UNIVERSITA' DEGLI STUDI DI PAVIA
DOTTORATO IN MEDICINA SPERIMENTALE

Novel Diagnostic and Prognostic Approaches to Systemic Vasculitides

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Outline

Abstract

Background. Giant cell arteritis (GCA) is the most common primary systemic vasculitis. GCA represents a medical emergency. Prompt recognition and treatment are pivotal to prevent irreversible ischaemic complications. The management of GCA has gone through a number of paradigmatic changes in the last few years, including novel diagnostic approaches and treatment options.

Objectives. During the course of this 3-year PhD programme, we aimed at investigating and improving the management of GCA by: (i) assessing the impact of the fast track ultrasonographic clinic of the Rheumatology Department, IRCCS Policlinico S. Matteo, University of Pavia on the risk of permanent visual loss and future relapse; (ii) evaluating the role of quantitative ultrasound assessment in terms of diagnostic and prognostic outcomes in GCA in an International study in collaboration with the University of Oxford; (iii) contributing to the update of the European recommendations on the management of large vessel vasculitis (LVV) by leading on the systematic literature review and participating in the recommendations development process.

Methods. Patients referred for suspected GCA to the fast track assessment clinic (FTA) of the Department of Rheumatology of the IRCCS Policlinico S. Matteo, University of Pavia, Italy, between October 1st, 2016 and June 30th, 2020 were recruited if a diagnosis of GCA was confirmed. The activity of the clinic was significantly modified by the severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) epidemics, therefore, patients assessed from March 2020 to June 2020 were considered separately. Frequency of permanent visual loss (PVL), relapse risk and large vessel (LV)-complications during follow-up were assessed.

The role of quantitative ultrasound findings data was assessed, in collaboration with the University of Oxford, from the data of a large cohort study: The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL Study). The FTA cohort of the University of Pavia has been included as an independent validation cohort. Patients with a positive colour duplex sonography (CDS) and a confirmed final diagnosis of GCA were included. Quantitative ultrasound data [number of sites with halos, intima-media thickness (IMT), presence of bilateral halos] at the level of the temporal arteries (TA) and axillary arteries (AX) were assessed. Ultrasound models were combined with clinical information models against two main outcomes: biopsy outcome [temporal artery biopsy (TAB) diagnostic for GCA] and the clinical outcome [visual sequelae and need for more intense immunosuppressive treatment at 6 months].

Two systematic literature reviews (SLR) were performed by searching MEDLINE, EMBASE and Cochrane CENTRAL library to retrieve the available evidence on diagnosis/monitoring and treatment strategies of LVV. An International task force approved by the European League Against Rheumatism (EULAR) was created to update the recommendations on the management of LVV based on the evidence produced by the SLRs.

Results. The GCA cohort included 160 patients [female 120 (75%), mean age 72.4±8.2 years]. Sixty-three (39.4%) evaluated with FTA, 97 (60.6%) with conventional approach. Since the introduction of FTA the need for TAB reduced by 93%. Median follow-up duration was shorter in the FTA group compared to the conventional one (0.9 vs. 5.0 years; $p<0.001$). Permanent visual loss (PVL) occurred in 8 (12.7%) FTA patients and 26 (26.8%) conventional ones ($p=0.03$). Median symptom latency of patients experiencing PVL was higher in the conventional group (23 days IQR 12-96 vs. 7 days IQR 4-10, $p=0.02$). During COVID-19 there was a significant increase in the occurrence of PVL (40%) including bilateral blindness despite a regularly operating FTA clinic. Cumulative incidence of relapses and time to first relapse did not change after FTA introduction. No difference in late complications (stenosis/aneurysms) was detected.

With the second part of our study on the role of ultrasound in the assessment of GCA we explored the value of evaluating the extent of disease with quantitative ultrasound findings. Quantitative ultrasound data were evaluated on 135 GCA patients from TABUL [female 92 (68%), age 73±8 years] and 72 patients from the independent cohort [female 33 (46%), age 75±7 years]. The best-fitting CDS model for TAB used maximum IMT and bilaterality of TA and AX halos. The best-fitting clinical model included raised inflammatory markers, polymyalgia rheumatica, headache and ischaemic symptoms. By combining CDS and clinical models a score to calculate the probability of having a positive TAB, given the ultrasonographic and clinical information, was derived. Model discrimination was fair (area under the receiver operating characteristic curve 0.77, 95% CI: 0.68, 0.84). No significant association was found for prediction of clinical outcome at 6 months.

The SLRs to inform the update of the European recommendations on the management of LVV confirmed the need to urgently refer the patient to a specialised team, including FTA clinics, to integrate CDS as the first confirmatory diagnostic tool in in centres with the adequate expertise in the management of this systemic vasculitis. The results of the SLR further confirmed the value of our previous two studies supporting the role of CDS in the daily management of GCA. The main treatment for LVV remain high-dose GC, however, more evidence has been retrieved to support the use of adjunctive immunosuppressants, including novel biologic treatments for GCA.

Conclusion. With our studies we have contributed to clarify the role of novel diagnostic approaches to the disease as part of fast track clinics and supported the role of ultrasound as a reliable diagnostic

tool. Our results confirm the advantages of implementing FTA including the use of ultrasound in the early diagnosis of GCA to significantly reduce the risk of permanent blindness. A quantitative ultrasound analysis (extension and degree of vascular involvement) supported by clinical findings is useful to identify patients with a positive biopsy, supporting the use of CDS as a surrogate tool to replace TAB. Relapse rate and LV-complications did not change upon FTA introduction, highlighting the need for better disease activity monitoring strategies and risk stratification at disease onset that would predict the occurrence of relapse. We did not demonstrate a prognostic value of quantitative ultrasound data in the short-term. Changes in diagnostic and therapeutic approaches to GCA were systematically reviewed and contributed to the update of the European recommendations on the management of LVV. The review highlighted some unresolved issues in terms of the prognostic stratification, optimal monitoring tests, ability to detect complications and treatment options which will need to be addressed by further studies.

1. Introduction

1.1 Systemic vasculitides

Systemic vasculitides (SV) are a group of rare diseases characterized by inflammation of vessel walls. SV can potentially affect any age groups and may present with a highly heterogenous clinical picture. Manifestations depend on the caliber of affected blood vessels, type of organs involved, underlying immunoinflammatory process, and individual host factors. Vessel wall inflammation causes endothelial disfunction, reduced blood flow and eventually vascular occlusion with potentially irreversible ischaemia, necrosis, and tissue damage.

Primary SV include a variety of clinical entities of unknown etiology but with well-defined clinical, pathological and therapeutic features. On the other hand, secondary vasculitis can be caused by another concomitant inflammatory disease, a neoplastic condition, a drug-induced adverse reaction, or an infection.

SV are defined according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature (1). SV can be categorized based on the predominant caliber of the vessels involved (large vessels, medium vessel, and small vessel vasculitis). Figure 1. Differences in the categorization reflect specific knowledge about etiology, pathogenesis, pathologic changes, demographics and clinical expression. Importantly, apart from categorization purposes, it is key to consider that vasculitis of can affect arteries of any size and that medium and large vessel vasculitis can often affect small arteries (1).

Large vessel vasculitis (LVV) predominantly affect large arteries (the aorta and its major branches) and is represented by giant cell arteritis (GCA) and Takayasu arteritis. The small vessel vasculitides (SVV) are divided into two categories, depending on the presence of immune deposits: immune

complex small vessel vasculitis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). AAV is a necrotizing vasculitis with few or no immune deposits mainly affecting small vessels, possibly associated with ANCA specific antibodies. The main clinical variants of AAV are: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA). Immune complex small vessel vasculitis is characterized by deposits of immunoglobulin and/or complement at the level of capillaries, venules, arterioles and small arteries. Immune complex vasculitis can be classified based on the possible etiology (e.g. hepatitis C virus associated cryoglobulinemic vasculitis) or a vasculitis secondary to a systemic disease (e.g. lupus or rheumatoid arthritis). Further types of SVV are anti-glomerular basement membrane disease, IgA vasculitis or hypocomplementemic urticarial vasculitis.

The main clinical entities considered as medium vessel vasculitis are polyarteritis nodosa and Kawasaki disease. Finally, some diseases may affect vessels of any caliber and are defied as variable vessel vasculitis, including Behçet's disease or Cogan's syndrome. The revised Chapel Hill nomenclature list is presented in Table 1.

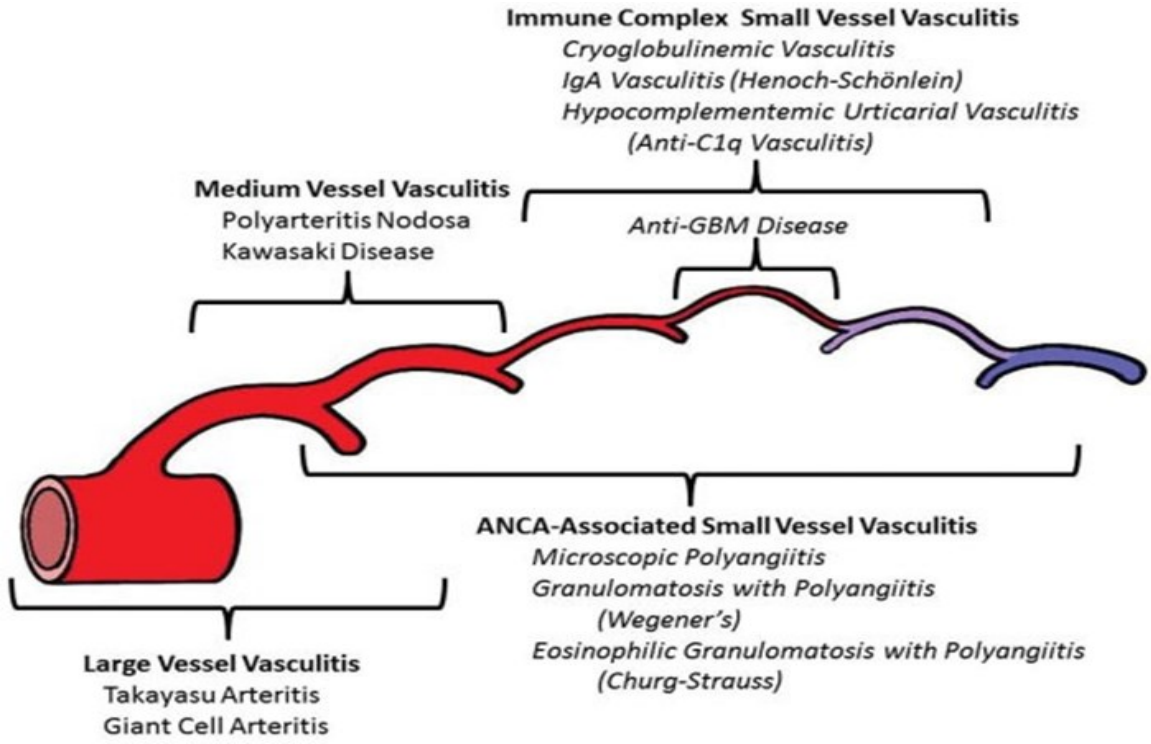


Figure 1. Distribution of vessel involvement by large vessel vasculitis, medium vessel vasculitis, and small vessel vasculitis according to 2012 Chapel Hill Consensus Conference (1).

Table 1. Revised International Chapel Hill Consensus Conference Nomenclature of vasculitides adapted from Jennette et al. 2013 (1).

Large vessel vasculitis
Takayasu arteritis
Giant cell arteritis
Medium vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Small vessel vasculitis
ANCA-associated vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Immune complex small vessel vasculitis
Anti-glomerular basement membrane disease
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch-Schönlein)
Hypocomplementemic urticarial vasculitis (anti-c1q vasculitis)
Variable vessel vasculitis
Behçet's disease
Cogan's syndrome
Single organ vasculitis
Cutaneous leucocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
Other
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
Vasculitis associated with probable aetiology
Hepatitis C virus-associated cryoglobulinaemic vasculitis
Hepatitis B virus-associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated AAV
Cancer-associated vasculitis
Others

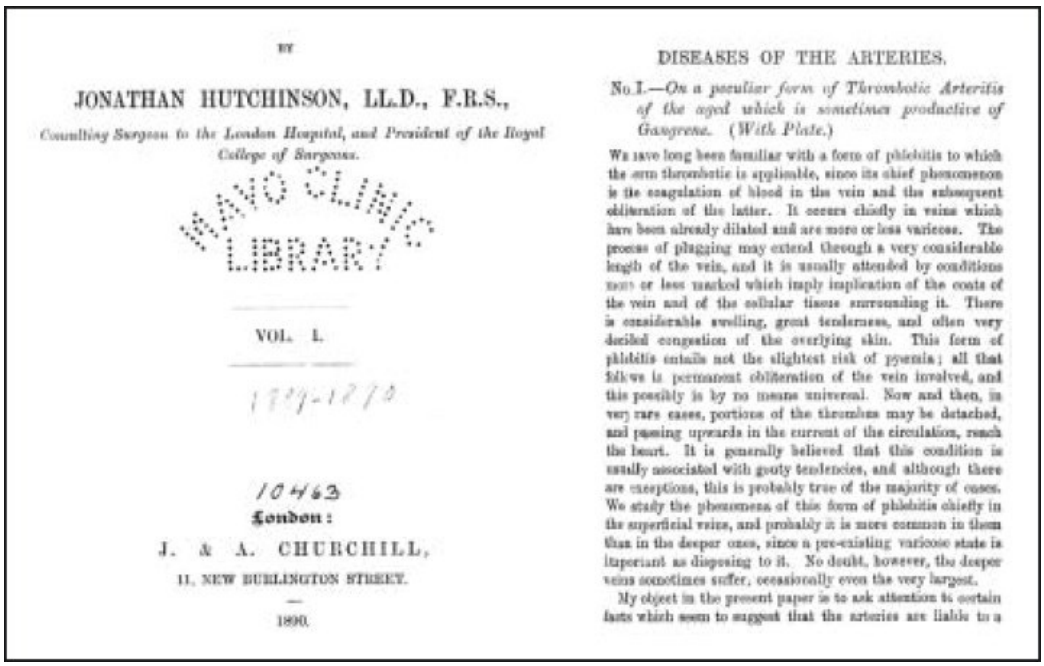
AAV:ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody

1.2 Giant cell arteritis

Giant cell arteritis (GCA) is a rare disease characterised by chronic inflammation of the vascular wall. GCA belongs to the group of large vessel vasculitides and predominantly affects the aorta and its major branches, particularly the extracranial branches of the external carotids including the temporal and the vertebral arteries. Medium and small arteries (e.g. ophthalmic, retinal and ciliary arteries) can often be affected and are responsible for the most severe complication of the disease: irreversible visual loss.

1.2.1 Historical background

The first report of the disease is attributed to Jonathan Hutchinson in 1890, a surgeon who described the case of "an old man with red streaks on his head which were painful and prevented his wearing his hat. The red streaks proved, on examination to be his temporal arteries which were found to be inflamed and swollen. During the first week of observation pulsation could be feebly detected in the affected vessels, but it finally ceased. The old gentleman lived" (2,3).



BY

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VOL. I.

London:

J. & A. CHURCHILL,

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1890.

DISEASES OF THE ARTERIES.

No. I.—*On a peculiar form of Thrombotic Arteritis of the aged which is sometimes productive of Gangrene.* (*With Plate.*)

We have long been familiar with a form of phlebitis to which the term thrombotic is applicable, since its chief phenomenon is the coagulation of blood in the vein and the subsequent obliteration of the latter. It occurs chiefly in veins which have been already dilated and are more or less varicose. The process of plugging may extend through a very considerable length of the vein, and it is usually attended by conditions more or less marked which imply implication of the coats of the vein and of the cellular tissue surrounding it. There is considerable swelling, great tenderness, and often very decided congestion of the overlying skin. This form of phlebitis entails not the slightest risk of pyæmia; all that follows is permanent obliteration of the vein involved, and this possibly is by no means universal. Now and then, in very rare cases, portions of the thrombus may be detached, and passing upwards in the current of the circulation, reach the heart. It is generally believed that this condition is usually associated with gouty tendencies, and although there are exceptions, this is probably true of the majority of cases. We study the phenomena of this form of phlebitis chiefly in the superficial veins, and probably it is more common in them than in the deeper ones, since a pre-existing varicose state is important as disposing to it. No doubt, however, the deeper veins sometimes suffer, occasionally even the very largest.

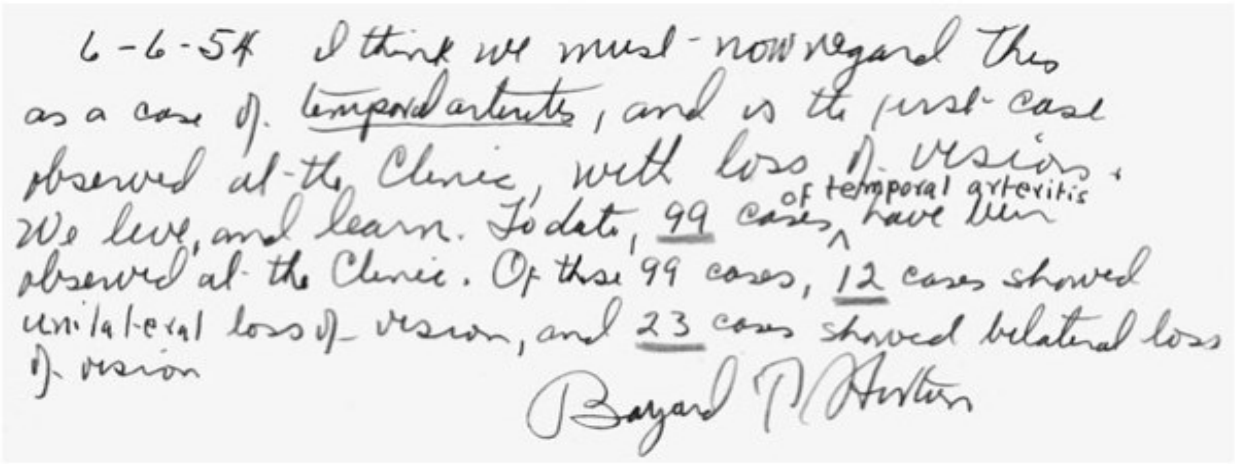
My object in the present paper is to ask attention to certain facts which seem to suggest that the arteries are liable to a

Figure 2. First description of the case of a patient with giant cell arteritis made by the surgeon Jonathan Hutchinson in 1890 (3).

Hutchinson appropriately defined the case as a peculiar case of thrombotic arteritis of the aged. Bayard Horton was the first to describe the histopathology of temporal arteritis.

In 1932 he described two patients with "an undescribed form of arteritis of the temporal vessels" (4). The disease was long known as Horton's arteritis. In 1937 seven cases reporting systemic symptoms, headache, fever, anaemia and jaw claudication were reported. Temporal artery biopsy showed granulomatous inflammation with giant cells and the condition was defined as a new type of vasculitis called temporal arteritis.

In 1941 it became more evident that similar pathological findings could be found also at the level of different extra-cranial large vessels, including the aorta and the term "giant cell arteritis" was introduced.


