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Vessel involvement in giant cell arteritis: an imaging approach

Pieter W. HOLM [1], Maria SANDOVICI [2], Riemer H. J. A. SLART [3, 4]
Andor W. J. M. GLAUDEMANS [3], Abraham RUTGERS [2], Elisabeth BROUWER [2*]

[1]Department of Internal Medicine; University of Groningen/University Medical Center Groningen, Groningen, The Netherlands; [2]Department of Rheumatology and Clinical Immunology, University of Groningen/University Medical Center Groningen, Groningen, The Netherlands; [3]Department of Nuclear Medicine and Molecular Imaging, University of Groningen/University Medical Center Groningen, Groningen, The Netherlands; [4]Department of Biomedical Photonic Imaging, University of Twente, Enschede, The Netherlands

*Corresponding author: Elisabeth Brouwer, Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, Hanzeplein 1, 9700RB, The Netherlands. E-mail: e.brouwer@umcg.nl

ABSTRACT

Vasculitis is classified based on the size of the involved vessels. The two major forms are small vessel vasculitis and large vessel vasculitis (LVV). Main forms of LVV are Takayasu arteritis, giant cell arteritis (GCA), isolated aortitis and chronic periaortitis. This manuscript will focus on GCA, named after the presence of giant cells in the artery vessel wall. A positive biopsy of the temporal artery is the gold standard for making a diagnosis of GCA. In the past 10 years the introduction of new imaging techniques in GCA patients has revealed a variable prevalence of extra cranial involvement, challenging the temporal artery biopsy as gold standard. Also, imaging has become important not only for diagnosing GCA but also for assessment of vascular damage in GCA and for the evaluation of treatment.

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Key words: Giant cell arteritis - Ultrasonography, Doppler, color - Tomography, X-ray computed - Magnetic resonance imaging.

Giant cell arteritis (GCA) is one of the major forms of large vessel and the most common form of vasculitis in persons older than 50 years of age.[1]

Patients with GCA can present with a spectrum of symptoms, the two ends of which can be divided in cranial and systemic symptoms.[2] One end of the spectrum consists of patients with cranial GCA (C-GCA), who present themselves with classical symptoms of GCA, such as headache, jaw claudication, scalp tenderness and visual disturbances. In these patients one can often find painful and enlarged temporal arteries. At the other end of the spectrum are the patients with systemic GCA (S-GCA), who have more systemic symptoms, such as low grade fever, night sweats, weight loss, limb claudication and polymyalgia rheumatic (PMR)-like symptoms (painful and stiff shoulders and hips). In S-GCA the aorta and its major branches (in particular the subclavian, axillary and proximal brachial arteries) are primarily involved and symptoms are often less specific. Some patients present with a combination of cranial and systemic symptoms. Furthermore, many patients who present with cranial symptoms will also have large vessel involvement on imaging. Conversely, patients with imaging-diagnosed large vessel GCA may have positive temporal artery biopsies without any cranial symptoms.

Presently the temporal artery biopsy is the gold standard for making a diagnosis of GCA. However, studies performed with radiographic and nuclear imaging

techniques in temporal artery biopsy positive and negative GCA patients have yielded a variable prevalence (50-80%) of extra cranial involvement. This depended on the patient population and the technique employed, which included ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA) and fluoro-D-glucose integrated with computed tomography (FDG-PET/CT) (Tables I-IV).

Ultrasonographic examination of inflamed temporal arteries, carotid arteries, subclavian and axillary arteries may document a so called ''halo sign'', corresponding to trans mural inflammation and endothelial edema of the vessel wall.[3-5]

Magnetic resonance imaging (MRI) and computerized tomographic scanning are not frequently used in the diagnosis of giant cell arteritis. Nevertheless, these techniques can visualize the extent of the disease and also can demonstrate the development of aneurysms/dissections as well as large artery stenosis in GCA.[6-10] FDG-PET is more and more used in patients with GCA, not only for the diagnosis but also for treatment evaluation. FDG-PET demonstrated involvement of the aorta and its main branches in 50% to 80% of patients. A drawback of the FDG-PET is that the cranial vessels are not visible due to the limited spatial resolution of the FDG-PET camera (approximately 4 mm) and physiological high uptake of FDG in the brain which may obscure uptake in the temporal arteries.[11-13]

In the present manuscript we summarize recent data on imaging techniques, including ultrasound, CTA, MRA and FDG-PET/CT, used to visualize vessel involvement in GCA.

