observation that the degree of vessel wall calcification at CT was inversely correlated with vascular SUV but not associated with the visual evaluation of the uptake. If the vessel's wall is completely calcified, inflammation should be over. The eye of an expert observer can recognise calcification sites and therefore exclude them from the evaluation; the automatic VOI includes them, and therefore their presence reduces mean SUV value. Furthermore, calculation of the SUV strongly depends on the interval between tracer injection and image acquisition. If this aspect is not correctly standardised, the numerical value can vary significantly.

In our experience, statins failed to influence clinical manifestations of LVV or laboratory parameters, with the notable exception of fever, which was less frequent in statin-treated patients. ESR and CRP concentrations were also marginally lower in this group. Total, and HDL and LDL cholesterol were not different between the two groups, an easily expected result, in hyper-cholesterolemic patients assuming statins.

Our study has several limitations: first, it is an observational retrospective study. Patients' records were screened for any treatment, including statins. It is possible that some patients did not remember exactly their medications and hence, some statin-users may have been mistakenly classified as non-users. This type of error, if present, could have determined a reduction in the association but not its increase. Second, the number of patients taking statins was low, but the observed significance indicates that the association between statins and reduced vascular uptake is rather strong. Third, the population involved in the study was heterogeneous and not well balanced, since the included patients had a diagnosis of either PMR, GCA or FUO, but not TAK; in addition, PMR patients were largely overrepresented, according to the case mix commonly seen in our outpatient clinic.

Finally, possible biases, such as the effect of a larger use of statins in males or an inverse association between atherosclerosis and vasculitis have been considered and excluded. Likewise, the fact that 28 % of patients was under GC treatment at the time of PET/TC has been evaluated. Although our goal was to perform PET-CT in steroid-naive patients in order to avoid a GC-related reduction of uptake, some of them were already on treatment. This was due to either the prevention of visual loss in patients presenting with temporal arteritis, or the PET-CT scan was undertaken during GC treatment for the suspicion of LVV in patients with a refractory disease. However, TVS was not different between patients assuming GC and GC-free patients. Furthermore, statin treatment and GC treatment were not related. As a result, we feel that GC treatment did not influence the results.

Statins reduce the progression of atherosclerotic plaques, as assessed by different imaging modalities, including intravascular ultrasound and coronary CT angiography (CTA) (45). This effect is not only mediated by the reduction of circulating cholesterol, but it is related to a change in the composition and microarchitecture of the plaque itself, possibly through an increase of microcalcium deposits (46). A meta-analysis of intravascular ultrasound studies showed that statins significantly reduce plaque and external elastic membrane volumes, with a reduction in fibrous plaque volume but an increase of dense calcium volume (47). In keeping with these findings, the patients taking statins from our study showed a higher ACL. A meta-analysis of FDG PET/CT studies showed that statins significantly decrease vascular TBR, independently of changes in circulating cholesterol and CRP(48). In another FDG PET/CT study, treatment with statins was associated with a continuous reduction in vascular TBR throughout a 1-year period, despite LDL levels remained stable from the third to the twelfth month, after an initial reduction (49).

Evolocumab, a monoclonal antibody that binds the proprotein convertase subtilisin/kexin type 9 (PCSK9), is approved for the treatment of familiar Hypercholesterolaemia. It reduces LDL cholesterol through an increase in its removal from blood by the liver. A trial of evolocumab demonstrated a significant reduction in LDL and lipoprotein (a), without significant changes in the TBR of the carotid arteries and thoracic aorta, suggesting a peculiar ef-

fect of statins on vessel wall inflammation (50). However, a small observational study suggested that a reduction in arterial FDG uptake might be seen after one year of treatment with evolocumab (51).

The protective endothelial effects and immunomodulatory properties of statins have been also documented in rheumatic diseases (52). In patients affected by Behçet's disease, atorvastatin can reduce CRP concentration and improve brachial artery flow-mediated dilatation (53). In rheumatoid arthritis, a double-blind, randomised, placebo-controlled trial showed that atorvastatin treatment induces a more rapid decrease of inflammatory indexes and swollen joints count in comparison with controls (54). Lastly, in Kawasaki's disease, statins probably reduce persistent coronary arterial inflammation as shown by FDG PET/CT (55), and improve endothelial function as shown by flow-mediated dilatation, with a consensual decrease in CRP concentration (56).

The effect of statins on vascular inflammation and damage may be mediated through different pathways. Statins appear to reduce the rate of progression of abdominal aortic aneurysms and are associated with lower rupture risk (57). A similar protective effect has also been suggested for thoracic aorta aneurysms (58). We have previously shown that patients with PMR and uptake of the thoracic aorta tend to have higher frequency and severity of aortic regurgitation, a possible herald of future dilation of the thoracic aorta. Given the multifaceted interplay between vasculitis and atherosclerosis, one might speculate that statins protect from the development of future aortic dilation in patients with LVV (59).

The potential anti-inflammatory features of statins observed in our study are in line with the observations of Pugnet *et al*. who reported a decrease of cardiovascular hospitalisation rate (60) and a faster GC tapering in statin-treated GCA patients compared with GCA patients not treated with statins (61). Other authors have highlighted an absence of disease-modifying properties of these molecules in GCA patients (44, 62) and lack of clinically relevant GC-sparing effects (63). Little or no evidence is available, instead, about the relationship between statins and LVV associated with PMR or FUO. Therefore, our study, which investigated mainly PMR subjects, supports the need for further investigation about the role of statins in vascular inflammation in this subgroup of patients.

Conclusions

The results of our clinical study indicate that statins may play some potential anti-inflammatory role and support the view that further studies should be performed to test this hypothesis. These observations are in line with the known pharmacological properties of statins, in particular with the literature data reporting their use in inflammatory conditions, such as atherosclerotic plaques and rheumatoid arthritis.

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