6-6-54 I think we must now regard this as a case of temporal arteritis, and is the first case observed at the Clinic, with loss of vision. We live and learn. To date, 99 cases of temporal arteritis have been observed at the Clinic. Of these 99 cases, 12 cases showed unilateral loss of vision, and 23 cases showed bilateral loss of vision

Bayard T Horton

Figure 3. Medical notes from Bayard Horton who first desribed the histopathological findings of „an undescribed form of arteritis oft he temporal vessels" (4).

In 1946 Kilbourne and Wolff observed the involvement of multiple cranial vessels proposing the nomenclature "cranial arteritis" (2). The disease was addressed with these different proposed definitions until the definitive consensus on the nomenclature of SV held in Chapel Hill in 2012.

Temporal arteritis was not considered a suitable term anymore since the acknowledgement that the disease may not always affect the temporal arteries (1).

1.2.2 Classification criteria

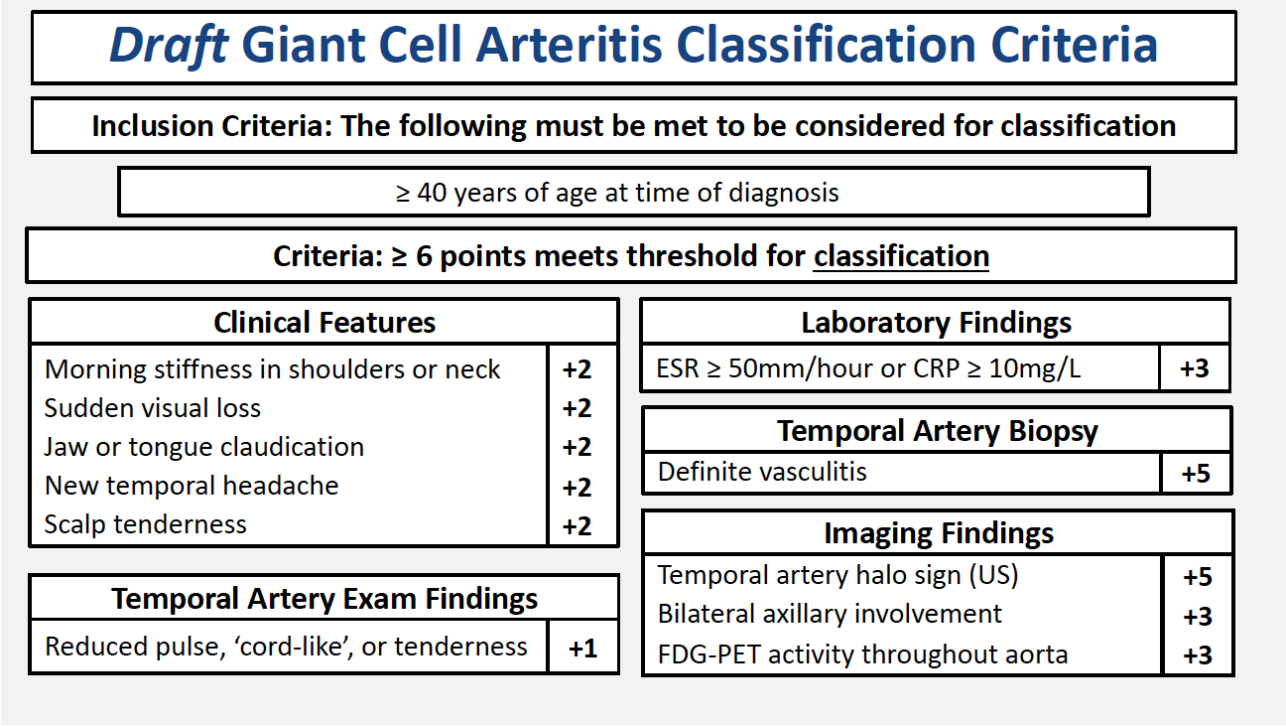
The classification criteria and subsequent updates reflect the historical evolution of the disease concept, initially considered to be a disease of the temporal arteries until it became clear that the disease can affect multiple cranial and extra-cranial arteries and is by all means a form of large vessel vasculitis. The original set of classification criteria were defined in 1990 by the American College of Rheumatology (ACR) (5). GCA can be classified if at least 3 out of 5 criteria are met. Table 2. Recently, a new set of ACR/EULAR endorsed criteria are being developed to overcome the limitations of the original set of 1990 ACR criteria and to include in the assessment of the disease newer diagnostic modalities (e.g. imaging) and represent more comprehensively the current knowledge of this SV. The new ACR/EULAR criteria have been developed through an enormous effort to collect a significant amount of clinical data of real patients diagnosed with GCA all over the world and of comparators conditions that could act as cofounders. The project is known as the Diagnostic and Classification Criteria in Vasculitis (DCVAS) and has collected data on 6991 patients with SV from 32 different Countries (6). The updated classification criteria for GCA are still a preliminary draft, however, they will comprise a scoring system taking into account different clinical, laboratoristic and radiological or pathological features of GCA. Table 3.

Table 2. American College of Rheumatology 1990 classification criteria for GCA (5).

Criterion	Definition
1. Age at disease onset ≥50 years	Development of symptoms or findings beginning at age 50 or older
2. New Headache	New onset of or new type of localized pain in the head
3. Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
4. Elevated erythrocyte sedimentation rate	Erythrocyte sedimentation rate ≥50mm/hour by the Westergren method
5. Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

For purpose of classification, a patient shall be said to have giant cell (temporal) arteritis if at least 3 of these 5 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%

*Table 3. Draft of the new ACR/EULAR classification criteria for GCA**



**Courtesy of Dr. Cristina Ponte, Rheumatology Department University of Lisbon, and Prof. Raashid Luqmani, Rheumatology Department University of Oxford*

1.2.3 Epidemiology and clinical characteristics

GCA is the most frequent type of SV in Caucasian. The disease typically affects adults above the age of 50 years with a peak incidence in the 7^{th}-8^{th} decade. GCA is more common in women than in men with a ratio of 3:1 (7). The literature suggests an increase in incidence with latitude, being maximum in the Northern hemisphere. In these regions, the annual incidence rates are 17/100,000 people per population age ≥ 50. In Southern European countries the incidence has been reported to be 12/100,000 (7). In Italy the incidence has been studied in the Reggio Emilia area (8). Over a 26-year period the incidence was 5.8/100,000 people aged ≥ 50 years. The study confirmed the female predominance (7.8 vs 3.3/100,000 ≥50 years of age, respectively) and a peak in the age range 70-79, with an average age at diagnosis of 74.4. The trigger of the disease is still unknown. Several infectious agents have been possibly associated (e.g. Mycoplasma pneumoniae, parvovirus B19, Chlamydia pneumoniae) (9). In recent years contradictory reports have suggested an association between herpes zoster virus infection and the occurrence of GCA. Nevertheless, a clear causative relationship has not been confirmed and further studies are needed to clarify the hypothesis (10–14). A seasonal distribution of GCA has also been proposed with controversial findings and reported peaks in late winter and autumn, but also during the summer months (7,15).

The onset of GCA is usually acute or subacute. The hallmark of GCA is the new onset of severe headache that, although being more typically located over temporal areas, it can be widespread or occipital. Other cranial symptoms such as visual complaints including amaurosis fugax, diplopia, or visual loss (10-30%), jaw claudication (50%) and tongue claudication, scalp tenderness increase the likelihood for diagnosis. Jaw claudication is believed to be caused by ischaemia of the masseter muscles, leading to pain when chewing or talking which reduces with rest.

Amaurosis fugax, diplopia, tongue pain or necrosis and jaw claudication are typical symptoms that may precede visual loss in GCA. Blindness due to GCA was reported with frequencies as high as

35% in the past, however, in recent years the risk for permanent visual loss is decreasing thanks to a better recognition of the disease and the introduction of fast-track GCA clinics including the use of imaging modalities (16–19). There is a 50% risk of contralateral blindness, usually within a few days from visual impairment occurrence, hence the need for urgent treatment initiation.

Anterior ischaemic optic neuropathy (AION), caused by occlusion of the posterior ciliary arteries, is the most frequent ischaemic complication responsible for visual loss, with the fundoscopic examination showing pale optic disc oedema. Less frequently, visual loss may occur due to posterior ischaemic optic neuropathy (PION), arterial occlusion of the central retinal artery or cilioretinal vessels, or occipital cortex infarction (20,21). Strokes or transient ischaemic attacks, most often occurring in the vertebrobasilar territory, have been reported in up to 11% of patients with GCA (22–29). Inflammation of the intracranial arteries is exceedingly rare (30).

Other ischaemic manifestations of GCA are tongue and scalp necrosis (31).

Polymyalgia rheumatica (PMR) is encountered in 40-60% of patients with GCA at diagnosis, while 16-21% of patients with PMR may develop GCA. Imaging techniques using vascular ultrasound and/or PET-CT have demonstrated evidence of subclinical large vessel involvement in up to 80% of GCA patients at diagnosis. Among patients with PMR, one third has signs of LVV on imaging (16,32).

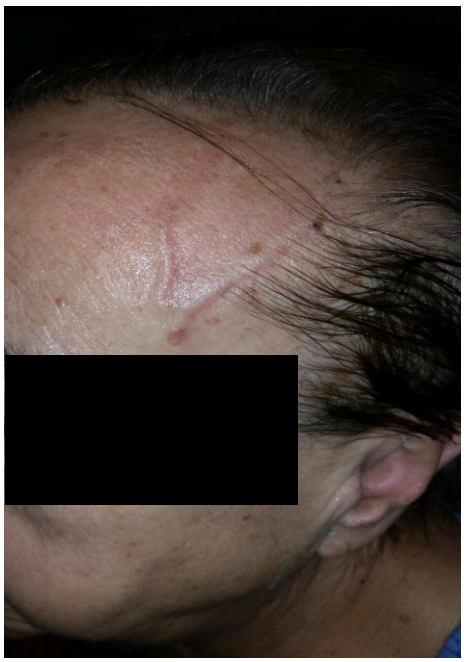


Figure 4. Swollen temporal artery of a patient with GCA

Constitutional symptoms (fever, malaise, anorexia, weight loss) are common, occurring in up to 50% of patients with cranial GCA and possibly representing the only symptoms (in about 15% of cases) in patients with large vessel (LV)-GCA.

Other less common symptoms include arms/legs claudication, and back or chest pain due to aortitis or aortic dissection. Unproductive cough and hoarseness may be rarer features of LVV (33,34). On examination heart murmurs, arterial bruits or decreased/absent pulses can be detected (35,36).

Patients with LV-GCA are usually younger and suffer from a more prolonged diagnostic delay compared with the classical cranial form of the disease. LV-GCA have less (or no) cranial symptoms and permanent vision loss (37–39).

The risk of aortic aneurysms is increased in patients with GCA (40,41). Aneurysms are usually a late complication of GCA, and need to be excluded even after 5-7 years from the diagnosis (42,43). Dissection or rupture of the aorta is reported in 1-5% of patients, mainly at the level of the ascending thoracic aorta (42,44–46).

1.2.4 **Diagnosis**

There are no diagnostic criteria for GCA and the diagnosis is based on a combination of symptoms, clinical findings, laboratory results, and the support of histological or imaging changes. Clinical findings detectable on physical examination in patients with suspected cranial GCA are the presence of thickened, nodular, tender frontal or parietal branches of the superficial TA. Pulses may be decreased or absent (34). Patients with LV-GCA may have decreased pulses or bruits on accessible large vessels (47), or display the signs of systemic involvement (weight loss, fever) (16). Laboratory findings reflect the systemic inflammatory nature of the disease. Acute phase reactants (ESR and CRP) are typically elevated, nevertheless, a normal ESR does not exclude GCA in the presence of characteristic clinical symptoms (48). CRP is more sensitive in detecting disease activity, and together with thrombocytosis has been reported as the strongest predictor of positive TA biopsy (49). Anemia of chronic diseases has been described in half of the patients at diagnosis. A mild elevation of liver enzymes, particularly alkaline phosphatase has also been described (34,48).

Temporal artery biopsy

The gold standard for diagnosis has been for many years temporal artery biopsy (TAB), but, although highly specific, it lacks adequate sensitivity and can yield false negative results in up to 60% of cases, due to delay in performing the test following initiation of glucocorticoids (GC), sampling errors, or the segmented nature of the abnormalities (50). Furthermore, TAB is not free from potential complications such as haematoma, scalp necrosis, infections and neurologic damage (51).

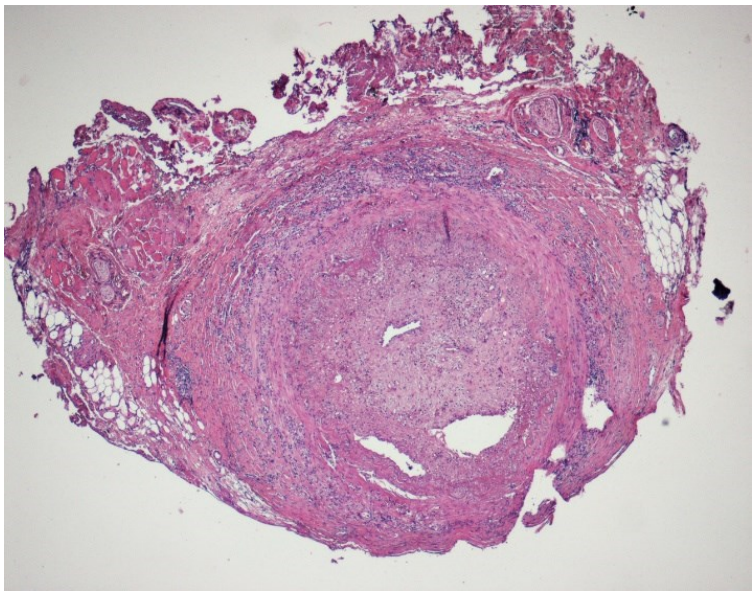


Figure 5. Temporal artery biopsy demonstrating a transmural inflammatory infiltrate with multinucleate giant cells and partial occlusion of the lumen. Image courtesy of Prof. Patrizia Morbini, Unit of Pathological Anatomy Department of Molecular Medicine, University of Pavia.

The typical histologic finding in patients with GCA is transmural inflammatory infiltrate together with fragmentation of the internal elastic lamina and detection of giant cells, more frequently at the intima-media junction. Figure 5. Giant cells can be detected, but are not necessary for the histopathological diagnosis of GCA. Histologic evidence of GCA can also be limited to periadventitial small vessel vasculitis (SVV) and/or vasa vasorum vasculitis (VVV). The length of biopsy is crucial to obtain reliable results (52). A TAB length post-fixation of at least 1.5 cm is considered an adequate sample. A tissue shrinkage post-formalin fixation of approximately 8% should be considered when sampling the artery specimen (53). The TAB should be peformed at the most symptomatic site. Ultrasound-guided biopsy has not been shown to improve diagnostic sensitivity (54). Furthermore, bilateral TAB can increase the diagnostic yield by 1-14%; therefore it is not routinely performed (55–62).

Conventional imaging

Conventional images tools are particularly indicated to detect large vessel involvement, particularly of deep arteries. Computed tomography (CT) and CT angiography (CTA) are useful to detect early changes with arterial wall thickening with mural enhancement and low-attenuation ring on delayed images. Calcifications, wall thickening with high attenuation can be seen in long-term abnormalities. Arterial stenosis, occlusion and dilatation can be visualized by CTA.

Magnetic resonance imaging (MRI) can detect wall thickening associated with oedema and mural contrast enhancement. Post-contrast T1 images are more sensible than T2 or fat-suppressed sequences, particularly to detect early signs of inflammation. MRA offers the same advantages of CTA in detecting arterial stenosis, although these can be over-estimated with MRI, occlusion and dilatation.

^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) is a particularly sensitive tool to detect early large vessel involvement. In a systematic review and meta-analysis, PET showed a sensitivity of 90% and specificity of 98% in diagnosing GCA. PET is particularly useful in those cases presenting with less typical symptoms such as fever of unknown origin or systemic symptoms (63).

Ultrasound and colour duplex sonography

Considering the drawbacks of TAB, and the limits and costs of traditional imaging techniques, efforts have been directed to finding a more accessible, rapid and less invasive diagnostic tool for GCA. Colour duplex sonography (CDS) of TA and large vessels is an emerging diagnostic tool (32). CDS can provide information about the presence of vessel wall oedema, known as a "halo", throughout the length of the vessel, potentially overcoming the problem of skip lesions often affecting the results of histological examination (64). Nevertheless, CDS use is still not widespread in routine clinical practice and requires skilled sonographers, being highly operator dependent.

Role of CDS in the diagnosis of GCA

Prompt diagnosis and treatment of GCA is important in order to prevent serious vascular complications, particularly permanent visual loss, which occurs in 15-20% of patients (31,65).

In 1997, Schmidt et al proposed the use of CDS in the diagnosis of temporal arteritis with sufficient confidence to avoid the need for TAB in selected patients (66). Figure 6.

Compared to TAB, ultrasound is a safe, well tolerated, rapid and less costly procedure. Moreover, CDS can be repeated, offers the advantage of allowing examination of the full-length superficial temporal artery (TA), and of extending the evaluation to other accessible cranial or extra-cranial vessels (67).

Since the first report from Schmidt et al. ultrasound has been applied in selected centres with high expertise in the use of this diagnostic tool. Only in the latest years there has been formal recognition of the advantages and reliability of ultrasound in the management of patients with GCA.

Five meta-analyses have confirmed the validity of CDS in diagnosing GCA (51,67–70). Table 4. The first meta-analysis of studies available through April 2004 (51) concluded that the presence of halo (overall sensitivity 69%, specificity 82% compared to TAB), stenosis or occlusion (sensitivity 68%, specificity 77%) improved the diagnostic yield for GCA, with a pooled sensitivity of 87% and a pooled specificity of 96% compared with the 1990 ACR criteria for GCA, despite significant heterogeneity between studies. In 2010, Ball and colleagues (68) analysed the results of 17 studies (n=998 participants) and concluded that CDS was relatively accurate for the diagnosis of GCA, recommending it as first-line investigation, with biopsy reserved for patients with negative sans. A third meta-analysis from Arida and colleagues (67) reported that the presence of unilateral halo sign was associated with an overall sensitivity of 68% and specificity of 91%, rising to a specificity of 100% in the presence of bilateral halos. Pooled odds ratio for a diagnosis of GCA in patients with a halo compared to those with a negative CDS was 34 (95%CI, 8.21-138.23) and increased to 65 (95% CI, 17.86-236.82) if halo was bilateral.