Methods

This overview has been prepared by screening the MEDLINE database from January 2006 to November 2015. Imaging studies which used ultrasound, CT(A), MR(A) and FDG-PET/CT to examine vessel involvement in GCA were selected, with a focus on prospective studies with original data, using state of the art techniques. We performed a database search with key search terms such as "large vessel vasculitis" and "giant cell arteritis", "imaging (Ultrasound, CT(A), MR(A) and FDG-PET/CT)", "prospective", and "diagnosis" and "outcome". Systematic reviews and meta-analysis were also screened. Only studies published in English language were considered. We selected 20 studies (maximum allowed for this overview), of which 14 original articles.

Results

Ultrasound

Color Doppler ultrasonography (CDUS) is a promising, easy accessible and noninvasive technique used to investigate not only the cranial arteries but also the carotid, subclavian and axillary arteries. Ultrasound of inflamed temporal arteries depicts a hypoechoic (dark) wall swelling ("halo") that disappears within 2-3 weeks with corticosteroid therapy, with or without stenosis. Studies evaluating CDUS as a diagnostic tool in GCA have reported a sensitivity ranging from as low as 10% to as high as 95%, bringing into question the diagnostic value of this method for clinical use. During recent years, resolution of ultrasonography images has improved substantially. Schmidt *et al.*[3] published in 2008 their findings on the ultrasound features of axillary, subclavian and proximal brachial arteries in 176 patients with *de novo* suspected temporal arteritis, PMR, arm claudication, unclear inflammation or pyrexia of unknown origin, who eventually were diagnosed with GCA. Of these patients 123 had the classic C-GCA and 53 the large vessel, S-GCA form. The ultrasound showed an abnormal temporal artery ("halo", stenosis or occlusion) in 95% of the C-GCA patients, whereas the temporal artery histology was pathological in 78% of these patients. The axillary, subclavian and proximal brachial arteries were affected in 98%, 61% and 21%, respectively in the 53 S-GCA patients. The axillar artery involvement was bilateral in 79%. Axillary arteries were stenotic in 51% or occluded in 2% of the patients and temporal artery ultrasound and histology were positive in 62% and 67% of S-GCA patients, respectively. In a later study in 2012 Habib *et al.* performed follow-up temporal artery ultrasound examination at 2, 4, 8, and 12 weeks after starting the treatment in GCA patients with abnormal CDUS.[4] They found a "halo" sign at baseline in 13 (81%) GCA patients fulfilling the ACR 1990 criteria for GCA and in 2 (12%) inflammatory control (including PMR) patients but in none of the healthy control subjects. The presence of a "halo" sign in total yielded 81% sensitivity and 88% specificity whereas the presence of bilateral "halo" sign yielded

100% specificity. Importantly, in all GCA patients with positive "halo" sign, directed temporal artery biopsy was positive. Follow-up CDUS examinations of GCA patients showed disappearance of the "halo" sign in 9 patients at 2 weeks and in 4 patients at 4 weeks with a mean of disappearance of 21 days after initiation of steroid treatment. In addition, there was a significant correlation between disappearance of halo sign and clinical and laboratory findings of remission after initiation of steroid therapy. A recent study by Diamantopoulos *et al.* convincingly showed that besides the temporal, subclavian, axillary and brachial arteries also the carotid arteries can be involved in GCA.[5] A positive clinical evaluation for GCA 6 months after the first evaluation by 3 rheumatologists was considered as the gold diagnostic standard. All patients underwent CDUS of the temporal, axillary, and common carotid arteries. Forty-six out of 88 patients were diagnosed to have GCA by the defined gold standard and had a positive CDUS of the temporal (44), common carotid (3), and axillary arteries (14).

In summary, these data suggest that in patients with bilateral "halo" sign a temporal artery biopsy is not necessary, while in patients with unilateral "halo" sign, an ultrasound-directed biopsy has an increased probability to confirm the clinical diagnosis of C-GCA. CDUS is not only useful in helping to diagnose C-GCA, but also in the follow-up of patients after initiation of therapy. Regarding the systemic GCA, especially axillary artery ultrasound increases the diagnostic yield for this form of GCA in patients with suspected temporal arteritis, PMR, arm claudication, unclear inflammation or pyrexia of unknown origin. Large scale studies such as the TABUL (Temporal artery biopsy vs ultrasound in diagnosis of giant cell arteritis), which is presently evaluated, will help us to get further insight into the reliability and validity of ultrasound in assessing inflamed vessels in GCA (Table I).

TABLE I.—*Colour Doppler ultrasonography studies in giant cell arteritis.*

Author (ref.)	Technique	Patient characteristics	Study design	Follow-up	Diagnostic value	Vascular damage
Schmidt [3]	Ultrasound 1997-2003 Ultramark 9, HDI Advanced technology Lab Bothell, WA, USA and 2003- Esaote Technos MPX, Genua, Italy	176 newly diagnosed GCA fulfilling ACR 1990 criteria 75/176 TAB positive Age: 70 F/M: 123/53	Prospective Recruitment 1997-2006 Primary outcome measure: Diagnostic value of CDUS	Baseline assessment only	Involvement Temporal artery 85/176 Axillary arteries 52/176 Subclavian arteries 32/176 Brachial arteries 11/176	Baseline Temporal artery 33% stenosis, 10% occlusion Axillary artery 51% stenosis, 2% occlusion Subclavian artery 21% stenosis, 0% occlusion Brachial artery 13% stenosis, 2% occlusion
Habib [4]	Ultrasound High Resolution Scanner Sonoace,9900 Prime, Medison, Korea stenosis or occlusions	16/32 newly diagnosed GCA fulfilling ACR 1990 criteria 15/16 TAB positive. 16 disease controls Age: 71 F/M: 19/13 30 age and sex matched controls Age: 70 F/M: 14/16	Prospective Recruitment 2008-2010 Primary outcome measure: diagnostic value of CDUS	Baseline Week 2,4,8 and 12 weeks after start of treatment	Involvement Temporal artery 13/16 HALO Disappearance HALO 2 weeks N.=2 4 weeks N.=4 8 weeks N.=16 Controls: 0/30 HALO	4/16 GCA had stenosis or occlusions 3/16 disease control had stenosis or occlusions 5/30 controls had stenosis or occlusions
Diamantopoulos [5]	Ultrasound Siemens Acuson Antares US system; Siemens Medical Systems, Ultrasound group.	46/88 newly diagnosed GCA 41/46 fulfilling ACR 1990 criteria 26/39 TAB positive. Age: 72 F/M: 33/13 42 disease controls Age: 70 F/M: 21/21	Retrospective April 2010-October 2012 Primary outcome measure: Added value of CDUS of the common carotid arteries in GCA	Baseline only	17/41 had large vessel involvement 2/17 involvement carotid artery 12/17 involvement axillary artery 3/17 involvement carotid and axillary artery	Not assessed

CTA

CTA is especially used for assessment of outcome in GCA. A drawback of this technique is the relative high dose of irradiation and the risk of contrast related side effects. Agard *et al.* studied 22 biopsy-proven GCA patients within 4 weeks after diagnosis.[6] The patients underwent an aortic CT scan and the results were compared with the aortic CT scan of 22 controls. They found that thickening of the aortic wall was more frequent among patients than controls (45.4% *versus* 13.6%; P<0.02). Aortic thickening (mean 3.3 mm) was located on the ascending part of the thoracic aorta in 22.7% of the patients, thickening of the abdominal aortic wall was noted in 27.3% of the patients, whereas no thickening was found in the control patients. Prieto-González *et al.* published 2 articles on the same cohort.[7, 8] In the first article they published the baseline data of 40 consecutive newly diagnosed, biopsy-proven GCA patients. Patients were treatment-naïve or had been treated with corticosteroids for <3 days. Vessel wall thickness and vessel diameter (dilation or stenosis) at 4 aortic segments (ascending aorta, aortic arch, descending thoracic and abdominal aorta) and at the main aortic branches were evaluated. S-GCA was detected in 27 patients (67.5%). The vessels involved were as follows: aorta (26 patients, 65%), brachiocephalic trunk (19 patients, 47.5%), carotid arteries (14 patients, 35%), subclavian arteries (17 patients, 42.5%), axillary arteries (7 patients, 17.5%), splanchnic arteries (9 patients, 22.5%), renal arteries (3 patients, 7.5%), iliac arteries (6 patients, 15%) and femoral arteries (11 patients, 30%). Dilation of the