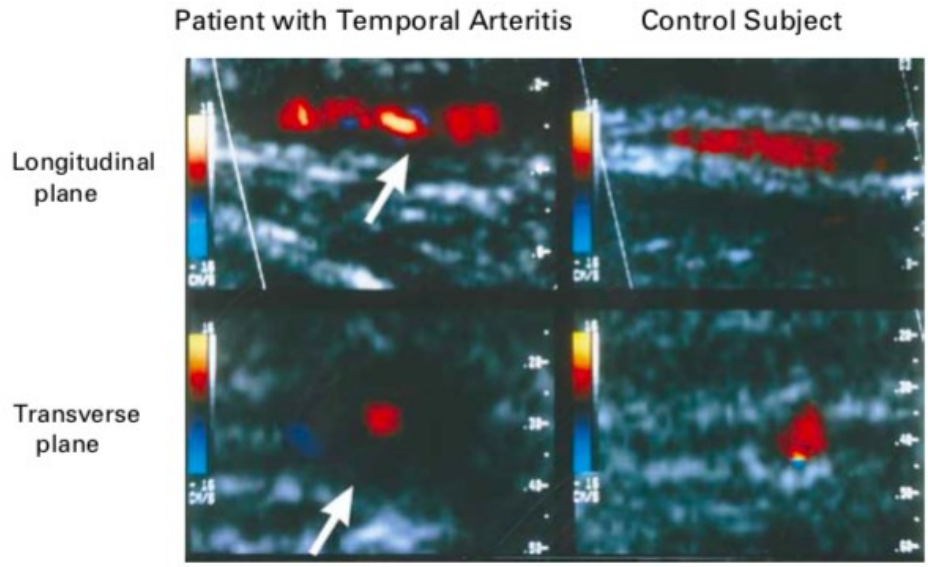


Figure 6. First description of the use of colour-duplex ultrasonography to detect temporal arteritis reported by Schmidt et al. in 1997 (66).

Another study from the same group demonstrated that, unlike halo, blood flow alterations (stenosis and/or occlusions) detected on TA were neither specific nor sensitive for GCA, being equally common among elderly individuals due to atherosclerotic changes (67,71). These findings were recently confirmed by the OMERACT task force (72).

Table 4. Meta-analyses evaluating the sensitivity and specificity of colour-duplex sonography findings in the diagnosis of GCA

Ultrasound finding	Reference standard for comparison	N Studies	N Patients	Sensitivity (95% CI)	Specificity (95% CI)
Karassa et al. 2005 (73)					
Halo sign	TAB	14	532	69 (57-79)	82 (75-87)
Stenosis or occlusion	TAB	15	813	68 (49-82)	77 (65-85)
Halo sign, stenosis or occlusion	TAB	7	332	88 (74-95)	78 (71-84)
Halo sign	ACR classification criteria	7	1092	55 (36-73)	94 (82-98)
Stenosis or occlusion	ACR classification criteria	4	933	66 (32-89)	95 (78-99)
Halo sign, stenosis or occlusion	ACR classification criteria	3	853	87 (80-91)	96 (89-98)
Ball et al. 2010 (74)					
Halo sign	TAB	9	357	75 (67-82)	83 (78-88)
Halo sign, stenosis or occlusion	TAB	9	397	83 (77-89)	82 (77-87)
Halo sign	ACR classification criteria	6	401	69 (60-77)	89 (84-92)
Halo sign, stenosis or occlusion	ACR classification criteria	7	571	78 (72-84)	88 (84-91)
Halo sign, stenosis or occlusion (no treatment prior to ultrasound)	TAB and/or ACR classification criteria	5	237	75 (65-84)	88 (82-93)
Halo sign, stenosis or occlusion (treatment prior to ultrasound)	TAB and/or ACR classification criteria	7	492	72 (65-79)	87 (82-90)
Arida et al. 2010 (75)					
Unilateral halo sign	ACR classification criteria	8	575	68 (61-74)	91 (88-94)
Bilateral halo sign	ACR classification criteria	4	380	43 (NR)	100 (NR)
Duftner et al. 2018 (76)					
Halo sign	Clinical diagnosis	8	605	77 (62-87)	96 (85-99)
Halo sign, stenosis or occlusion	Clinical diagnosis	3	560	78 (57-90)	89 (78-95)
Halo sign	TAB	7	289	70 (56-81)	84 (73-91)
Halo sign or stenosis	TAB	2	50	77 (23-97)	91 (75-97)
Halo sign, stenosis or occlusion	TAB	5	611	78 (48-93)	91 (70-98)
Rinagel et al. 2019 (77)					
Halo sign	TAB	20	1096	68 (57-78)	81 (75-86)
Halo sign, stenosis or occlusion	TAB	11	1061	78 (64-87)	79 (73-85)

ACR - American Colleague of Rheumatology; CI - confidence interval; clinical diagnosis; NR - Not reported; TAB - temporal artery biopsy

Buttgereit et al. in 2016 (65) undertook a systematic literature review, reporting the sensitivity of CDS across 10 studies (n = 696 patients) ranging from 55% to 100% and specificity from 78% to 100%. The presence of a positive compression sign, defined as the persistence of a visible vessel wall on compression of the lumen with the ultrasound probe in the presence of inflammation-induced wall thickening, had a sensitivity of 75%-79% and a specificity of 100% for a diagnosis of GCA in a study

of 140 suspected cases [(78,79). The compression sign is a simple and robust sonographic marker with excellent inter-observer agreement (79). Patients with typical clinical features and characteristic imaging findings may not require a biopsy to confirm the diagnosis of GCA (65).

In 2018 a systematic literature review and meta-analysis informing the development of European League Against Rheumatism (EULAR) recommendations for the use of imaging in LVV demonstrated a sensitivity of 77% (95%CI 62-87%) and a specificity of 96% (95%CI 85-99%) assessed over eight studies (n=605) investigating the value of the halo sign in comparison with clinical diagnosis. Similar results were confirmed when using TAB as the reference standard diagnosis.

Finally, the meta-analysis from Rinagel at al. on twenty studies (70) reported a sensitivity of 68% (95% CI 57-78%) and a specificity of 81 (95% CI 75-86%).

Despite the good specificity shown by the above mentioned studies, careful clinical evaluation and assessment of the pre-test probability of diagnosis of GCA are still required, because the halo sign can rarely be found in other forms of vasculitis (granulomatosis with polyangitiis or polyarteritis nodosa) and infections with secondary vasculitis (71,80). Anecdotic reports suggested a possible association of a positive CDS with malignancies, particularly lymphoproliferative disorders involving the TA, or amyloidosis (81,82).

Role of CDS in predicting a positive TAB

Some authors have suggested that CDS has a good positive predictive value up to 80% in predicting TAB positivity (83) and that CDS-guided selection of the arterial segment to be biopsied can increase TAB sensitivity (71). However, other groups have reported that the use of CDS only modestly increased the probability of biopsy-proven GCA and did not improve the diagnostic accuracy of a

careful physical examination; nevertheless, these results were affected by poor quality of the ultrasound equipment and an unrealistically high cut-off value of 1.0 mm for the intima-media thickness of TA (84).

A recent randomized study from Germanò et al. (85) reported that CDS-guided TAB did not improve the sensitivity of biopsy to diagnose GCA compared to standard TAB. Muratore and colleagues (86) compared CDS findings with histological patterns and showed a poor correlation between CDS and specific histologic patterns in GCA. An abnormal CDS was significantly less common in patients with histologic evidence limited to periadventitial small vessel vasculitis (SVV) and/or vasa vasorum vasculitis (VVV), compared to classic transmural inflammatory infiltrate. The sensitivity of the halo sign was 20% and with an 80.6% specificity for the diagnosis of SVV and/or VVV, compared to a sensitivity of 82.5% and comparable specificity for classic biopsy-proven GCA. Moreover, bilateral halos (known to be highly specific for GCA) were detected in 16.7% of patients with SVV or VVV compared to 69.5% of the patients with classic GCA. Nevertheless, the value of SVV or VVV in the diagnosis of GCA are recently being reconsidered and further studies are needed.

Role of CDS in the follow- up of patients with GCA and influence of treatment

The role of CDS in the follow up of patients with GCA, particularly in the detection of disease flares and remission still needs to be defined. Moreover, the timing for resolution of CDS findings in response to GC treatment is unclear, with previous reports ranging from 2 days to several weeks (26). Hauenstein and colleagues (87) evaluated the impact of the duration of GC treatment on CDS findings in a cohort of 59 patients, demonstrating that the sensitivity of CDS rapidly decreases with treatment (ranging from 85% showing resolution within the first day of GC treatment, to 50% in patients scanned within 2-4 days or > 4 days from GC initiation). In one study patients were scanned twice weekly until halo resolution. The halo sign disappeared within a mean of 16 days (range, 7-56 days) (66). In a study of 32 consecutive patients, CDS was performed at week 2, 4, 8 and 12 from the first detection of an abnormal result. The halo was reported to disappear after a mean of 21 days following

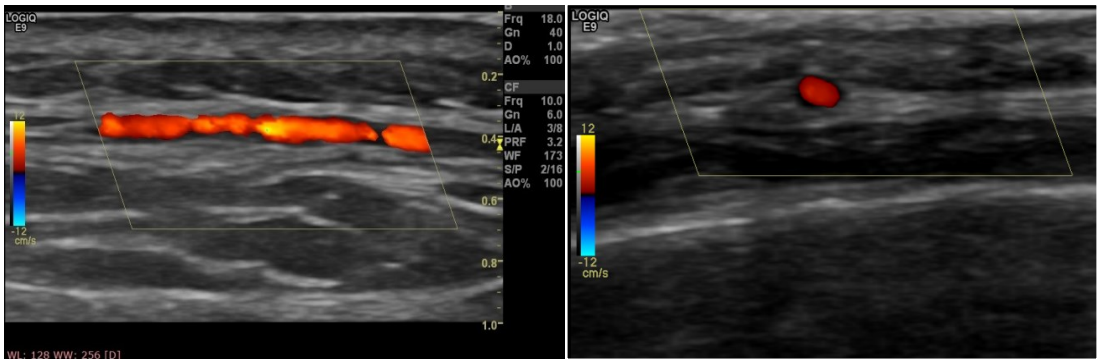
initiation of treatment. De Miguel et al. (88) explored the sensitivity to change of CDS in monitoring changes in GCA in 30 consecutive patients. They reported a mean time until halo disappearance of 11 weeks, with 50% of cases showing halo resolution within the first 8 weeks of observation. Patients with a smaller number of affected branches experienced halo resolution more quickly. Among the 13 relapsing patients, the halo characteristics seemed to differ in terms of fewer branches affected, lower erythrocyte sedimentation rate (ESR) values and a shorter time to achieve a negative halo, particularly in patients experiencing their first flare.

In the TABUL study, a cross-sectional analysis of 312 patients with GCA and positive CDS was performed; the size of the halo was significantly smaller in patients who had received more than 4 days of GC treatment, compared to those receiving up to 4 days of treatment, as well as correlating with the presence of ischaemic symptoms, supporting the early use of ultrasound as a potential prognostic marker and monitoring tool (66,89,90).

In extracranial arteries, like the axillary arteries (AX), the wall thickening can persist for months or years although vessel wall diameter decreases and echogenicity increases with treatment (91).

Which vessels to assess

When examining the TA in patients with suspected GCA, the complete length of the common superficial TA with its frontal and parietal branches in transverse and longitudinal views should always be examined bilaterally. Figure 7.



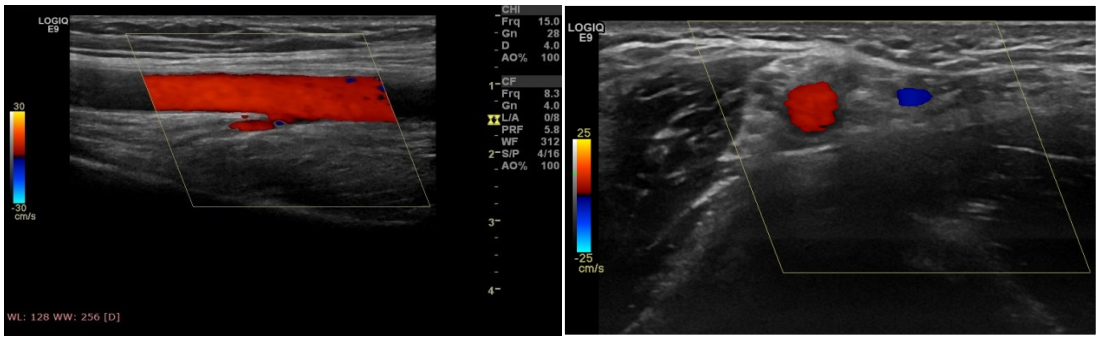


Figure 7. Normal frontal branch of the right temporal artery longitudinal and transverse views (upper panel). Normal aspect of a right axillary artery, longitudinal and transverse views.

Involvement of extra-cranial arteries is common in GCA (78,92,93) and has been described in up to 83% of cases (94). The thoracic aorta (45-65%) and the subclavian/axillary arteries (30-75%) have been reported to be the most affected sites. PET and MRI studies have shown that subclavian/axillary arteries inflammation is virtually always accompanied by thoracic aortitis (92). Up to 50% of patients may present with extra-cranial GCA without concomitant involvement of TA (95,96). Ultrasonographic studies have demonstrated that the AX are the most frequently involved extra-cranial vessels accessible by CDS, and that inflammation is often bilateral (92,47,97).

Therefore, the evaluation of AX in addition to TAs can increase the diagnostic yield of CDS in GCA (96) Patients with concomitant involvement of large vessels are typically females, of younger age, with a lower incidence of overt symptoms of cranial GCA such as headache, jaw claudication or anterior ischaemic optic neuropathy and whose disease course correlates less well with inflammatory markers (78,80,92,96).

Amongst a series of 46 patients with GCA, 17 (37%) had involvement of large vessels assessed by CDS (80). Two patients (12%) with large vessel involvement (carotid or axillary arteries) had a negative CDS of the TA. Of the patients with a halo of the TA, 12 (70%) had concomitant involvement of the AX, 1 (5.8%) of the carotid artery, and 2 (12%) had both carotid and AX involved. Having a positive ultrasound of the TA, common carotid, and AX raised sensitivity to 100%, with a specificity of 96%. Czihal et al. (92) reported that up to 61% of a cohort of 43 patients with GCA

showed signs of extra-cranial vessel involvement, 39% of them showing exclusive extra-cranial CDS signs of vasculitis. All patients with extra-cranial vasculitis had bilateral involvement of subclavian or AX arteries. Carotid artery involvement was found in 12 (28%) cases, with only 3 (7%) patients showing concomitant involvement of all branches (temporal, axillary, subclavian and carotid arteries). Interestingly, patients with concomitant TA and subclavian/axillary involvement experienced a significantly higher number of flares and more frequently required steroid-sparing agents. These studies highlight the importance of evaluating large vessels in all patients with a suspicion of GCA.

The minimum acceptable CDS assessment of patients with suspected GCA should routinely include both the TA and the AX. This core assessment is recognized to increase the sensitivity of the technique and to reliably represent the presence of extra-cranial involvement in other areas (18).

Abnormal ultrasound findings in GCA

Blood vessels are normally visualised as anechoic longitudinal tubular structures in the longitudinal plane and as round structures in the transverse plane that may be compressed. Figure 8.

A halo is defined as an hypoechoic (most commonly concentric) rim of wall swelling around the artery lumen that is visible in two planes and does not disappear upon compression (66,78). Figure 9. The compression sign should always be performed in the presence of a suspected halo. If a halo is detected, the sonographer should document the maximum thickness of halo observed in the longitudinal plane in mm. The measurement should start as close to the limit of the vessel wall as possible, and include the halo thickness up to the limit of the CF signal. Cut-off measurements to identify a thickness that is regarded as consistent with active inflammation have been described. The limit for a pathological halo in the TA has been set at > 0.3 mm, with measurements > 0.7 mm predicting a positive TAB result (66). For the axillary artery, a wall thickness (or intima-media complex - IMC) of > 1.0 mm may indicate large vessel involvement, and is defined to be diagnostic of vasculitis if > 1.5 mm (96).

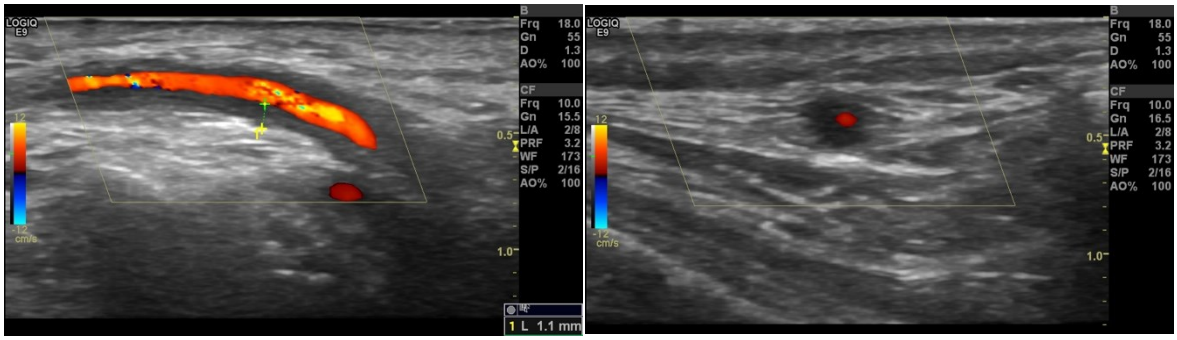


Figure 8. Halo sign at the level of the left common superficial temporal artery, longitudinal and transverse views.

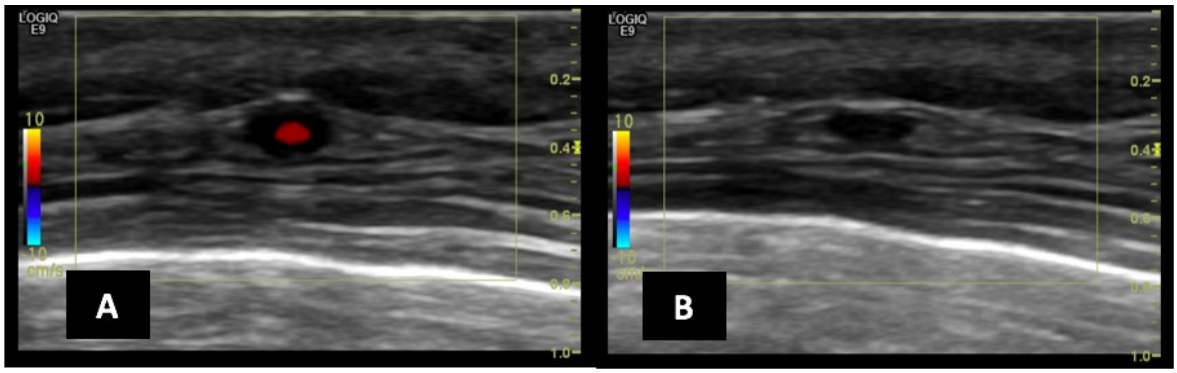


Figure 9. Halo sign at the level of the frontal branch of the right temporal artery, transverse view, before applying compression, in a patient with active GCA. Panel B: evidence of a positive compression sign with the halo persisting despite firm compression applied with the transducer.

A recent study evaluating the intima-media thickness (IMT) in 40 GCA patients compared to controls confirmed that the halo size, besides to the morphologic parameters, can effectively distinguish normal from inflamed arteries with specific cut-offs according to the vessel assessed. The cut-off was set at 0.42 mm for the common superficial TA, 0.34 mm for the frontal branch, 0.29 mm for parietal branch, 0.37 mm for the facial artery and 1.0 mm for AX (98). Although the IMT values can assist the evaluation of TA, the ultrasonographic aspects and the non-compressible character of the detected oedema should guide the evaluation. Table 5.