TABLE II.—*CT studies in giant cell arteritis*

Author (ref.)	Technique	Patient characteristics	Study design	Follow up	Diagnostic Value	Damage Outcome
Agard [6]	**Helical aortic CT scan** Philips a.v.e.1 model (Philips Rotterdam the Netherlands)	22 newly diagnosed GCA TAB positive. Disease duration < 4 weeks Age: 74 F/M: 17/5 Controls n=22 inflammatory controls Age: 71 F/M: 17/5	Prospective study Jan 1998-Jan 1999 **Primary outcome measure:** aortic abnormalities at baseline in newly diagnosed GCA patients	Baseline	10/22 GCA and 3/22 controls had a thickening of the thoracic aortic wall. 5/22 GCA and 0/22 controls had a thickening of the ascending thoracic aortic wall.	3/22 GCA and 1/22 controls had a thoracic aneurysm. 5/22 GCA and 2/22 controls had a thoracic aneurysm and/ or ectasia.
Prieto-González [7]	**CT angiography CTA** Multislice spiral CT scanners (Somatom Sensation 64 and Somatom Definition Flash, Siemens Medical Solutions, Malvern, PA, USA)	40/71 newly diagnosed GCA TAB positive. Age: 79 F/M: 27/13 No GC N.=22 Shirt GC N.=18 Controls N.=32 cancer patients without inflammation Age: 70 F/M: 21/21	Prospective study Nov 2006-March 2011 **Primary outcome measure:** large vessel involvement after 1-year follow-up	baseline	34/40 had large vessel involvement 26 thoracic aorta (12 ascending, 23 arch, 23 descending aorta) 19 abdominal aorta 10 panaortitis 23 non-aortic involvement (19 brachiocephalica, 14 carotid arteries, 17 subclavian arteries, 7 axillary arteries, 9 splanchic arteries, 3 renal arteries, 6 iliac arteries, 11 femoral arteries, 22 widespread LVV	Aortic dilatation in 6/40 GCA patients with thoracic aortitis
Prieto-González [8]	**CT angiography CTA** Multislice spiral CT scanners (Somatom Sensation 64 and Somatom Definition Flash, Siemens Medical Solutions, Malvern, PA, USA)	35/40 GCA TAB positive. After 1 year treatment with GC. Age: 80 F/M: 25/10 Relapsing GCA N.=5	Prospective study Nov 2006-March 2011 **Primary outcome measure:** large vessel involvement as estimated by MRI in GCA	13.5 months follow up	19/35 had abnormal CTA findings Wall thickening 17/35 LVV 5/35 aortic dilation 15 thoracic aorta (4 ascending, 11 arch, 13 descending aorta) 9 abdominal aorta 3 panaortitis 12 non aortic involvement (9 brachiocephalica, 4 carotid arteries, 5 subclavian arteries, 4 axillary arteries, 4 splanchic arteries, 4 renal artery, 2 iliac arteries, 5 femoral arteries	1 patient developed reduction in the inferior mesenteric artery diameter. No patients had clinical signs or symtoms related to vascular stenosis.

thoracic aorta was already present in 6 patients (15%). They performed a second CTA in 35 patients, on regular treatment, after a median follow-up of 13.5 months. Arterial wall thickening was still present in 17 patients (68% of the patients who initially had LVV). The number of affected segments and wall thickness at various aortic segments significantly decreased and no patients developed new lesions, new aortic dilation or increase in previous dilation. Contrast enhancement, indicating a decrease in inflammation disappeared in 15 (93.75%) of 16 patients in whom this finding could be assessed.

In summary, these data suggest that the CT can be used at diagnosis and follow up and that especially dilatations of the thoracic aorta are detected and were found to be present already in recently diagnosed GCA patients (Table II).

MRI (A)

A number of studies have investigated the value of the MRI for diagnosing the presence of vasculitis in the cranial large vessels. In this short overview we choose to focus on the value of MRI (A) for the diagnosis of S-GCA. Koenigkam *et al.* studied the presence of extracranial involvement in patients with GCA and/or PMR and 20 controls with 3-dimensional contrast-enhanced MRA images of the aortic arch and its branches.[9] They found that the most common lesions were bilateral axillary stenosis or obstruction, observed by 2 independent readers in 8 patients (28%). Among the 19 patients with MRA lesions in the subclavian/axillary arteries, 12 (75%) had biopsy-proven GCA, but only 5 (41%) of these patients had clinical features of large artery disease. More interesting and holding a great promise for the near future is the combination of the MRI with the FDG-PET. A recent study by Einspieler *et al.* reported that a total of 16 FDG-PET/MRI and 12 FDG-PET/CT examinations performed in 12 patients with LVV,[10] Total Body Ratios (TBRs) and standardized uptake value (SUV_{max}) values and visual scores correlated well between FDG-PET/MRI and FDG-PET/CT. In the combined FDG-PET/MRI, FDG-PET alone revealed abnormal FDG uptake in 86 vascular regions and MRI/MRA indicated 49 vessel segments with morphological changes related to vasculitis, resulting in a total number of 95 vasculitis regions in combination with FDG-PET.

In summary, the MRI is able to pick up inflammation and stenosis of the aorta and it's main braches. With the combination of the MRI with the FDG-PET there was an increase in the detection of involved vessels from 86 vascular regions detected with the FDG-PET alone to 95 vascular regions, when the MRI and the FDG-PET were combined (Table III).

^{18}FDG FDG-PET

^{18}FDG-PET/CT is presently widely used for the diagnosis and assessment of disease activity of especially systemic GCA. FDG-PET visualizes glucose metabolism in the vessels since-FDG is taken up by cells with a high metabolic rate such as inflammatory cells in vasculitis (lymphocytes, monocytes, macrophages and

TABLE III.—*MR studies in giant cell arteritis.*

Author (ref.)	Technique	Patient characteristics	Study design	Follow-up	Diagnostic value	Damage outcome
Koenigkam [9]	**MRA 1.5 T system** (Avanto, Siemens, Medical, Solutions Erlangen, Germany or Intera, Philips Medical Systems Eindhoven, The Netherlands) Gadolinium enhanced (Gd BOPTA, Multi Hance, Bracco Imaging, SpA, Milan, Italy)	28 GCA or PMR ACR classification criteria were used for GCA (all [16] biopsy positive) and healy criteria were used for PMR N.=12 Age 69 F/M 22/6 Controls N.=20	Retrospective study By chart and imaging review **Primary outcome measure:** large vessel involvement in newly diagnosed biopsy proven GCA	Transversal	Not assessed	19 of the 28 patients had significant luminal alterations (stenosis grade >2) observed mainly in the subclavian and or axillary arteries. 2 had stenosis grade 2 of the vertebral arteries
Einspieler [10]	**PET/MRI MRA** (Siemens, Medical, Solutions Erlangen, Germany) Semiquantitative scoring; 0 no uptake, I low grade uptake, II intermediate grade uptake, III High grade uptake (higher than liver) also TBR and SUV_{max} were caculated	12 patients Age 62 F/M 10/2 GCA 10 treated patients Reference group 16	Prospective study August 2011-March 2014 **Primary outcome measure:** application of fully integrated PET/MRI in patients with LVV	Baseline	15/16 had Grade 2 to 3 PET findings and also a positive MRI	Vessel narrowing or aneurysms were found in 7 cases

Giant cells, which makes this technique useful for imaging vasculitis. Many reviews and studies on methodology have been written but there are still no existing evidence based guidelines how to analyze and interpret the scans and original and prospective data are scarce. Blockmans *et al.* published as one of the first on consecutive GCA patients who underwent a FDG-PET scan before treatment with methylprednisolone.[11]The FDG-PET scans were repeated at 3 and 6 months in case the initial FDG-PET scans showed vascular FDG uptake. The scans were scored at 7 different vascular areas and a Total Vascular Score (TVS) was calculated, ranging from 0 to 21.

At GCA diagnosis, vascular FDG uptake was noted in 29 out of 35 GCA patients, especially in the subclavian arteries (74%), but also in the aorta (>50%) and up to the femoral arteries (37%). The total vascular score decreased from a mean SD score of 7.9±5.5 at baseline to 2.4±3.5 on repeated FDG-PET scan at 3 months (P<0.0005), but did not further decrease at 6 months. Prieto-González et al studied 32 consecutive, biopsy-proven, GCA patients treated with glucocorticoids for