Table 5. Proposed intima-media thickness values in patients with GCA and in controls prposed by Schäfer et al. (99)

Arterial segment	IMT Healthy controls in mm (mean ± SD)	IMT GCA Patients with GCA (mean ± SD)	Cut-off (mm)	Sensitivity (%)	Specificity (%)
Common superficial temporal arteries	0.23 ± 0.04	0.65 ± 0.18	0.42	100	100
Frontal branches	0.19 ± 0.03	0.54 ± 0.18	0.34	100	100
Parietal branches	0.20 ± 0.03	0.50 ± 0.17	0.29	97.2	98.7
Facial Arteries	0.24 ± 0.05	0.53 ± 0.16	0.37	87.5	98.8
Axillary arteries	0.59 ± 0.10	1.72 ± 0.41	1.0	100	100

IMT: intima-media thickness; GCA: giant cell arteritis; SD: standard deviation

Stenosis is demonstrated by finding a localized over 2-fold increase in flow velocity, while occlusion is the absence of flow (66,67). However, these findings do not add information in the diagnosis of GCA over the detection of halo.

Other abnormalities not exclusive to GCA, but important to be recorded are the presence of concomitant arteriosclerosis visualised as heterogeneous, hyperechoic, irregularly delineated wall alteration. While a moderate level of tortuosity is physiological, significant tortuosity should be recorded because this can influence the reliability of the assessment.

1.2.5 Current management of GCA, disease course and unmet needs

Patients with LVV are at high risk of permanent ischaemic sequelae, for this reason, they are treated with high dose GC urgently and for long periods – typically, years. GCA is a rheumatology emergency.

The majority of patients with suspected GCA should be seen in a rapid-access clinic, given the nature of the disease and the need for rapid immunosuppression to protect vision. However, there is no established agreed definition of a rapid access service for GCA and, as a result, some institutions lack the resources to provide fast track assessment (FTA) of suspected GCA. TAB can remain positive for 2-6 weeks after the commencement of treatment, while the use of CDS is currently limited as it requires high level of experience and training. Nevertheless, the institution of fast-track ultrasound clinics has demonstrated to effectively reduce ischaemic complications (up to 88% lower compared to the conventional standard of care) and costs (90,100).

Ultrasound is being integrated in FTA and represents a valuable tool in the hands of the assessing physician who can obtain information on the cranial and/or extra-cranial involvement during the same assessment. The current management of GCA is based on the pre-test clinical probability of the diagnosis (based on the clinical presentation and laboratory findings) together with imaging or histologic findings. In centres with the adequate expertise and equipment quality to perform ultrasound, this is the preferred first imaging tool for patients with suspected cranial GCA. If a patient has a high clinical probability of GCA and a positive imaging, the diagnosis can be confirmed. On the contrary, in case of a low clinical probability and a negative test the diagnosis can be excluded. In all intermediate situations, further testing, including TAB should be required (101). Figure 10.

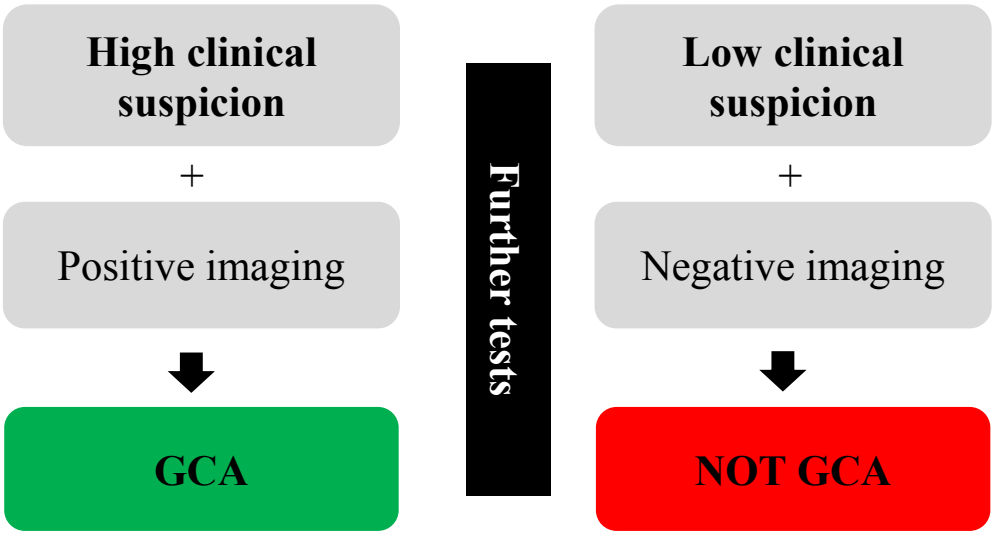


Figure 10. Current management of GCA in the setting of fast track clinics. Further tests include temporal artery biopsy or other imaging modalities.

Several unmet needs in the management of GCA are still unresolved. Amongst these, the definition of the optimal monitoring of GCA, and accurate recognition or prediction of disease relapse are two major unresolved issues. Despite early treatment with high dose GC, up to 34-79% relapse (102,103). To date, there is no good evidence to help predict which patients are likely to relapse, and the identification of relapsing patients is complicated by the fact that symptoms are often non-specific and laboratory tests can be normal (103).

Furthermore, tools to predict the risk of relapse would permit a more patient-tailored therapeutic approach and follow-up planning. This information will be even more valuable now that new biological therapies have been approved for the treatment of GCA and others being investigated (104,105).

A crucial role in the management of GCA is emerging for CDS. Since the pioneering papers in the 90's (66), vascular ultrasound has gained a central role in the diagnosis and the follow-up of patients with LVV. The advantages of ultrasonography are its ability to reveal vessel wall and lumen changes,

its noninvasiveness, and the capability to examine several vessels in a single session. Moreover, follow-up scans can be obtained to monitor patients over time. The role of imaging in the follow-up of GCA is still being studied. Similarly, the exact role of ultrasound in predicting or identifying flares still needs to be further addressed. Available CDS data across studies are largely qualitative, with a binary (positive/negative) assessment of CDS results. A "positive" CDS supporting a diagnosis of GCA has been defined, qualitatively, as the presence of a halo at one or more vascular sites (18,106). However, the value of specific CDS findings such as halo size (maximum or average thickness), number of temporal artery branches involved, total number of anatomical sites with halo, or the presence of bilateral halos in predicting diagnosis and outcome are still to be defined. Moreover, a standardized, quantitative score to grade the severity and extent of vascular involvement detected by CDS in GCA has not yet been developed (107). Despite some areas of uncertainty, this rapid, accessible, repeatable and safe tool offers promising perspectives to change the future management of GCA.

Finally, several changes in the therapeutic strategy to control the disease are under investigation and have been recently approved in line with the improved acknowledgement of the pathogenetic changes underlying GCA.

2. Objectives

During the course of this PhD programme, we aimed at investigating and improving the management of giant cell arteritis (GCA) by:

(i) assessing the impact of the fast track ultrasonographic clinic of the Rheumatology Department, IRCCS Policlinico S. Matteo, University of Pavia on the risk of permanent visual loss and future relapse;

(ii) evaluating the role of quantitative ultrasound assessment in terms of diagnostic and prognostic outcomes in GCA;

(iii) contributing to the update of the European recommendations on the management of large vessel vasculitis by leading on the systematic literature review and participating in the recommendations development process.

3. Methods

3.1 Methods for aim 1 and 2: the assessment of the fast track clinic impact and evaluation of the role of quantitative ultrasound on diagnostic and prognostic outcomes.

3.1.1 Included population

Patients referred for suspected GCA to the fast track assessment clinic (FTA) of the Department of Rheumatology of the IRCCS Policlinico S. Matteo, University of Pavia, Italy, between October 1st, 2016 and June 30th, 2020 were recruited if a diagnosis of GCA was confirmed. The activity of the clinic was significantly modified by the severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) epidemics, therefore, patients assessed from March 2020 to June 2020 were considered separately.

An historic retrospective cohort of patients with a confirmed diagnosis of GCA assessed with conventional practice at the same Institution between January 1st, 2005 and September 30th, 2016 was used as control group in comparison to the FTA.

Patients were recruited at baseline visit during the first FTA assessment to confirm the diagnosis of GCA. In patients with a confirmed diagnosis, regular follow-up according to clinical practice needs was performed (usually within one month of diagnosis and then every 3 months for the first year, and every 3-6 months thereafter).

A group of patients with a positive colour duplex sonography (CDS) at baseline who consented to be regularly assessed with CDS were recruited in a substudy to analyse the optimal timing and findings of CDS assessments, the Prognosis of Temporal Arteritis (PROTEA Study) performed in strict collaboration with the University of Oxford. During the PhD programme I have personally contributed to the design and development of the PROTEA study in collaboration with the University

of Pavia and University of Lisbon having been developed after a research fellowship which I undertook in 2016 at the University of Oxford.

CDS examinations as part of PROTEA were performed at baseline, week 1, week 3, week 6, month 3, month 6, month 9, month 12 and then every six months in line with the British Society of Rheumatology recommendations for the routine clinical care of patients with GCA (108).

The study has been approved by the Institutional Review Board of the University of Pavia and patients consented to their data use.

For the assessment of quantitative ultrasound data, the FTA cohort of the University of Pavia has been included as a validation cohort. The original assessment has been performed on patients included in The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL Study) whose data have been shared as part of a collaboration with the University of Oxford. According to the study design patients with a suspected diagnosis of new-onset GCA had undergone both ultrasound and TAB within 7 days of commencing high-dose GC. The detailed methods and results of the TABUL study have been previously described (90). We selected patients with a positive CDS and a confirmed final diagnosis of GCA.

The diagnosis of GCA was confirmed in all cases by an expert rheumatologist on the basis of typical symptoms, data on inflammatory markers, and imaging (CDS, ^{18}FDG PET-CT) or temporal artery biopsy (TAB) findings.

3.1.2 Fast Track Assessment

FTA was implemented at the Rheumatology Department of the IRCCS Policlinico S. Matteo, University of Pavia, Italy since October 1st, 2016. FTA consists in the referral within one working day of a suspected GCA case to an expert rheumatologist, who performs the clinical examination and CDS of temporal and axillary arteries. Other anatomical sites (e.g. facial arteries, occipital arteries, carotid arteries) could be assessed according to the patient's clinical picture. Patients can be referred

to the FTA from the general practitioner or other Specialist from other Departments. Patients enrolled after October 2016 were considered FTA if they received a rheumatologist's evaluation within one working day after the first medical contact. Since the FTA implementation, the same rheumatologist (S.M.) performed the clinical and ultrasonographic assessment.

During each visit clinical and imaging information were collected. Clinical manifestations, laboratory tests, date of symptoms onset, date of diagnosis, comorbidities, information on treatment, and follow-up, including relapses were extracted from the clinical records and recorded on an electronic database. Data were extracted retrospectively for the conventional historic cohort. FTA patients were assessed prospectively since diagnosis. Treatment followed current recommendations for the cohorts considered, including high-dose GC (1 mg/kg/day; maximum 60 mg/day) maintained for one month and then tapered while monitoring disease activity. In patients with recent onset of ischaemic visual symptoms i.v. methylprednisolone was prescribed for the first 3 days (1 g/day). Adjunctive immunosuppressive treatment (most frequently Methotrexate or Tocilizumab) were prescribed to relapsing patients (109,110). Permanent visual loss was defined by the complete or partial visual impairment caused by vasculitic damage of the visual pathway [e.g. anterior ischaemic optic neuropathy (AION); posterior ischaemic optic neuropathy (PION)] confirmed after ophthalmologic assessment. Symptom latency was calculated as the time interval between the onset of the first symptom attributable to GCA (e.g. date of headache or other cranial symptoms onset, girdle inflammatory pain onset, systemic symptoms onset) and the diagnosis. LV-GCA was defined as the presence of extra-cranial LV involvement (e.g. aortic, axillary arteries) detected by imaging (most frequently CDS and/or ^{18}FDG PET-CT) with or without temporal artery involvement. Relapse was defined as the reoccurrence of symptoms and signs of GCA, with or without elevation of the inflammatory markers, with the need to increase the dosage of GC or to add or increase the dose of another immunosuppressive drug. Disease complications during follow-up are defined by the occurrence of stenosis or aneurysms/dissections and/or ischaemic complications.

3.1.3 Ultrasonographic assessment

CDS was performed by the same rheumatologist experienced in vascular ultrasound for the assessment of large vessel vasculitis (S.M.).

CDS assessment of arteries in patients with suspected GCA requires the use of a linear probe with a grey-scale (GS) frequency of 10 MHz or greater and a colour Doppler (CD) frequency of at least 6 MHz, using a vascular pre-set and applying CD mode.

For TA branches a linear high GS frequency, preferably of 15 MHz or greater, linear or hockey stick transducer is recommended.

For axillary, vertebral, subclavian, carotid and femoral arteries a linear transducer with a GS frequency can be lower. When scanning subclavian arteries in obese individuals, a linear or curved transducer with a lower frequency (<10 MHz) is preferable.

Patients were assessed with the MyLab Seven Esaote ultrasound machine with a high-frequency (18-6 MHz) linear transducer.

A vascular pre-set on the ultrasound machine was selected. Table 6 shows the typical grey scale settings required for assessing arteries for GCA.

CD was used to aid visualization of the vessel's lumen. Power Doppler was applied in case of very low blood flow/occlusion, or in deep/tortuous vessels. High CD frequency for temporal arteries (> 6 MHz) was applied. The frequency can be lowered when examining larger vessels. Table 7 shows CD settings for assessment of arteries for GCA. Focus was set at 5 mm for temporal arteries and 3 cm for axillary arteries. A Doppler frequency of 10 MHz was applied. Pulse repetition frequency (PRF) was set at 2-3 KHz for temporal artery, and at 3-4 KHz for axillary arteries. A low wall filter was selected to allow the identification of low velocity flow. The colour box was adjusted to obtain an angle steer correction ≤ 60 degrees.

The common, parietal, and frontal branches of each temporal artery and the axillary arteries in longitudinal and transverse plans were assessed at each visit.

Table 6. Definitions and details of typical grey scale settings applied for assessing arteries in GCA (18).

Grey scale settings	**Description**	**Example of recommended value***
Frequency	Regulates the length of the ultrasound wave and therefore the penetration of the beam.	18 MHz
Focus	Represents the level (or levels if multiple focuses are selected) of depth at which the ultrasound beam is focused. Depth can then be adjusted to detect AX or other branches according to the patient's characteristics.	5 mm for TA. 2-3 cm for AX.
Depth	Determines the penetration depth of the ultrasound beam. (The penetration of the ultrasound beam however is determined by the frequency).	1-2 cm for TA. 3-4 cm for AX.
B-mode gain	This function can be adapted to adjust brightness; it should be kept within ranges ideal to avoid false reading of halo because of excessive or inadequate brightness. Gain can also be adjusted through the Time Gain Compensation controls (TGC) which allows to select gain in specific areas of the image (near-, mid- and far-field).	35-45 dB
Line Density	This adjusts the spatial resolution of the image by regulating the number of scan lines. Increasing the line density increases image quality and detail but decreases the frame rate.	3
Frame rate	Indicates the number of frames per second that can be acquired. It can be considered as temporal resolution. A high frame rate is crucial in small, fast moving tissues.	>15 images per second
Dynamic Range	Regulates the intensity between the shades of grey displayed.	40-66 dB

TA: temporal artery; AX: axillary artery. *These examples of recommended values are taken from a GE LOGIQE9 Ultrasound machine and can vary according to the manufacturer.

When performing the CDS of TA, patients lied in a recumbent or semi-recumbent position on their side or on their back. The first part of the common superficial TA can be detected at the level of the tragus. The probe was applied in the transverse and subsequently the longitudinal plane or vice versa. After completing a sweep of the artery in one plane, the probe was rotated by 90 degrees and a further sweep performed in the opposite plane. The level of the bifurcation between frontal and parietal branches of TA serves as the marker point to define the start of the frontal and parietal branches respectively. The AX was examined by placing the ultrasound probe over the mid axillary line, and sweeping along the expected course of the artery. The transducer should be applied either in the longitudinal or transverse plane and swept along until the posterior humeral circumflex artery is identified. The area directly distal to the humeral circumflex artery which represents the proximal

brachial artery was also examined. The sweep was repeated with the probe rotated at 90 degrees, so that both longitudinal and transverse scans were performed.

Table 7. Definitions and details of typical colour Doppler settings applied for assessing arteries in GCA (18).

Colour Doppler settings	**Description**	**Example of recommended value***
Frequency	Regulates the length of the ultrasound wave and therefore the penetration of the beam.	About 10 MHz
Pulse Repetition Frequency (PRF)	Represents the Doppler sampling frequency (how many pulses of sounds are emitted per second into the tissue). High PRF should be selected when analysing high blood velocities to filter underlying noise signals; however, these filters also remove slow flows, therefore the PRF should be adjusted during scanning and adapted to the vessels' flow velocity. PRF should also be adjusted (increased) to avoid systolic aliasing, an artefact leading to the visualization of pixels with an opposite direction than the surrounding flow, arising when the Doppler shift of the moving blood is higher than half of the PRF. When the PRF is too high, diastolic flow gaps might be enhanced.	2-3 KHz for TA. > 3 KHz for AX (Dependent on machine and flow velocity).
Wall filter	Wall filters are added to remove noise (e.g. pulsation from moving vessel walls). The lowest possible wall filter (strictly connected with low PRFs) should be selected to identify low velocity flow.	Low values, may have to increase to assess AX
Colour box	This requires an angle steer correction to obtain an angle between the scan lines and the direction of blood flow ≤ 60 degrees to avoid poor CD signals and inaccurate readings.	≤ 60 degrees
Colour flow gain	This setting needs to be constantly adjusted to ensure precise filling of the vessel lumen with colour, while avoiding under- or over-filling, therefore creating a potential misinterpretation for halo or a blooming/bleeding artefact.	2-18
Flow direction	It is useful to confirm the direction of flow, particularly in vertebral arteries in order to exclude subclavian steal syndrome. Conventionally, the flow is red if it is directed towards the transducer, typically applying to arteries and blue if the flow is directed away, usually for veins. The direction of flow is influenced by the probe position (it will change if the transducer is rotated 180°) or if the box is steered to the opposite direction. When this happens the colour interpretation should be inverted to avoid confusion.	Invert function off

TA: temporal artery; AX: axillary artery. *These examples of recommended values are taken from a GE LOGIQE9 Ultrasound machine and can vary according to the manufacturer.

The presence of a halo was defined according to the accepted definitions as a homogenous, hypoechoic wall thickening, well delineated towards the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans (111). The compression sign was applied in transverse views to confirm the findings (112). Table 8. CDS was defined as positive if displaying a halo at the level of at least one branch of the temporal artery or at least one axillary artery. Intima-media thickness was measured at the site of maximum thickness on longitudinal plans.