TABLE IV.—*PET/CT studies in giant cell arteritis.*

Author (ref.)	Technique	Patient characteristics	Study design	Follow-up	Diagnostic value	Damage outcome
Blockmans [11]	18F-fluorodeoxyglucose positron mission tomography Siemens PET HRplus scanner with an axial field of view of 15.5 cm (Siemens, Munich, Germany). PET scans were reviewed by 2 nuclear medicine specialists who were unaware f the treatment or the clinical status of the patient	35 newly diagnosed GCA fulfilling ACR 1990 criteria 33/35 TAB positive Age: 72.7 F/M: 25/10	Consecutive Recruitment May 2000 and July 2003 Primary Outcome Measure; FDG uptake in the ifferent vascular beds and in the larger joints of patients ith biopsy-proven GCA at diagnosis and after 3 and 6 months of steroid therapy	Baseline 3 and 6 months	At diagnosis, vascular FDG uptake was noted in 29 patients (83%), specially in the subclavian arteries (74%), but also in the aorta (>50%) and up to the femoral arteries (37%). Total vascular score decreased from a mean±SD score of 7.9±5.5 at baseline to 2.4±3.5 on repeat PET scan at 3 months (P<0.0005), but did not further decrease at 6 months	Not assessed
Prieto-González [12]	Hybrid PET/CT (Biograph, Siemens) and an ECAT EXACT HR+BGO PET and a helicoidal CT scanner (Somatom, Emotion). Patients fasted 4 h before injection f 370 MBq of 18F-FDG. Whole-body PET data were acquired 60 min after in three-dimensional mode and for 5 min er bed position	32 newly diagnosed GCA fulfilling ACR 1990 criteria All TAB positive. 17 used steroids, 3 days 20 controls with cancer GCA Age: 79 F/M: 23/9 20 age and sex matched controls Age: 79 F/M: 14/6	Prospective, Recruitment Nov 2006-March 2011 Primary outcome easure: FDG uptake by different ascular territories in a cohort of newly diagnosed patients and controls	Baseline	Vessel and uptake value SUV Ascending aorta 2.63±0.57 Aortic arch 2.61±0.50) Descending thoracic aorta 2.78±0.65 Abdominal aorta 2.97±0.60 Right subclavian artery 2.46±0.54 Left subclavian artery 2.26±0.56 Right carotid artery 2.33±0.52 Left carotid artery 2.32±0.51 Right axillary artery 1.21±0. Left axillary artery 1.09±0.34 Right iliac artery 2.41±0.67 Left iliac artery 2.46±0.47 Right femoral artery 1.68±0.39 Left femoral artery 1.50±0.37 Liver 2.76±0.57	Not assessed
Stellingwerff [13]	FDG PET LDCT scans were performed on a Biograph CT camera system (Siemens Medical Systems, Knoxville, TN) and were performed according to a standardized protocol (EANM Guidelines, 2010–2011)	GCA patients (12 GC naive, age: 69.6 F/M: 9/3 6 on GC Age: 69.4 F/M: 6/0 3 control groups inflammatory Age: 67.7 F/M: 15/3 therosclerotic, Age: 69 F/M: 14/5 Cancer controls Age: 58.8 F/M: 14/2	Prospective, Recruitment Nov 2009-Dec 2012 Primary outcome easure: o evaluate all elevant scoring methods for the diagnosis of GCA using FDGPET/CT in a group of well classified GCA patients compared with 3 different control groups.	Baseline	SUV_{max} Liver 3.010±0.52 Inferior caval vein 2.26±0.73 Superior caval vein 2.13±0.45 *Aorta ascendens* 3.17±0.64 *Aorta arcus* 2.87±0.62 *Aorta descendens* 3.32±0.77 Abdominal aorta 3.67±1.21	Not assessed

≤3 days and compared the data with 20 controls, who underwent FDG-PET/CT for cancer staging.[12] SUV_{max} was calculated at four aortic segments, supra-aortic branches and iliac-femoral territory. They found that the mean SUVmax was significantly higher in patients compared to controls in all vessels explored. In line with this study Stellingwerf *et al.* recently reported on FDG FDG-PET/CT scans of GCA patients (12 glucocorticoid-naive, 6 on glucocorticoid treatment) and 3 control groups (inflammatory, atherosclerotic, and normal controls).[13] They found that the number of vascular segments with diffuse FDG uptake patterns was significantly higher in GCA patients without glucocorticoid use compared to all control patient groups. They also found that the *arcus aortae*, ascending, descending and abdominal aorta showed an increased uptake especially in the newly diagnosed GCA patients before start of steroids.

In summary, the FDG-PET is an excellent tool for diagnosing systemic vessel inflammation, drawbacks are the limited capacity to detect involvement of cranial vessels and the rapid decrease in sensitivity after steroid treatment (Table IV).

Vascular damage

Damage assessment in GCA has been performed in the past with a combination of techniques. Martínez García *et al.* studied fifty-four patients with GCA (14 men and 40 women) after a median follow up of 5.4 years (range 4.0-10.5 years) after onset of GCA.[14] The screening protocol included a chest radiograph, abdominal ultrasound, and CT scan when aortic aneurysm was suspected or changes with respect to the baseline chest radiograph were observed. Significant ASD was defined as focal dilatation (saccular or fusiform aneurysm) or, in case of diffuse dilatation, when the aortic diameter exceeded 4 cm at the ascending aorta or reached at least 4 cm in the aortic arch/descending aorta or 3 cm at the abdominal aorta. They found significant aortic structural damage (aneurysm/dilatation in12 patients (22.2%) and 5 of them were candidates for surgical repair. Aortic aneurysm/dilatation was found more frequent in men (50%) than women (12.5%). In 2014 they published their follow up data of the same group and published that 12 (33.3%) of the 36 patients rescreened (after 4 years) developed structural damage mostly in the thoracic aorta.[15] Sixteen (29.6%) of the initial cohort developed damage affecting up to 33.3% after long term follow-up (after 10 years). They also found that aortic diameters at the ascending and descending aorta significantly increased over time and also that at the time of the damage assessment the GCA was in remission. However, aortic dilatation and aneurysms are also prevalent in the general older population and the study presented no comparable controls.