Table 8. Definition of ultrasonographic findings in GCA and parameters that were assessed (66,78,101,106)

Normal	Completely normal vessel appearance; there is no evidence of halo, arteriosclerosis or tortuosity. For temporal arteries: Pulsating, compressible artery with anechoic lumen surrounded by mid-to hyperechoic tissue. Using ultrasound equipment with high resolution, the intima-media complex is presenting as a homogenous, hypo-or anechoic structure delineated by two parallel hyperechoic margins ("double line pattern") may be visible. For axillary arteries: Pulsating, hardly compressible artery with anechoic lumen; the intima-media complex presents as a homogenous, hypo-or anechoic echostructure delineated by two parallel hyperechoic margins ("double line pattern"), which is surrounded by mid- to hyperechoic tissue.
Halo	A halo appears to be present. This observation should be made before applying the compression test (for the temporal artery and its branches). The halo is defined as homogeneous, hypoechoic wall swelling, well delineated towards the luminal side, visible both in longitudinal and transverse planes; it is most commonly concentric in transverse scans.
Positive compression sign	This applies to the temporal artery and its branches. Any apparent halo seen should be confirmed using this technique. The thickened arterial wall remains visible upon compression. The hypoechogenic vasculitic vessel wall thickening contrasts with the mid-to hyperechogenic surrounding tissue.
Maximum halo size (measured in mm in longitudinal view)	The longitudinal plane of view should be used to document the size of the halo (halo size is most commonly between 0.4 mm and 1.0 mm on temporal arteries, and above 1.0 mm on axillary arteries).
Significant vessel tortuosity present?	This applies to the temporal artery and its branches. Is the artery difficult to visualise in one plane along its course, potentially making it difficult to interpret the presence or absence of halo or arteriosclerosis. Most temporal arteries and their branches are a little tortuous, but this should be recorded if the tortuosity makes it difficult to interpret the scan findings.
Arteriosclerosis present?	Arteriosclerosis is defined as heterogeneous and in part hyperechoic, irregularly delineated, eccentric vessel wall alteration. This may be present in arteries, independently of the presence or absence of halo.

3.1.4 Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were displayed as means with standard deviation (S.D.) if normally distributed or as medians with interquartile range (IQR) in case of non-normal distribution. Ratios were presented with 95% confidence intervals (C.I.). For comparison between groups, the independent-samples t-test for continuous variables and the chi-squared test for categorical variables were applied. For non-parametric numerical variables, the Wilcoxon signed-rank test was used. Statistical analysis was performed the software R Studio (R version 3.6.3 2020-02-29, Copyright © 2020 The R Foundation for Statistical Computing). P values <0.05 were considered to be significant.

For the role of the quantitative ultrasound findings the following specific analyses were performed. Data were analysed using Stata 15.1 (StataCorp, College Station, TX, USA). Differences in the CDS variables according to clinical, laboratory, histological and outcome characteristics were tested using the Wilcoxon–Mann–Whitney test for continuous variables and the v2 test or Fisher's exact test for dichotomous variables. In order to identify a comprehensive score inclusive of different ultrasonographic parameters that could be combined with clinical and laboratory findings, the CDS logistic models were fitted against two major outcomes: TAB diagnostic for GCA and clinical outcome at 6 months [defined as visual loss, Vasculitis Damage Index ocular items, GC >10 mg/day of prednisone-equivalent (based on median value for TABUL cohort) at 6 months and/or the need for adjunctive immunosuppressants]. Clinical logistic models were fitted against TAB diagnostic for GCA and clinical outcome at 6 months. The variables to be included in these models were identified a priori based on the available evidence or the hypothesized clinical evidence. The best CDS and clinical models were combined (according to the Akaike information criterion, the lower the better) to identify independent correlates of a TAB diagnostic for GCA and of clinical outcome at 6 months. The best-fitting CDS and clinical/laboratory models were combined to develop a comprehensive score (the GCA-US score). For model discrimination we computed the model area

under the receiver operating characteristic (ROC) curve and its 95% CI. The final model was validated with a 10-fold cross-validation. The association between the GCA-US score and the clinical outcome at 6 months was tested on the independent cohort (107).

3.2 Methods for aim 3: the update of the European recommendations on the management of large vessel vasculitis

3.2.1 Systematic literature reviews

Two systematic literature reviews (SLR) were performed by searching MEDLINE, EMBASE and Cochrane CENTRAL library from inception of each database (1946, 1974 and 1993, respectively) until 31st of December 2017 (113,114). Internal protocol according to EULAR guidelines. One SLR focused on diagnosis/monitoring literature, the second one on treatment strategies. Table 9. There were no language restrictions. References from included studies were screened. An example of the search strategy based on the key terms used for Medline is presented in Table 10 and Table 11.

Table 9. Items addressed by the systematic literature reviews (113,114).

SLRs informing the 2018 update of EULAR recommendations for the management of LVV	
Participants were adult ≥ 18 years old patients with the following diagnoses: giant cell arteritis or Takayasu's arteritis, or other types of large-vessel vasculitis (isolated aortitis or IgG4-related disease with vasculitis).	
SLR 1: Diagnosis and monitoring	**SLR 2: Drug and surgical treatment**
• Diagnosis: recognition, referral criteria, fast-track diagnosis, role of imaging for diagnosis, role of biopsy for diagnosis, interdisciplinary work-up, considerations for sub-types of disease such as cranial/ischaemic/large vessel, isolated aortitis, IgG4-related disease, LVV disease in other vasculitides • Prognostic and therapeutic implications of disease phenotypes: cranial vs extra-cranial, isolated aortitis, other forms including IgG-4 related disease, imaging, other biomarkers, comorbidities and complications, disease damage versus activity • Long-term follow-up of patients: clinical assessments and frequency, imaging, patient-reported outcomes, physical therapies and management of complications • Patient education and other aspects of patients-centered care	• Drug therapy: dosing, length of therapy, outcome and treatment-related side effects for the following drugs: glucocorticoids, methotrexate and other non-biologic immunosuppressive agents, tocilizumab and other biologic agents • Specific treatment of organ complications: loss of vision and stroke), relapsing, refractory, glucocorticoid-dependent disease • Revascularisation procedures: indications for referral, management of aneurysms and/or vessel stenosis • Adjunctive therapies and prophylaxis: aspirin, cardiovascular and cerebrovascular disease, infections, vaccination, osteoporosis

Table 10. Search strategy for the SLR focusing on diagnosis/monitoring – MEDLINE terms

("Giant cell arteritis"[MeSH Terms] OR "Takayasu arteritis"[MeSH Terms] OR "Aortitis"[MeSH Terms] OR "large vessel vasculitis"[Title/Abstract] OR "giant cell arteritis"[Title/Abstract] OR "temporal arteritis"[Title/Abstract] OR "Horton's disease"[Title/Abstract] OR "Horton's arteritis"[Title/Abstract] OR "Takayasu arteritis"[Title/Abstract] OR "Takayasu's arteritis"[Title/Abstract] OR "aortitis"[Title/Abstract] OR "periaortitis"[Title/Abstract] OR "IgG4"[Title/Abstract])
AND
("biomarkers"[MeSH Terms] OR "biomarkers"[Title/Abstract] OR “fast-track”[Title/Abstract] OR
“patient referral”[Title/Abstract] OR “Referral and Consultation”[MeSH Terms] OR "Rehabilitation"[MeSH Terms] OR "Rehabilitation"[Title/Abstract] OR "Physical therapy"[Title/Abstract] OR "Diagnostic Imaging"[MeSH Terms] OR "Diagnostic Imaging"[Title/Abstract] OR "Classification"[MeSH Terms] OR "Classification"[Title/Abstract] OR
"Pathology"[MeSH Terms] OR "Histology"[MeSH Terms] OR "Diagnosis"[MeSH Terms] OR "Diagnosis"[Title/Abstract] OR "Symptom Assessment"[MeSH Terms] OR "Interdisciplinary Communication"[MeSH Terms] OR "Physical Examination"[MeSH Terms] OR "Patient Education
as Topic"[MeSH Terms] OR "Patient Reported Outcome Measures"[MeSH Terms] OR "Single Photon Emission Computed Tomography Computed Tomography"[MeSH Terms] OR "PETCT"[Title/Abstract] OR "Positron-Emission Tomography"[MeSH Terms] OR "Positron-Emission Tomography"[Title/Abstract] OR "F-FDG Positron-Emission Tomography"[Title/Abstract] OR "PET"[Title/Abstract] OR "Tomography, X-Ray Computed"[MeSH Terms] OR "Computed Tomography"[Title/Abstract] OR "CT"[Title/Abstract] OR "Ultrasonography"[MeSH Terms] OR "Ultrasonography"[Title/Abstract] OR "Ultrasonography, Doppler, Duplex"[MeSH Terms] OR "Color duplex sonography"[Title/Abstract] OR "Color duplex ultrasonography"[Title/Abstract] OR
"Magnetic Resonance Angiography"[MeSH Terms] OR "Magnetic Resonance Angiography"[Title/Abstract] OR "Angiography"[MeSH Terms] OR "Magnetic Resonance Imaging"[MeSH Terms] OR "Magnetic Resonance Imaging"[Title/Abstract] OR "MRI"[Title/Abstract] OR "temporal artery biopsy"[Title/Abstract] OR "temporal artery biopsies"[Title/Abstract] OR "cranial arteritis"[Title/Abstract] OR "extra-cranial arteritis"[Title/Abstract])
AND
("Remission"[Title/Abstract] OR "Relapse"[Title/Abstract] OR "complication"[Title/Abstract] OR
"complications"[Title/Abstract] OR "disease activity"[Title/Abstract] OR "damage"[Title/Abstract]
OR "Recurrence"[Title/Abstract] OR "refractory"[Title/Abstract] OR "Comorbidity"[MeSH Terms]
OR "Comorbidities"[Title/Abstract] OR "Mortality"[MeSH Terms] OR "Mortality"[Title/Abstract]
OR "Health Status"[MeSH Terms] OR "Health Status"[Title/Abstract] OR "Functional Status"[Title/Abstract] OR "Symptom Flare Up"[MeSH Terms] OR "flare"[Title/Abstract] OR "Recurrence"[MeSH Terms] OR "Treatment Outcome"[MeSH Terms] OR "Treatment Outcome"[Title/Abstract]))
NOT
(Case Reports [Publication Type])

The SLRs were extended to all study designs (except case reports of less than 2 patients). Meta-analyses and SLRs were reviewed and included if relevant. Diagnostic and monitoring aspects regarding the use of imaging were excluded due to the publication of specific EULAR recommendations on the use of imaging for LVV (69,101).

Table 11. Search strategy for the SLR focusing on treatment – MEDLINE terms

(((((“Giant cell arteritis” [mesh] OR “Takayasu arteritis” [mesh] OR “Aortitis” [mesh] OR “large vessel vasculitis” [tiab] OR “giant cell arteritis” [tiab] OR “temporal arteritis” [tiab] OR “Horton’s disease” [tiab] OR “Horton’s arteritis” [tiab] OR “Takayasu arteritis”[tiab] OR “Takayasu’s arteritis”[tiab] OR aortitis [tiab] OR periaortitis [tiab] OR IgG4 [tiab])))
AND (“drug therapy”
[mesh] OR "vascular surgical procedures"[MeSH] OR therapy [tiab] OR treatment [tiab] OR treatments [tiab] OR glucocorticoid [tiab] OR glucocorticoids [tiab] OR steroid [tiab] OR steroids [tiab] OR corticosteroid [tiab] OR corticosteroids [tiab] OR prednisone [tiab] OR methylprednisolone [tiab] OR prednisolone [tiab] OR deflazacort [tiab] OR methotrexate [tiab] OR
immunosuppressive [tiab] OR azathioprine [tiab] OR cyclophosphamide [tiab] OR leflunomide [tiab] OR cyclosporine [tiab] OR mycophenolate [tiab] OR dapsone [tiab] OR “biological therapy” [tiab] OR “biological agents” [tiab] OR “tumor necrosis factor” [tiab] OR etanercept [tiab] OR infliximab [tiab] OR adalimumab [tiab] OR tocilizumab [tiab] OR “interleukin 6” [tiab] OR abatacept [tiab] OR ustekinumab [tiab] OR rituximab [tiab] OR angioplasty [tiab] OR endovascular
[tiab] OR revascularization [tiab] OR revascularisation [tiab] OR management [tiab] OR aspirin [tiab] OR antiplatelet [tiab] OR anticoagulant [tiab]))
AND (“Patient Safety” [Mesh] OR efficacy
[tiab] OR effectiveness [tiab] OR “treatment outcome”[mesh] OR safety [tiab] OR complication[tiab] OR complications [tiab] OR “adverse effect” [tiab] OR “adverse effects” [tiab] OR “adverse event” [tiab] OR “adverse events” [tiab] OR “recurrence” [Mesh] OR recurrence [tiab]
OR “remission induction” [Mesh] OR remission [tiab] OR relaps* [tiab] OR refractory [tiab] OR flare* [tiab] OR stroke [tiab] OR “cerebrovascular disorders” [Mesh] OR cerebrovascular [tiab] OR
“blindness” [Mesh] OR blindness [tiab] OR visual [tiab] OR infection [tiab] OR infections [tiab] OR “aneurysm” [Mesh] OR aneurysm [tiab] OR aneurysms [tiab] OR stenosis [tiab] OR ischemic [tiab] OR ischaemic [tiab]))
NOT Case Reports [Publication Type])

Two reviewers (including S.M.) independently screened all titles and abstracts to identify eligible studies to be assessed by full text. Both reviewers independently extracted data from eligible papers and summarized evidence in the summary of evidence (SoE) tables using a standardised data extraction form (115,116). Included studies were organized according to diagnosis (giant cell arteritis vs Takayasu's arteritis vs other forms of LVV) and according to research question (type of diagnostic tool, biomarkers, monitoring tools, outcome assessment or type of drug or surgical intervention). Levels of evidence (LoE) were assigned according to the Oxford Centre for Evidence-based Medicine LoE (117). Risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool (118) for randomized controlled trials (RCTs) and the Newcastle-Ottawa scale for observational studies (119). The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II and the Quality In Prognosis Studies (QUIPS) were used for observational studies according to specific outcomes studies (115,116,118,120,121).

3.2.2 Recommendations development

After approval by the EULAR Executive Committee, a task force including 24 members was assembled. The group was formed by 19 clinical experts from Europe, India and China, two fellows, one health professional and two patients' representative affected by LVV. I was a member of the task force in quality of fellow. The recommendations were developed in accordance to the 2014 EULAR standardized operating procedures for EULAR-endorsed recommendations (121). A Delphi was performed among the task force members to define key research questions to be addressed by the SLRs. An in-person meeting was held to present the data obtained from the two SLRs which formed the basis for the generation of the recommendations. The agreed recommendations were approved by voting by the members of the task force. Agreement of at least 75% was required for each statement. Levels of agreement on a 0-10 scale on each recommendation were obtained. A list of undervolted issues as part of a research agenda was created (110).

4. Results

4.1 The impact of the fast track ultrasonographic clinic on the risk of permanent visual loss and future relapse

The results of this research project have been published in the paper "Fast-track ultrasound clinic for the diagnosis of giant cell arteritis changes the prognosis of the disease but not the risk of future relapse" by Monti et al. and are summarized below (*in press*).

4.1.1 Assessment at the time of GCA diagnosis

One-hundred and sixty patients were recruited, 120 were females (75%), the mean age at diagnosis was 72.4±8.2 years.

Sixty-three (39.4%) patients were recruited since the introduction of the FTA. The control historical cohort was composed of 97 (60.6%) patients who had been assessed with a conventional approach.

FTA patients were older (75.1±7.6 vs. 70.6±8.2 years old; $p<0.001$). At the time of diagnosis, a larger percentage of patients without comorbidities was observed in the non-FTA group (16.7% vs. 3.8%; P=0.02). Nevertheless, major cardiovascular comorbidities including coronary artery disease, dyslipidaemia, diabetes, stroke, peripheral artery disease and hypertension were similar between the two cohorts ($P>0.05$) except for heart failure (1.0% conventional vs. 7.5% FTA; P=0.03).

Overall, 19.4% (ranging 15.5%-25%) of patients with newly diagnosed GCA had a previous diagnosis of polymyalgia rheumatica.

FTA contributed to reduce the time to diagnosis (62 days IQR 20-122 in the conventional cohort vs. 33 days IQR 15-83 in the FTA cohort; P=0.035). Table 11. The reduction of diagnostic delay was especially true for patients with cranial GCA (61 days IQR 15-107 vs. 30 days IQR 13-53; P=0.007). Importantly, among patients with permanent visual loss (PVL) the duration of symptoms (since the

onset of the first symptom attributable to GCA) before receiving a diagnosis of GCA was significantly higher in the conventional group (23 days IQR 12-96 vs. 7 days IQR 4-10; P=0.02).

The type of major vessel district involvement was similar between the FTA and the conventional group (cranial GCA 82.5% vs. 77.3% respectively; P=0.4). The clinical presentation was similar between the two groups: the frequency of PMR, headache, amaurosis fugax, jaw claudication and fever was not different between the two cohorts (P>0.05). Some symptoms were more frequently reported in the FTA group compared to the conventional practice group: weight loss (30.2% vs 13.4%; P=0.01), tongue claudication (11.1% vs 1.0%; P=0.004) and scalp tenderness (20.6% vs 5.2%; P=0.003). PVL occurred in 8 (12.7%) patients in the FTA group compared to 26 (26.8%) in the conventional one (P=0.03).

Table 11. Clinical features of the cohort (conventional approach versus fast track approach) at baseline

	Total (N=160)	Conventional (N=97)	FTA (n=63)	P value
Age at diagnosis, mean (S.D.), years	72.4 (8.2)	70.6 (8.2)	75.1 (7.6)	<0.001
Female, n (%)	120 (75)	77 (79.4)	43 (68.3)	0.1
Previous PMR, n (%)	31 (19.4)	15 (15.5)	16 (25.4)	0.1
Symptom latency, median (IQR), days	46 (15-101)	62 (20-122)	33 (15-83)	**0.04**
Symptoms latency of patients with PVL, median (IQR), days	14 (8-65)	23 (12-96)	7 (4-10)	**0.02**
Comorbidities				
Coronary heart disease	15 (10.1)	9 (9.4)	6 (11.3)	0.7
Dyslipidaemia	30 (20.1)	18 (18.8)	12 (22.6)	0.6
Diabetes mellitus	18 (12.1)	14 (14.6)	4 (7.5)	0.2
Stroke	14 (9.4)	11 (11.5)	3 (5.7)	0.2
Peripheral artery disease	7 (4.7)	5 (5.2)	2 (3.8)	0.2
Hypertension	85 (57.0)	53 (55.2)	32 (60.4)	0.5
Heart failure	5 (3.4)	1 (1.0)	4 (7.5)	**0.03**
Other comorbidities	102 (68.5)	73 (76.0)	39 (73.6)	0.7
No comorbidities	18 (12.1)	16 (16.7)	2 (3.8)	**0.02**

FTA: fast track approach; SD: standard deviation; PMR: polymyalgia rheumatica; IQR: interquartile range; PVL: permanent visual loss

The relative risk of blindness in the conventional group was 2.11 (95% C.I. 1.02-4.36; P=0.04) as compared to FTA. The overall occurrence of ischaemic manifestations of GCA (AION, PION and cerebrovascular accidents) was higher in the non-FTA cohort (28.9 vs. 12.7; P=0.02). Table 12.

Table 12. Clinical characteristics at the time of diagnosis in the two cohorts: conventional approach (no FTA) versus fast track assessment

	No FTA (N=97)		FTA (N=63)		P value
Symptoms at diagnosis					
Constitutional (fever or weight loss), n (%)	36	(37.1)	28	(44.4)	0.4
Fever ≥ 38°C (≥100.4 F), n (%)	32	(33.0)	17	(27.0)	0.4
Weight loss ≥2 kg, n (%)	13	(13.4)	19	(30.2)	0.01
Any cranial symptom, n (%)	88	(90.7)	53	(84.1)	0.2
Any ocular symptom, n (%)	37	(38.1)	17	(27.0)	0.1
Permanent visual loss, n (%)	26	(26.8)	8	(12.7)	**0.03**
Amaurosis fugax, n (%)	14	(14.4)	7	(11.1)	0.5
Diplopia, n (%)	4	(4.1)	1	(1.6)	0.4
Jaw claudication, n (%)	33	(34.0)	29	(46.0)	0.1
Tongue claudication, n (%)	1	(1.0)	7	(11.1)	0.004
Scalp tenderness, n (%)	5	(5.2)	13	(20.6)	0.003
Headache, n (%)	77	(79.4)	45	(71.4)	0.3
PMR, n (%)	48	(49.5)	32	(50.7)	0.9
Increased ESR/CRP, n (%)	79	(90.8)	59	(96.7)	0.2
ESR (mm/h), median (IQR)	82	(48-102)	78	(63-96)	0.5
CRP (mg/L), median (IQR)	35	(20-99)	59	(24-98)	0.5
Anaemia (<12 g/dL in females, <13 g/dL in males), n (%)	38	(65.5)	17	(77.2)	0.3
Haemoglobin, mean (S.D.), g/dL	11.4	(1.6)	11.5	(1.4)	1.0
Cranial GCA	75	(77.3)	52	(82.5)	0.4
LV-GCA	22	(22.7)	11	(17.5)	0.4
Ischaemic GCA	28	(28.9)	8	(12.7)	**0.02**

FTA: fast track assessment; PMR: polymyalgia rheumatica; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; IQR: interquartile range; SD: standard deviation; LV-GCA: large vessel giant cell arteritis

Forty-four (45.4%) patients of the conventional cohort underwent TAB, with 25 (56.8%) samples being compatible with GCA at histological examination. TAB was performed in 3 patients of the FTA cohort, with two showing no signs of active vasculitis and one being unreliable due to a sampling error. TAB sensitivity was 53.2% (95% C.I. 38.1%-67.9%).

Within the FTA group, all 63 (100.0%) patients were evaluated with CDS at the time of diagnosis. Of these, 52 displayed specific ultrasound findings of GCA. Figure 11; Figure 12.

CDS showed a sensitivity of 82.5% (95% C.I. 70.9%-91.0%). Thirty-one (49.2%) patients had bilateral halo at CDS. Forty-three presented with halo sign exclusively at temporal arteries, 4 had only axillary artery halos, 5 had both districts involved.

Temporal artery abnormalities on examination at the time of referral was a predictor of positive CDS (43.8% vs. 10.0%; P=0.046), and it was strongly correlated to a positive halo sign at the level of the temporal arteries (47.7% vs. 7.1%; P=0.006), as well as to bilateral halo sign (51.7% vs. 24.1%; P=0.03).

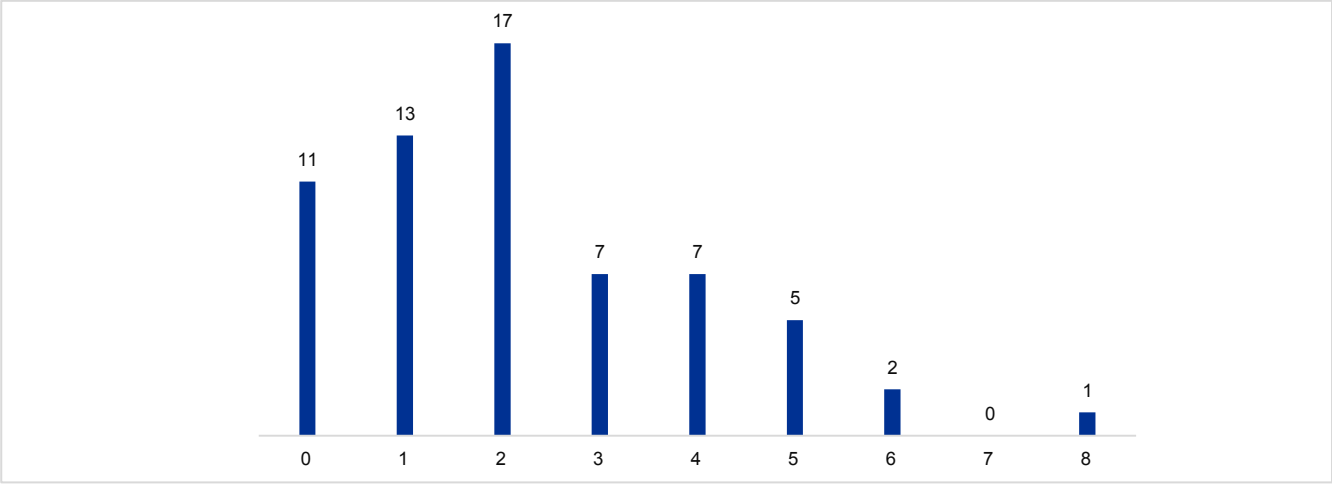


Figure 11. CDS findings of patients evaluated with the fast track approach. Number of patients according to number of sites with halos (0-8 sites including the different branches of the temporal artery and the axillary arteries).

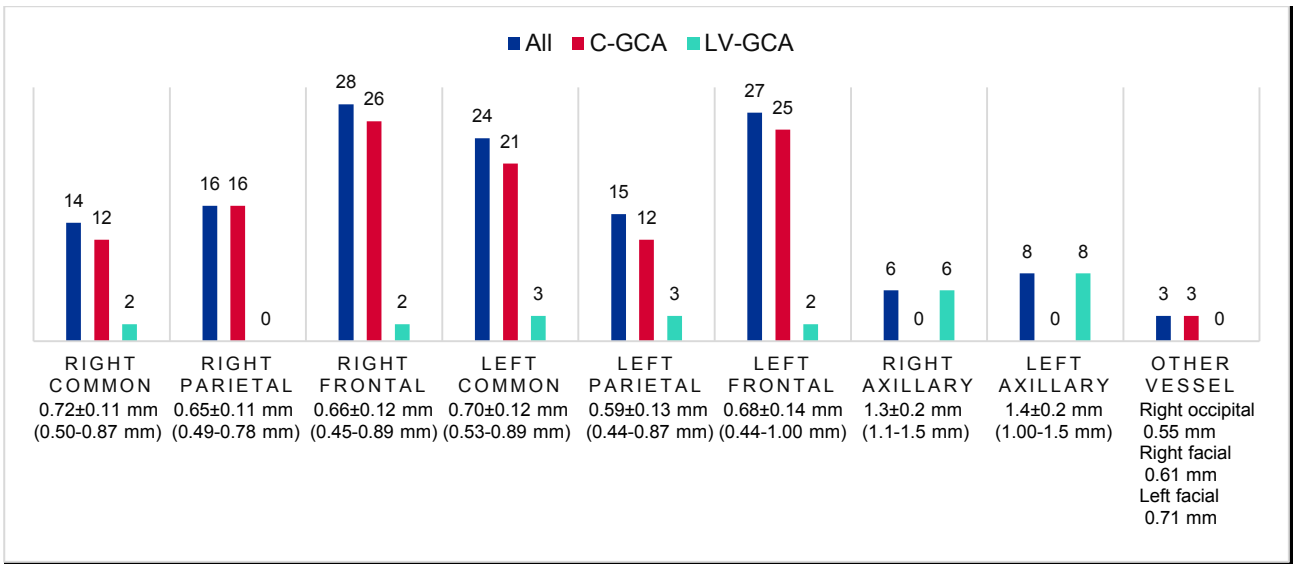


Figure 12. Ultrasonographic findings with distribution and intima-media thickness of patients evaluated with the fast track approach. Positive colour duplex sonography in each vascular district, the average halo thickness (±S.D., range) is reported below. C-GCA: cranial giant cell arteritis; LV-GCA: large-vessel giant cell arteritis.

Forty-two patients who underwent CDS (66.7%) had previously received GC for a median time of 12 days (IQR 3-101). Twenty-two patients (34.9%) had been treated with high-dose GC therapy (≥30 mg/day) for a median time of 4 days (IQR 3-8). The median prednisone-equivalent dosage on the day of scan was 37.5 mg/day (IQR 10-50).

CDS sensitivity was lower in patients with high-dose GC doses protracted for >5 days (N=10), reducing to 60.0% (95%C.I. 26.2%-87.8%).

4.1.2 Assessment during follow-up and relapses

The median follow-up duration was 3.2 years (IQR 1.0-5.9 years). Follow-up duration was shorter in the FTA group compared with the conventional one [0.9 years (IQR 0.2-2.0) vs. 5.0 years (IQR 3.5-8.7); P<0.001].

During follow-up, 82 patients relapsed (51.3%). The median time to disease reoccurrence was 8 months (IQR 3-20 months). The calculated relapse rate per 10 person-years was 3.0 (95% C.I. 2.6-3.4 years). Fifty (31.3%) patients experienced more than one relapse. In the conventional group there were 64 (66%) relapses overall, over a longer follow-up duration; in the FTA 18 (28.6%) relapses were observed. The calculated relapse rate per 10 person-years did not differ between the two cohorts: [2.9 (95% C.I. 2.5-3.4) in the conventional group vs. 3.6 (95% C.I. 2.3-5.2) in the FTA. Table 13.

The cumulative incidence of relapse and time to first relapse did not change after FTA was implemented (P=0.23). Figure 13.

During follow-up there were no new cases of PVL related to disease relapses. Symptoms at the time of first relapse were different between the two groups. In the FTA cohort a higher percentage of patients were presenting with PMR relapses (50.0% vs. 23.4%; P=0.03), whereas cranial symptoms (22.2% vs. 64.1%; P=0.002), especially headache (16.7% vs. 48.4%; P=0.02), were more frequent in the historical cohort. None of the FTA patients with ischaemic GCA relapsed during follow-up (0.0% with ischaemic disease vs. 26.6% without ischaemic GCA; P=0.01).

The ongoing therapy at the time of relapse was similar between the two groups. The median dose of prednisone was 12.5 mg/day vs. 13.75 mg/day between the two cohorts (P=0.4).

Out of 18 patients of the FTA group with a confirmed GCA relapse, 14 CDS scans were performed (77.8%). Six scans had signs of active disease (42.9%) in patients with confirmed relapses. Bilateral halo was found in 2 patients with relapse (33.3%).

Regarding the non-FTA group, 13 patients were evaluated with CDS for relapse assessment. The total number of CDS was 22, with 10 of them showing a halo (45.5%) of which four were bilateral halos (40.0%).

Table 13. Characteristics of relapses between the conventional (no FTA) and the fast track cohorts

	No FTA (N=64)		FTA (N=18)		P value
Age at relapse, mean (S.D.), years	70.3	(8.1)	72.7	(7.7)	0.3
Females, n (%)	50	(80.0)	12	(66.7)	0.2
Previous PMR, n (%)	12	(18.8)	5	(27.7)	0.4
Time to 1st relapse (if any), median (IQR), months	8.5	(3.8-20.3)	7.5	(3.3-10.8)	0.4
Relapse rate per 10 person-years, median (95% C.I.)	2.9	(2.5-3.4)	3.6	(2.3-5.2)	0.3
Any cranial symptom, n (%)	41	(64.1)	4	(22.2)	**0.002**
Any ocular symptom, n (%)	4	(6.3)	0	(0.0)	0.3
Permanent visual loss, n (%)	0	(0.0)	0	(0.0)	nd
Amaurosis fugax, n (%)	4	(6.3)	0	(0.0)	0.3
Jaw claudication, n (%)	4	(6.3)	1	(5.6)	0.9
Tongue claudication, n (%)	0	(0.0)	0	(0.0)	nd
Scalp tenderness, n (%)	3	(4.7)	0	(0.0)	0.4
Headache, n (%)	31	(48.4)	3	(16.7)	**0.02**
PMR, n (%)	15	(23.4)	9	(50.0)	**0.03**
Increased ESR/CRP, n (%)	41	(67.2)	12	(66.6)	0.9
ESR, median (IQR), mm/h	36	(25-53)	32	(22-47)	0.2
CRP, median (IQR), mg/L	11.0	(5.4-18.6)	12.5	(5.2-26)	0.9
GC dose, median (IQR), mg/day	12.5	(7.5-25)	13.75	(10-25)	0.4
Immunosuppressive drug, n (%)	9	(14.1)	0	(0.0)	0.09
Cranial GCA	48	(75.0)	16	(88.9)	0.2
LV-GCA	16	(25.0)	2	(11.1)	0.2
Ischaemic GCA	17	(26.6)	0	(0.0)	**0.01**

FTA: fast track assessment; SD: standard deviation; PMR: polymyalgia rheumatica; IQR: interquartile range; CI: confidence interval; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; GC: glucocorticoids; GCA: giant cell arteritis; LV-GCA: large vessel GCA

Anaemia at the time of diagnosis (Hb <11 g/dL) was associated with a higher relapse risk (HR 1.96 95% C.I. 1.04-3.69; P=0.04). Microcytosis (MCV <80 fL) at the time of diagnosis was found to be a good predictor of early disease relapse (HR 2.80 95%C.I. 2.33-3.26; P=0.03). A platelet count above 450000/mm^3 was another predictor of relapse (HR 2.67 95%C.I. 1.24-5.7; P=0.01).

The risk of multiple disease relapses was associated with LV-GCA (HR 2.02 95%C.I. 1.07-3.81; P=0.03).

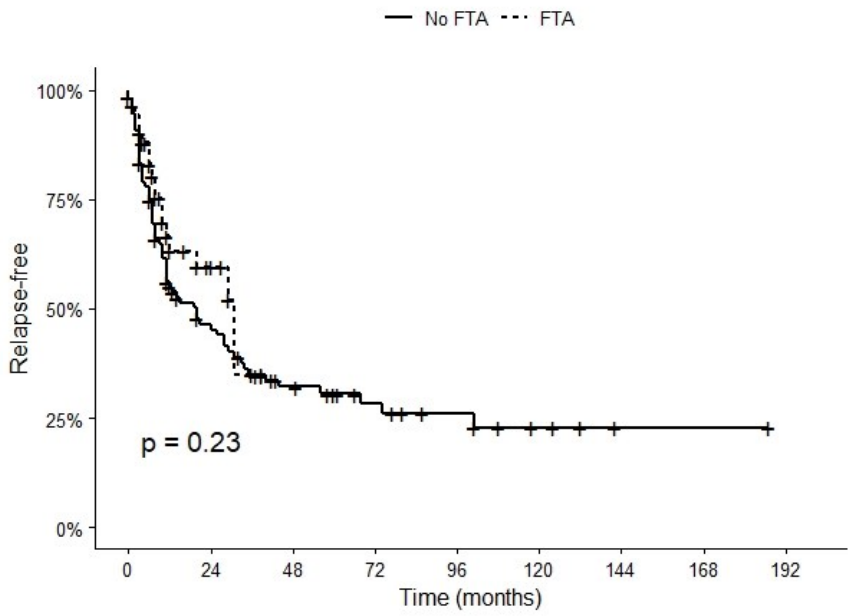


Figure 13. Time to first relapse before (no FTA) and after (FTA) the fast track assessment introduction.

At the end of the follow-up, 38 patients (23.7%) were taking an adjunctive immunosuppressive (IS) drug (34 methotrexate, 3 Tocilizumab, 1 azathioprine) initiated after a median time of 10 months (IQR 5-29 months) from diagnosis. There were no significant differences in the requirements for

adjunctive IS between the two cohorts. LV-GCA patients were at higher risk of requiring IS (HR 2.42 95%C.I. 1.16-5.04; P=0.02).

Large vessel complications (aneurysm, stenosis, vessel ectasia or dissection) were found to be more frequent in patients with LV-GCA (HR 4.58 95%C.I. 1.92-10.92; P=0.006) (Figure 14). There were no differences between the FTA and the conventional cohort.

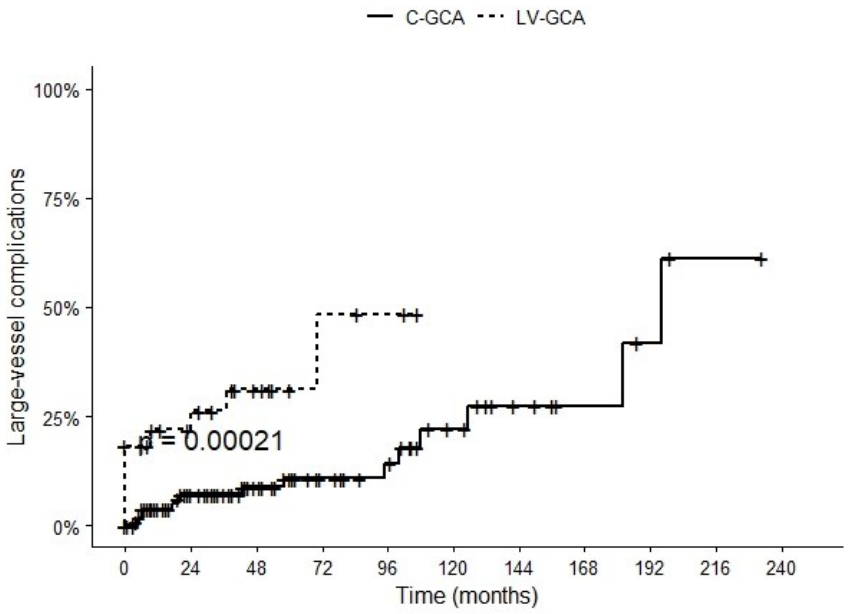


Figure 14. Cumulative incidence of large vessel complications among large-vessel giant cell arteritis (LV-GCA) compared to cranial GCA (C-GCA). Large vessel complications include thoracic/abdominal aortic aneurysm or dissection and stenosis, aneurysm or ectasia of other large arteries.

4.1.3 Fast track clinic at the time of COVID-19

During the lockdown period due the SARS-CoV-2 pandemic outbreak in Italy (March-April 2020) there was a significant decrease in the number of patients referred to the clinic compared to the

preceding months (9 visits compared to 4) and to the corresponding period in the previous year (16 visits compared to 4) despite a regularly operating service (Figure 15). Since the end of the strict lockdown period the number of new referrals has increased again (15 new visits in the period May-June 2020), nevertheless, a delay in referral has been recorded since the pandemic outbreak. Overall there have been 10 confirmed diagnoses of GCA during the COVID-19 period, female (80%), mean age 76±5 years. The rate of permanent visual loss due to GCA has significantly increased during the pandemic. Moreover, the rate of bilateral blindness due to AION has occurred in two patients during the period of only two months (March-April 2020) compared to one case over the previous four years (October 2016-February 2020) of the FTA activity. PVL occurred in 4 (40%) of GCA patients assessed since March 2020 (vs. 12.7% in the previous FTA period; P=0.03). The duration of symptoms prior to diagnosis since the COVID-19 outbreak in patients developing PVL has increased to 23 days (IQR 15-56) compared to 7 days (IQR 4-10) of the normal FTA activity. The two patients developing bilateral blindness were referred after a mean of 31 days since the onset of the first symptoms attributable to GCA.