Kermani *et al.* reported that in a population-based incident cohort of patients diagnosed with GCA with a median length of follow-up of 8.8 years that the cumulative incidence of any large vessel (LV) manifestation at 10 years was 24.9% for patients diagnosed with GCA between 1980 and 2004.[16] The incidence of any LV event was high within the first year of GCA diagnosis. The incidence of aortic aneurysm/dissection increased 5 years after GCA diagnosis. They also found that among patients with GCA, aortic manifestations were associated with increased mortality (HR=3.4; 95% CI 2.2 to 5.4) This was also confirmed by a recent meta-analysis performed by Mackie *et al.* in which they reported that based on the analyses of routinely collected administrative data that there is a threefold risk of TAA/dissection in GCA compared with controls. They concluded that on average, five to ten patients with GCA would need aortic imaging to detect one previously unknown TAA/TAD.[17] Robson *et al.* found in a later study and in a different population a twofold increased risk.[18] They used the UK General Practice Research Database parallel cohort study and studied 6999 patients with GCA and 41; 994 controls, matched on location, age and gender. This twofold risk, however, should be considered within the range of other risk factors including male gender, age and smoking. The protective effect of diabetes in the development of aortic aneurysms in patients with GCA was also demonstrated in their study.

Concluding, there seems to be an increased risk of aortic damage in patients with GCA (Table V).

Discussion

Imaging is an important tool for both diagnosis and damage assessment in GCA. Much progress has been made in the recent years especially in the application and standardization of the ultrasound in GCA. Besides, the FDG-PET/CT is nowadays widely accepted and

TABLE V.—*Vascular damage in giant cell arteritis.*

Author (ref.)	Technique/methods	Patient characteristics	Study design	Follow-up	Vascular damage
Garcia Martinez [14]	Chest radiograph, abdominal ultrasound, CT when indicated	54 patients with GCA Age: 79 F/M: 40/14 No controls	Cross sectional screening of prospectively followed patients 2000-2005 Primary outcome measures: aortic damage at follow-up	Long term follow-up 5.4 (4-10.5 y)	Long-term follow-up 5.4 years 12 pts (22,2%) had structural aortic damage, 5 patients candidates for surgical repair
García-Martínez [15]	Chest radiograph, abdominal ultrasound, CT when indicated	54 patients with GCA Age: 79 F/M: 40/14 No controls	Cross sectional screening of prospectively followed patients Primary outcome measures: aortic damage at follow-up	Long term follow-up N.=36 8.7 (6.9-13.6 y) N.=14 12.8 (10.3-16)	Long-term follow-up 12.8 years 12 (33.3%) of the 36 patients who completed the second or third screenings and 16 (29.6%) of the 54 patients encompassing the initial cohort, developed structural damage
Kermani [16]	Imaging, histopathological or autopsy proven stenosis, aneurysm or dissection/rupture	204 patients with GCA diagnosed between 1950 and 2004 Age at diagnosis: 76 F/M: 163/41	Primary outcome measures: Incidence LV manifestations and survival	Long-term follow-up. Median length: 8.8 years	Long-term follow-up Cumulative incidence of LV manifestations was 24.9% Survival was decreased in aortic aneurysm or dissection, but not in stenoses Aortic manifestations were associated with increased mortality (HR=3.4; 95% CI 2.2 to 5.4)

used as a diagnostic tool in S-GCA. CTA seems superior with respect to damage assessment. MRI (A) is an upcoming technique, and may in the near future, especially in combination with a FDG-PET be used not only for making a diagnosis but also for determining disease extent and disease activity and investigating damage in both C-GCA and S-GCA.

For cranial GCA, CDUS seems the best imaging technique, which is easily accessible, has a low cost and has no side effects. Since patients without cranial symptoms may have involvement of the cranial vessels, it is advised that all patients suspected of having GCA have to undergo a CDUS. Importantly, the persons performing the CDUS must be trained to perform a standardized CDUS of the temporal, carotid, subclavian, axillary and brachial arteries.[5] Especially the axillar artery ultrasound was documented to increase the yield of S-GCA.[3]

CT can be useful in diagnosing GCA. Especially an increase in thickness of the aortic wall in combination with vascular wall enhancement is indicative of an active vasculitis of the vessel wall. A drawback is the relative high irradiation dose and the risk of contrast-induced side effects in the elderly GCA patients.[14] For estimating outcome or vascular damage this technique is excellent, but for screening purposes less expensive modalities such as a chest X-ray and ultrasound of the abdominal aorta seem more appropriate.[19] The MRI (A) combines imaging of the vascular luminal pathology with mural thickening and enhancement reflecting inflammation