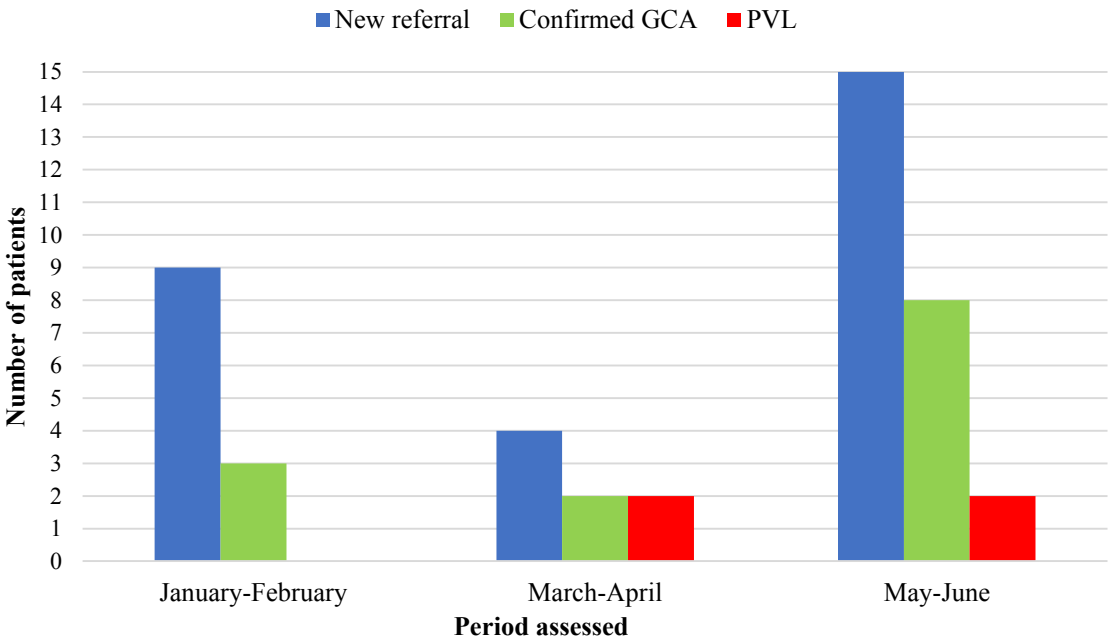


Figure 15. Comparison of the fast track clinic activity amongst different periods of 2020, including the lockdown months due to COVID-19 pandemic (March-April).
GCA: giant cell arteritis; PVL: permanent visual loss

4.2 The role of quantitative ultrasound assessment in terms of diagnostic and prognostic outcomes in GCA

The results of this research project have been published in the paper "The impact of disease extent and severity detected by quantitative ultrasound analysis in the diagnosis and outcome of giant cell arteritis" by Monti et al. (107) and are summarized below.

4.2.1 Population characteristics

One-hundred and thirty-five patients included in the TABUL Study (female: 68%, mean age 73±8 years) who had a positive CDS and a final confirmed diagnosis of GCA. The discriminatory ability of CDS on diagnosis was assessed by comparing the 135 patients with GCA with 44 patients who

had a positive CDS showing a halo, but did not have a final diagnosis of GCA. Of the 135 patients, 128 (95%) were recorded to have a halo in at least one site of a temporal artery (TA) (either the common branch of the TA, parietal or frontal branches). Bilateral halos were reported in 71 of cases (52%). Thirty-seven patients (27%) had axillary (AX) involvement, of whom 16 (12%) had bilateral halos of the AX arteries. Among the patients with a positive CDS of the AX, 7 (5%) had exclusive AX involvement.

The independent cohort consisted of 72 patients (female: 46%; mean age 75±7 years) with a confirmed clinical diagnosis of GCA and a positive CDS. Five subjects with a positive CDS were diagnosed as not having GCA. Sixty-three patients (87%) had at least one site with a halo at the TA (bilateral in 54% of cases). Twenty-four patients (33%) had AX involvement (bilateral in 8%). Only 6 patients had isolated AX involvement (8%).

Detailed frequencies of CDS findings and halo characteristics in each cohort are presented in Table 14. The distribution of patients according to the number of sites with halos for each cohort is presented in Figure 16. One vascular site showing a halo was recorded for 28% of patients in TABUL and 35% in the independent cohort. Two sites with a halo were reported in 21% and 29% of patients, respectively. A minority of patients showed active involvement in more than six vascular sites (4.4% in TABUL and 0% in the independent cohort).

Table 14. Frequency of ultrasound findings and halo characteristics considered for the analysis in the TABUL and in the independent cohort.

CDS variable	Detailed description	Frequency and halo size - TABUL	Frequency and halo size – Independent cohort
Overall number of sites with halo	Number of sites with halo in TA + number of sites with halo in AX	128 patients with halo in TA + 37 with halo in AX **min 0; max 8 sites**	63 patients with halo in TA + 24 with halo in AX **min 0; max 6 sites**
Number of halos in TA	Sum of sites with halo in TA	128 patients with halo in TA **min 0; max 6 sites**	63 patients with halo in TA **min 0; max 6 sites**
Average halo thickness in TA	Average halo thickness among sites with halo in TA	Data available for 125 patients **Average 0.6 ± 0.28 mm**	Data available for 63 patients **Average 0.56 ± 0.13 mm**
Average halo thickness in AX	Average halo thickness among sites with halo in AX	Data available for 37 patients **Average 1.3 ± 0.85 mm**	Data available for 24 patients **Average 1.38 ± 0.3 mm**
Maximum halo thickness in TA	Maximum halo thickness among sites with halo in TA	Data available for 125 patients **min 0.1; max 3.2 mm**	Data available for 63 patients **min 0.3; max 1.4 mm**
Maximum halo thickness in AX	Maximum halo thickness among sites with halo in AX	Data available for 37 patients **min 0.6 mm; max 6.7 mm**	Data available for 37 patients **min 1.0 mm; max 2.4 mm**
Bilateral halo in TA	Defined as the presence of a bilateral halo on any branch of the TA	**71 of 135 patients (52%)**	**39 of 72 patients (54%)**
Bilateral halo in AX	Defined as the presence of a halo on both AX arteries	**16 of 135 patients (12%)**	**6 of 72 patients (8%)**

TA: temporal artery, AX: axillary artery

The clinical characteristics of the populations included in the analysis are presented in Table 15. Patients were more frequently female in TABUL compared to the independent cohort (68% vs 46%; p=0.002); there were no significant differences in age between the two cohorts.

The mean duration of GC treatment prior to CDS assessment was significantly longer in the independent cohort (14.5±15.5 vs 1.9±1.8 days; p<0.001); however, GC had been prescribed significantly more frequently to patients enrolled in TABUL compared to the independent cohort (74% vs 53%; p=0.003).

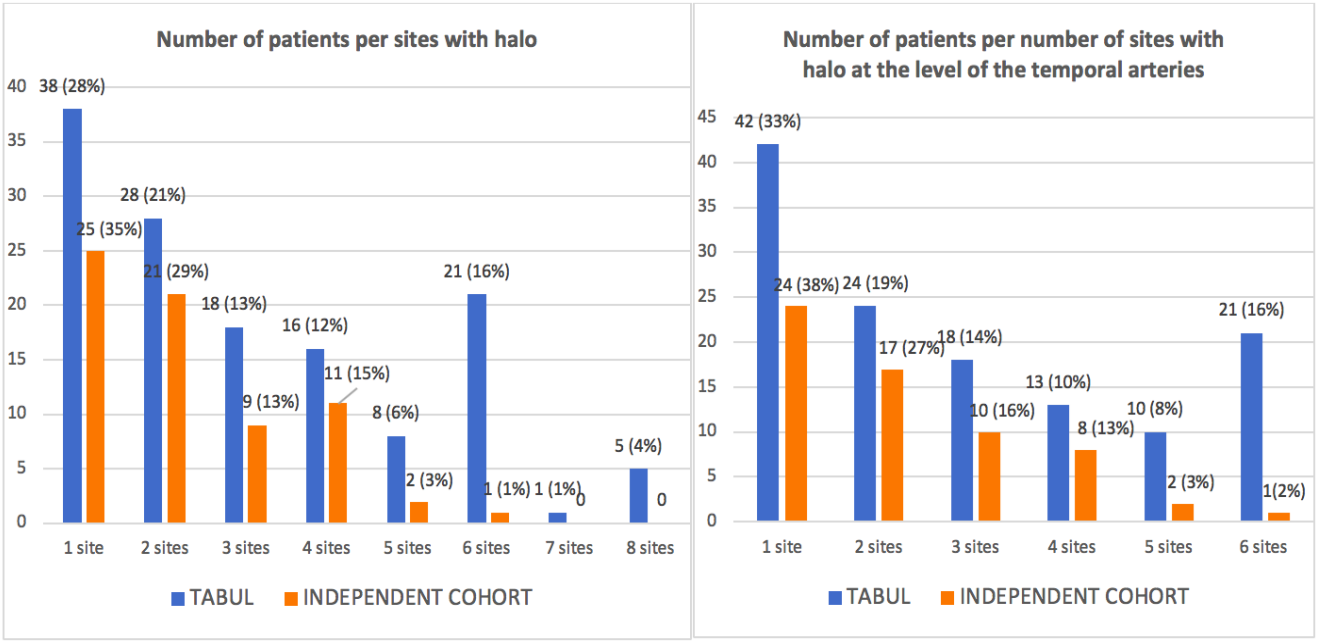


Figure 16. Distribution of patients according to the number of sites with halos for each cohort

Clinical presentation differed for frequency of systemic symptoms (58% of cases in TABUL vs 19% in the independent cohort; p<0.001) and PMR, less frequently reported in TABUL patients (18% vs 44%; p=0.0001). There were no significant differences regarding ischaemic symptoms at presentation or rate of PVL between the two cohorts**.**

Table 15. General characteristics of patients with giant cell arteritis in the two cohorts

	Patients with GCA with positive CDS – TABUL (N=135)	**Patients with GCA with positive CDS – independent cohort** (N=72)	P
Female (n; %)	92 (68%)	33 (46%)	0.002
Age (mean; sd)	73 (8)	75 (7)	0.086
High-dose GC prior to CDS	100 (74%)	38 (53%)	0.003
Number of days on GC on the day of CDS scan, mean (sd)	1.9 (1.8)	14.5 (15.5)	<0.001
TAB findings			
TAB diagnostic for GCA	76 (56%)	na*	
Media infiltrate	20 (15%)	na	
Transmural infiltrate	26 (19%)	na	
Small vessel or adventitia	18 (13%)	na	
Laboratory findings/Symptoms			
Elevated ESR/CRP¶	131 (97%)†	70 (97%)†	1
General symptoms pre-GC	96 (71%)	29 (40%)	<0.001
Headache pre-GC	93 (69%)	57 (79%)	0.126
Jaw claudication pre-GC	62 (46%)	37 (51%)	0.494
Visual symptoms pre-GC	57 (42%)	40 (56%)	0.055
PMR pre-GC	25 (18%)	32 (44%)	0.0001
General symptoms current on day of CDS	78 (58%)	14 (19%)	<0.001
Headache current on day of CDS	69 (51%)	35 (49%)	0784
Jaw claudication current on day of CDS	39 (29%)	19 (26%)	0.647
Visual symptoms current on day of CDS	30 (22%)	18 (25%)	0.626
PMR current on day of CDS	24 (18%)	20 (28%)	0.096
Any visual loss#	22 (16%)	18 (25%)	0.117
Ischaemic symptoms at presentation (jaw/tongue claudication, amaurosis fugax, double vision, stroke)	81 (60%)	50 (69%)	0.226
BVAS 6 months			
BVAS ocular	11 (8%)	7 (10%)	0.627
BVAS nervous	11 (8%)	19 (26%)	0.0004
BVAS=0	93 (69%)	39 (54%)	0.033
BVAS ≥ 1	28 (21%)	26 (36%)	0.019
BVAS ≥ 5	12 (9%)	3 (4%)	0.187
BVAS ≥ 10	2 (1%)	0	na
VDI 6 months**			
VDI =0	77 (57%)	36 (50%)	0.336
VDI =1	29 (21%)	17 (24%)	0.621
VDI = 2	10 (7%)	3 (4%)	0.386
VDI =3	1 (0.7%)	3 (4%)	0.093
VDI =4	3 (2%)	2 (3%)	0.652
VDI =5	1 (0.7%)	1 (1%)	0.818
VDI diplopia	12 (9%)	12 (17%)	0.089
VDI blindness	13 (10%)	12 (17%)	0.147
GC > 10 mg/day at 6 months	39 (29%)	25 (35%)	0.375
Adjunctive immunosuppressive drug at 6 months#	12 (9%)	34 (47%)	<0.001

* in the independent cohort of patients with GCA, only one TAB was performed (and without any artery obtained in the specimen). #TABUL: methotrexate (n=10); leflunomide (n=2). Independent cohort: methotrexate (n=32); leflunomide (n=1); IL-6 inhibitor (n=1). #any visual loss defined as: permanent visual loss in at least one eye and/or evidence of anterior ischaemic optic neuropathy due to GCA. ¶ elevated ESR/CRP: ESR > 15 mm/hour and or CRP > 5 mg/L; † Data not available for 2 patients.

4.2.2 Ultrasound and clinical models (TABUL cohort)

The association of four different ultrasound models including quantitative features detected on CDS was tested against two main outcomes: the biopsy outcome (TAB diagnostic for GCA), n=76 patients (56%), and the clinical outcome (composite prognostic measure at 6 months from diagnosis), n=55 patients (41%) (Table 16). There was a significant association between total number of halos, halo thickness at the level of the TA and bilateral TA halos with the biopsy outcome. The best model (with the lowest AIC) for a positive TAB included a combination of the following variables: maximum IMT at the TA > 0.70 mm (median value for the cohort), bilateral TA halos, maximum AX IMT > 1.30 mm (median value for the cohort), and bilateral AX halos (Model 4 CDS).

The association of four clinical models based on the most frequent and relevant symptoms of GCA was tested against the same two main outcomes (TAB outcome and prognostic outcome). The best model (with the lowest AIC) included the number of ischaemic symptoms at presentation, PMR and elevated ESR/CRP values (Model 3 clinical).

None of the clinical models reached statistical significance in predicting the biopsy outcome, although a significant association of elevated ESR/CRP values with the biopsy outcome was found.

None of the clinical models predicted the clinical outcome at 6 months, with only systemic symptoms showing significant association with the 6-months outcome (Table 17).

Table 16. Association between the ultrasound combined models and the biopsy and clinical outcome – TABUL cohort

BIOPSY OUTCOME (TAB diagnostic for GCA)					**CLINICAL OUTCOME** (visual loss + more intensive treatment at 6 months)				
	OR	**95% CI**	**AIC**	**p**		**OR**	**95% CI**	**AIC**	**p**
MODEL 1 CDS			***162.39***	***0.008***	***MODEL 1 CDS***			***172.49***	***0.406***
Total halos	1.36	1.09-1.69		0.007	Total halos	0.97	0.80-1.18		0.788
Average TA IMT > 0.60 mm	2.26	1.02-5.02		0.044	Average TA IMT > 0.60 mm	0.97	0.45-2.07		0.932
Average AX IMT > 1.20 mm	1.15	0.47-2.82		0.762	Average AX IMT > 1.20 mm	1.53	0.45-3.58		0.325
MODEL 2 CDS			***161.48***	***0.079***	***MODEL 2 CDS***			***170.53***	***0.790***
Maximum TA IMT > 0.70 mm	4.43	2.01-9.78		<0.001	Maximum TA IMT > 0.70 mm	1.09	0.53-2.26		0.378
Maximum AX IMT > 1.30 mm	1.34	0.57-3.16		0.508	Maximum AX IMT > 1.30 mm	1.48	0.66-3.35		0.342
MODEL 3 CDS			***156.83***	***0.597***	***MODEL 3 CDS***			***173.91***	***0.118***

Average TA IMT > 0.60 mm	2.81	1.25-6.33		0.013	Average TA IMT > 0.60 mm	0.90	0.43-1.87	0.773
Bilateral TA	4.61	2.06-10.32		<0.001	Bilateral TA	1.10	0.52-2.33	0.796
Average AX IMT > 1.20 mm	1.72	0.57-5.23		0.339	Average AX IMT > 1.20 mm	1.18	0.40-3.44	0.764
Bilateral AX	1.31	0.27-6.46		0.736	Bilateral AX	1.67	0.40-7.06	0.485
MODEL 4 CDS			***155.91***	***0.351***	***MODEL 4 CDS***		***173.99***	***0.620***
Maximum TA IMT > 0.70 mm	3.16	1.36-7.34		0.007	Maximum TA IMT > 0.70 mm	1.00	0.46-2.19	0.994
Bilateral TA	3.53	1.56-7.98		0.003	Bilateral TA	1.09	0.50-2.39	0.823
Maximum AX IMT > 1.30 mm	1.54	0.52-4.60		0.440	Maximum AX IMT > 1.30 mm	1.20	0.41-3.48	0.737
Bilateral AX	1.15	0.23-5.72		0.868	Bilateral AX	1.63	0.38-6.98	0.510

*****ischaemic symptoms: presentation with jaw or tongue claudication, amaurosis fugax, double vision, stroke; #ESR ≥ 50 mm/hour and/or CRP > 40 mg/L; §systemic symptoms: fever, weight loss, night sweats

Table 17. Association between the clinical combined models and the biopsy and clinical outcome – TABUL cohort

BIOPSY OUTCOME (TAB diagnostic for GCA)					**CLINICAL OUTCOME** (visual loss + more intensive treatment at 6 months)				
	OR	**95% CI**	**AIC**	**p**		**OR**	**95% CI**	**AIC**	**p**
MODEL 1 CLINICAL			***148.77***	***0.707***	***MODEL 1 CLINICAL***			***147.85***	***0.688***
Any ischaemic symptoms*	1.30	0.56-3.05		0.542	Any ischaemic symptoms*	2.27	0.97-5.31		0.059
PMR	0.62	0.23-1.68		0.342	PMR	1.21	0.45-3.25		0.707
Elevated ESR/CRP#	2.96	1.32-6.66		0.009	Elevated ESR/CRP#	0.50	0.22-1.12		0.093
MODEL 2 CLINICAL			***149.14***	***0.824***	***MODEL 2 CLINICAL***			***147.36***	***0.599***
Systemic symptoms§	0.97	0.37-2.52		0.951	Systemic symptoms§	2.69	1.01-7.17		0.048
PMR	0.66	0.24-1.85		0.434	PMR	1.06	0.39-2.91		0.907
Elevated ESR/CRP#	2.81	1.26-6.30		0.012	Elevated ESR/CRP#	0.47	0.21-1.06		0.070
MODEL 3 CLINICAL			***147.59***	***0.189***	***MODEL 3 CLINICAL***			***148.59***	***0.543***
Number of ischaemic symptoms*	1.33	0.84-2.11		0.219	Number of ischaemic symptoms*	1.46	0.94-2.27		0.091
PMR	0.57	0.21-1.58		0.278	PMR	1.20	0.44-3.24		0.719
Elevated ESR/CRP#	3.02	1.34-6.78		0.008	Elevated ESR/CRP#	0.46	0.21-1.03		0.059
MODEL 4 CLINICAL			***149.09***	***0.551***	***MODEL 4 CLINICAL***			***147.86***	***0.697***
Headache	0.90	0.36-2.21		0.815	Headache	2.37	0.96-5.87		0.061

PMR	0.68	0.25-1.84	0.442	PMR	1.17	0.43-3.15	0.762
Elevated ESR/CRP#	2.79	1.25-6.21	0.012	Elevated ESR/CRP#	0.46	0.21-1.04	0.062

*ischaemic symptoms: presentation with jaw or tongue claudication, amaurosis fugax, double vision, stroke; #ESR ≥ 50 mm/hour and/or CRP > 40 mg/L; §systemic symptoms: fever, weight loss, night sweats.