With the use of the FDG-PET it possible to identify the focus of inflammation. FDG-PET may therefore diagnose GCA at an earlier stage than MRA or CTA and seems superior especially in the combination with a low dose CT for diagnosing S-GCA. Low dose CT can also be used to evaluate atherosclerosis that may partly interfere with vascular wall FDG activity. Due to the high physiological uptake by the brain and the limited spatial resolution the FDG-PET is not suitable for assessment of the cranial large vessels.[13]

An important finding or limitation is that all imaging techniques (CDUS, CT(A), MRI(A), FDG-PET) are highly influenced by the use of corticosteroids. Ideally, imaging should be performed before start of corticosteroids.[4, 11, 15] Another major point is that the lack of standardized guidelines on how and when to apply the different imaging modalities makes it difficult to decide which imaging techniques (CDUS, CT(A), MRI(A), FDG-PET) should be used for making a definite diagnosis of both cranial and systemic GCA.[20] In line with this,

the interpretation of data from imaging studies in GCA are hampered by the scarcity of prospective studies presenting original data, the heterogeneity of the GCA populations examined in each study and the variety in the use of qualitative and semi-quantitative methods for imaging analyses.

The long-term consequences of vascular inflammation in C-GCA and S-GCA are not entirely clear. It is known that vessel wall inflammation may lead to intimal hyperplasia and subsequent stenosis, as well as to changes in vessel wall architecture and possible aneurysm formation. In case of GCA, aortic inflammation seems to be frequent but is mostly asymptomatic unless vessel wall damage leads to dissection, aneurysms or aortic valve dysfunction. Stenosis is thought to occur mainly in an early stage of the disease, whereas aneurysms seem to occur at later stages, even after years of follow-up. From the studies presented it is difficult to derive a complete picture. For instance, in most CDUS studies the vertebral arteries were not evaluated, and the cranial vessels were not assessed in the CT studies. Based on epidemiological studies one could state that there is an increased risk of aortic damage in patients with GCA and that screening for aneurysms should be performed. Which techniques that should be used for screening and how often GCA patients should be screened is still a matter of debate. In the British Society of Rheumatology Guidelines it is stated that every two years a chest radiograph should be performed to monitor for aortic aneurysm.[19] However, it is unclear whether chest radiography is a sufficiently sensitive as screening tool.[17] Robson *et al*. suggested in their recent study based on data from the UK General Practice Research Database that the National Health Service AAA Screening program which screens (US) all men at the age of 65 years might detect most aneurysms especially in persons with an increased risk (male gender, ex- or current smoker, use of anti-hypertensive drugs, cardiovascular disease) and that a separate screening program is not necessary.[18] Thus, in order to elucidate this item, more research needs to be performed. Also, as advised by Mackie *et al*. before ordering imaging, clinicians should consider whether, and how, detecting aortic pathology would affect the patient's management.

Based on the data derived from the presented articles we state that (Table VI):

1. CDUS is valuable for investigating not only the cranial vessels but also the carotid, subclavian, axillary and brachial vessels in patients suspected of GCA;
2. CTA is an excellent tool for assessment of damage in GCA;
3. MRA, especially combined with FDG-PET can assess both cranial and systemic vessels;
4. the FDG-PET/CT is the preferred technique when systemic vessel inflammation is suspected or when a patient presents with fever and with a variety of nonspecific symptoms fitting with GCA to diagnose or exclude GCA;
5. vigilance and screening for aortic aneurysms should be considered in all patients with proven GCA. The time points and optimal techniques used for screening of thoracic aneurysms is still a matter of debate.

Important to mention is that at this moment it is difficult to achieve evidence based data since most of the included and performed studies in patients with GCA consist of heterogeneous groups of patients that were

TABLE VI.—*Overview of the advantages and the disadvantages of the techniques used.*

Imaging	Advantage	Disadvantage
CDUS	Easy accessible Non-invasive Indicates optimal biopsy location	Not suitable for all vessels
CT-A	Highly useful for imaging outcome and vascular damage	Less useful for diagnosis and imaging vessel involvement High irradiation dose Risk of contrast-induced nephropathy
MRA	Combines metabolic with anatomical information	Less sensitive than PET/CT as found by Einspieler *et al.*
PET-MRA	Less irradiation	
FDG-PET	More accurate than MRI in visualizing metabolic changes; Visualized extent of disease	All vessels are visualized Less useful for leg arteries Not useful for cranial arteries
FDG PET-CT	Excellent combination of metabolic changes with anatomical morphology such as stenosis and calcifications	Irradiation dose Less useful for cranial arteries

scanned at different time points (before, during and after treatment), with or without the use of steroids and with different techniques and equipment. Moreover, the fast development of imaging techniques precludes a good comparison between the different studies. More research is clearly needed and international initiatives on standardization for the CDUS (TABUL Study) and FDG-PET fortunately are underway.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.
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