4.2.3 GCA-US score

The best fitting CDS and clinical models were combined to derived a simple score to compute the probability of a TAB diagnostic for GCA.

The final model AUC-ROC was 0.77 (95 % C.I. 0.68-0.84); after 10-fold-cross-validation it became 0.66 (95 % C.I. 0.55 - 0.76).

The score can be easily computed using the algorithm shown in Figure 17 (left panel) and the expected probability of positive biopsy is derived from Figure 17, right panel. Two simulated cases are reported.

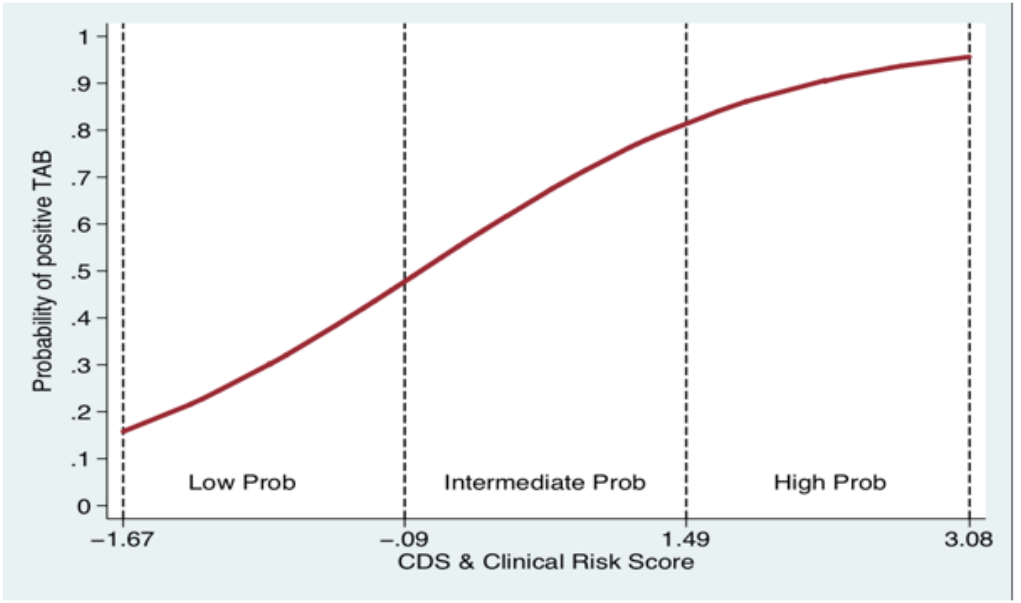
(1) Coefficients for score calculation

Variable	Coefficient
Maximum TA IMT > 0.70 mm	1.09
Bilateral TA	1.06
Maximum AX IMT > 1.30 mm	0.54
Bilateral AX	0.27
Any ischaemic (jaw claudication, visual*, stroke)	0.44
PMR	-0.38
Elevated APR (ESR ≥ 50 mm/h; CRP > 40 mg/L)	0.97

(2) Categorization into risk groups

Risk Tertile	Score value	Probability of positive TAB
Low	-1.67; -0.09	35% (95% CI 32-37)
Intermediate	-0.08; 1.49	66% (95% CI 64-68)
High	1.50; 3.08	89% (95% CI 88-91)

(3) Nomogram to derive the probability of positive TAB, given the score



(4) Simulated Examples

Case 1: Patient with ESR of 51 mm/hour, headache, jaw claudication, right TA involvement with max TA IMT 0.71 mm at CDS: 0.97 + 0.44 + 1.09 = 2.5
This corresponds to a high risk of having a positive TAB. This patient has a probability between 88% and 91% of having a positive TAB.

Case 2: Patient with CRP of 54 mg/L, headache, PMR, right AX involvement at CDS with max IMT 1.60 mm: 0.9 -0.38+0.54= 0.76
This corresponds to an intermediate risk of having a positive TAB. This patient has a probability between 64% and 68% of having a positive TAB.

*visual: double vision, amaurosis fugax. TA: temporal artery; IMT: intima-media thickness; AX: axillary artery; PMR: polymyalgia rheumatica; APR: acute phase reactants.

Figure 17. GCA-US SCORE. Combination of ultrasonographic and clinical models to stratify patients according to the risk of having a positive temporal artery biopsy.

4.2.4 Application of the ultrasound and clinical models on the independent cohort

The CDS and clinical models were used to assess the association with the clinical outcome at 6 months in the independent cohort confirming the lack of association (Tables 18 and 19).

Table 18. Association between the ultrasound combined models and the clinical outcome at 6 months – Independent cohort

CLINICAL OUTCOME AT 6 MONTHS (visual loss + more intensive treatment at 6 months)				
	OR	**95% CI**	**AIC**	**p**
MODEL 1 CDS			***51.29***	***0.349***
Total halos	1.52	0.75-3.08		0.241
Average TA IMT > 0.60 mm	1	*		*
Average AX IMT > 1.20 mm	3.01	0.55-16.48		0.204
MODEL 2 CDS			***49.82***	***0.173***
Maximum TA IMT > 0.70 mm	1	**		**
Maximum AX IMT > 1.30 mm	3.00	0.55-16.22		0.202
MODEL 3 CDS			***49.26***	***0.241***
Average TA IMT > 0.60 mm	1	*		*
Bilateral TA	3.08	0.64-14.75		0.159
Average AX IMT > 1.20 mm	3.18	0.50-20.13		0.219
Bilateral AX	1	§		§
MODEL 4 CDS			***49.39***	***0.551***
Maximum TA IMT > 0.70 mm	1	**		0.551
Bilateral TA	1.78	0.38-8.43		0.468
Maximum AX IMT > 1.30 mm	2.25	0.36-14.20		0.389
Bilateral AX	1	§		§

*Average TA IMT not 0 predicts success perfectly; ** Maximum TA IMT not 0 predicts success perfectly; § Bilateral AX not 0 predicts success perfectly. TA: temporal arteries; IMT: intima-media thickness; AX: axillary arteries; CDS: colour duplex sonography; OR: odds ratio; CI: coinfidence interval; AIC: Akaike Information Criterium

Table 19. Association between the clinical combined models and the clinical outcome at 6 months– Independent cohort

CLINICAL OUTCOME AT 6 MONTHS (visual loss + more intensive treatment at 6 months)				
	OR	**95% CI**	**AIC**	**p**
MODEL 1 CLINICAL			***60.73***	***0.545***
Any ischaemic symptoms*	1.89	0.45-7.88		0.382
PMR	1.28	0.31-5.34		0.734
Elevated ESR/CRP#	1.40	0.33-5.94		0.648
MODEL 2 CLINICAL			***54.49***	***0.657***
Systemic symptoms§	7.51	0.87-64.94		0.067
PMR	1.42	0.33-6.21		0.637
Elevated ESR/CRP#	1.07	0.24-4.74		0.928
MODEL 3 CLINICAL			***60.95***	***0.061***
Number of ischaemic symptoms*	1.34	0.59-3.04		0.480
PMR	1.25	0.30-5.22		0.758
Elevated ESR/CRP#	1.34	0.32-5.63		0.691
MODEL 4 CLINICAL			***61.37***	***0.266***
Headache	0.76	0.14-4.24		0752
PMR	1.34	0.32-5.65		0.690
Elevated ESR/CRP#	1.29	0.31-5.43		0.118

*ischaemic symptoms: presentation with jaw or tongue claudication, amaurosis fugax, double vision, stroke; #ESR ≥ 50 mm/hour and/or CRP > 40 mg/L; §systemic symptoms: fever, weight loss, night sweats. PMR: polymyalgia rheumatica; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; OR: odds ratio; CI: coinfidence interval; AIC: Akaike Information Criterium

To overcome the lack of TAB data in the independent cohort, whether the predictive probability of a positive biopsy (given the clinical and CDS information) was different between the two cohorts was tested by applying the GCA-US score, and found that there was no difference in the probability of having a positive TAB if the patients from the independent cohort had undergone a biopsy (mean

probability of a positive TAB in TABUL 0.64±0.22 compared to 0.61±0.21 in the independent cohort; p=0.254).

Given the absence of TAB data in the independent cohort, we could not formally validate the GCA-US score on an independent cohort.

4.3 Systematic literature review informing the update of the European recommendations on the management of large vessel vasculitis

The results of this research project have been published in the papers "Systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis: focus on giant cell arteritis" by Monti et al. (114) and "2018 Updated of the EULAR recommendations on the management of large vessel vasculitis" by Hellmich, Agueda, Monti et al. (110) and are summarized below.

4.3.1 Results of the systematic literature review

After removal of duplicates, the SLR focused on diagnosis and monitoring of LVV yielded 4389 articles and the one focused on treatment yielded 6226 articles. One hundred and twenty-two and 165 studies (respectively) were included for full-text review. Of these, 62 and 76 studies, respectively, focused on GCA. Details are represented in Figures 18 and 19.

A meta-analysis of the collected evidence was not performed due to pronounced heterogeneity of the included studies in terms of design, inclusion criteria, methodology, type of intervention and outcome.

General management and diagnosis

Disease Patterns of GCA

Standardised definitions for different disease patterns are lacking, leading to difficulties in comparability between studies. Nevertheless, 12 papers focusing on disease subtypes in GCA and on their clinical and prognostic implications were retrieved. Patients with LV-GCA are more likely to be younger (96,122,123) and female (91,124) and suffer from a longer diagnostic delay (91,92,123) compared to those with cranial involvement. Headache, jaw claudication, scalp tenderness and visual

complications are less frequent (91,123–125), while limb claudication and PMR are more characteristic (92,123,124). Relapse rates were higher in LV-GCA (4.9 vs 3.0/10 person-years; p<0.001) (92,125) with discordant results on the need for more intensive immunosuppressive regimens (91,92,123,125–127). LV involvement with aortic aneurysm/dissection is associated with increased mortality in GCA (128).

In summary, disease patterns of GCA are mainly represented by cranial- and LV-GCA. This distinction may have clinical and prognostic implications. (LoE 3b)

Role of temporal artery biopsy in GCA

The SLR identified 13 retrospective observational papers (129–141) and three prospective studies, (90,142,143) on the diagnostic role of TAB and associated clinical features. TAB should be performed as soon as possible, since in one large study including 381 patients sensitivity decreased rapidly with high dose of GC treatment (48% within 3 days vs 33% ≥ 7 days) (90). Nevertheless, another study on 535 patients had shown similar percentages of TAB positivity regardless of previous GC treatment (31% in untreated patients vs 35% in patients exposed to GC before TAB; p=0.4). The frequency of positive TAB reduced with ongoing GC therapy > 7 days but persisted in 28% of cases treated with GC for over 2 weeks. Moreover, one small pathological study (40 patients with initial positive TAB) reported that signs of vasculitis may still be demonstrated on repeated biopsies obtained after 3 (n=10), 6 (n=12), 9 (n=9) or 12 months (n=9) of GC therapy but with decreasing probability of finding changes suggestive of GCA. (142)

The recently published TABUL Study has reported a TAB sensitivity compared to clinical diagnosis of 39%, with 100% specificity. (90)

The length of TAB is important to increase the diagnostic yield. The cut-off with the highest positive predictive value for a positive TAB has been reported to be ≥ 0.7 cm after specimen fixation (90,129).

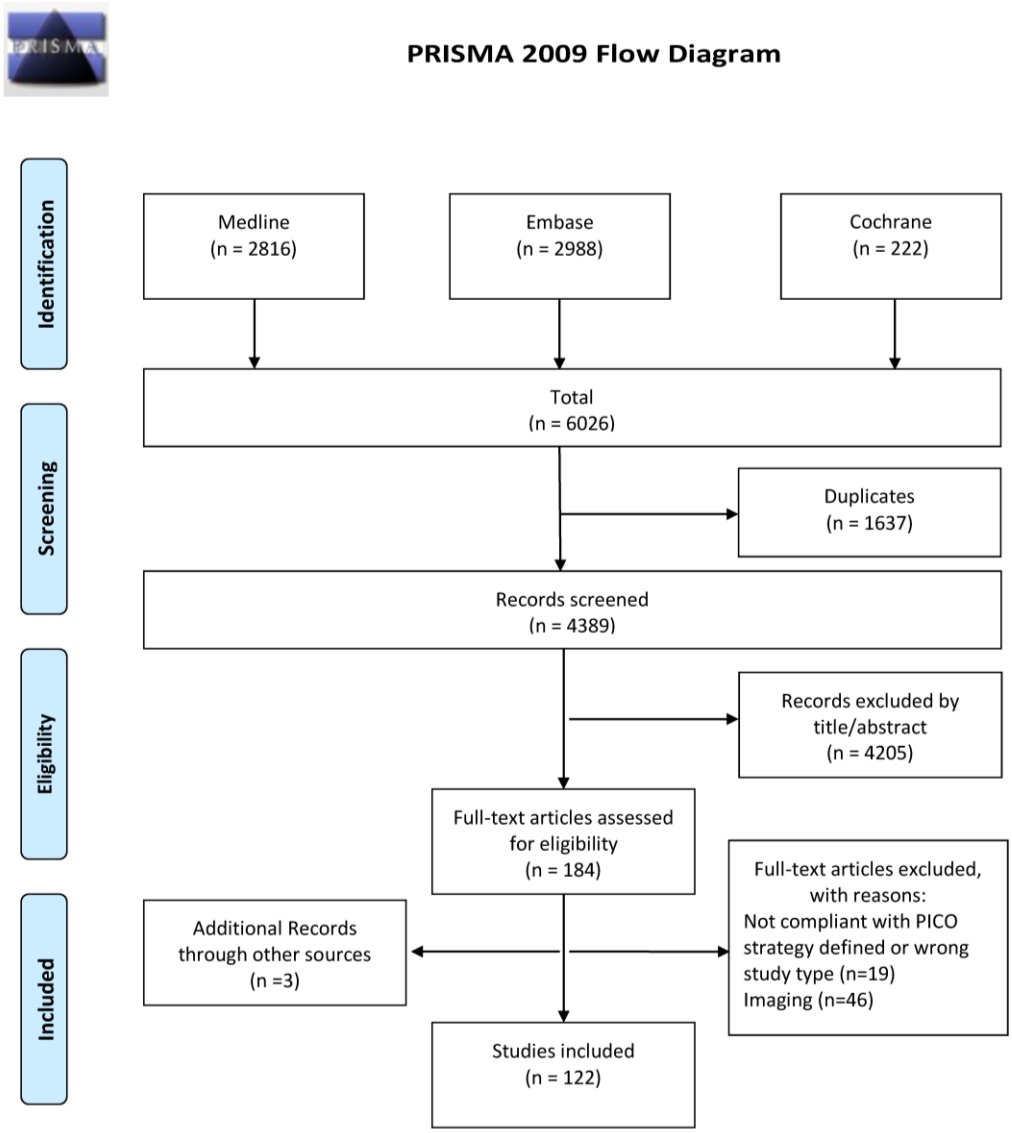


Figure 18. Flowchart of the systematic literature review results on diagnosis and monitoring of large vessel vasculitis

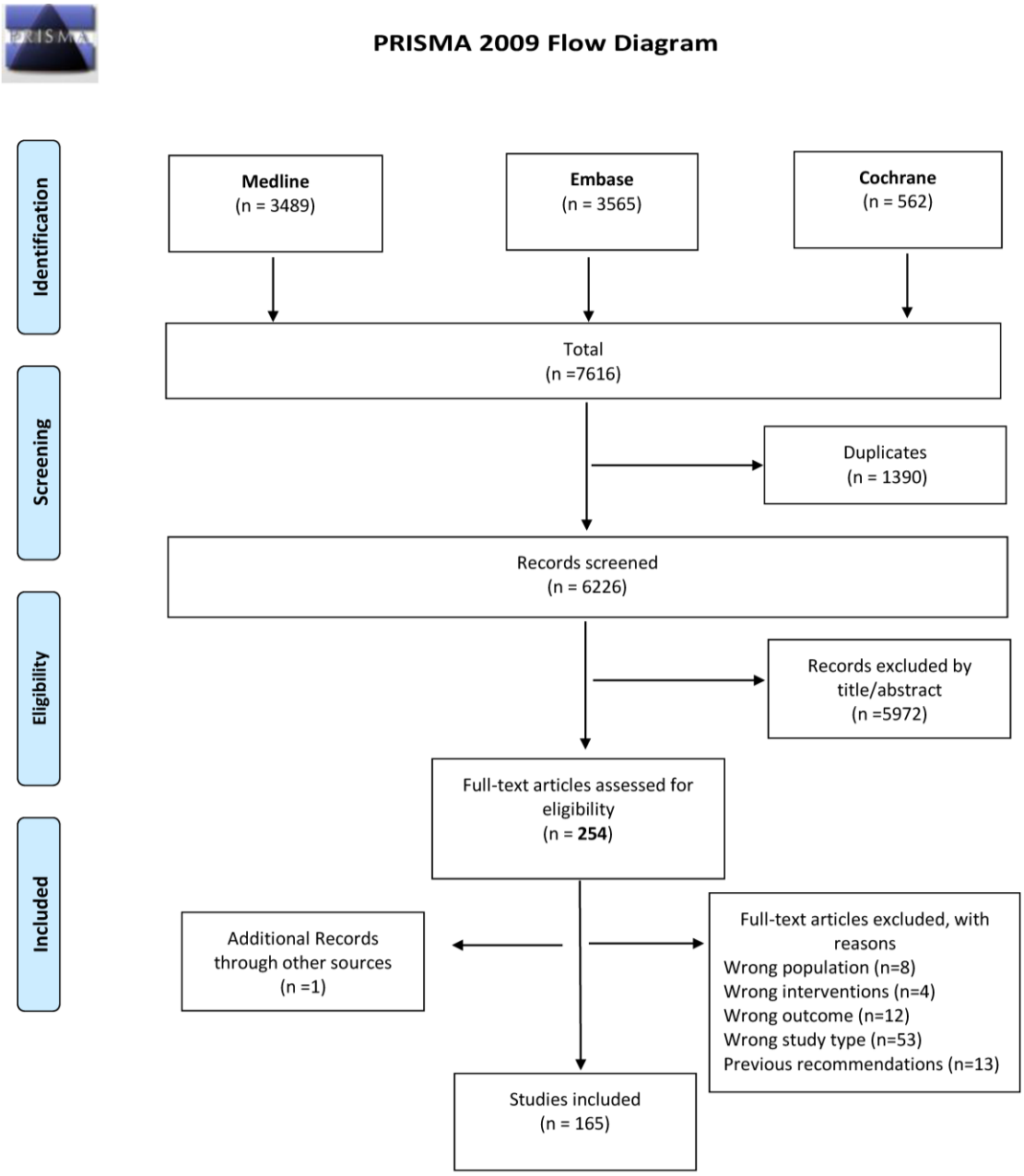


Figure 19. Flowchart of the systematic literature review results on treatment of large vessel vasculitis

A retrospective multicenter study reported that when the inflammatory infiltrate involves the media and media-intima junction the cut-off should be ≥ 0.5 cm (144).

Histological patterns of inflammatory infiltrate distribution (e.g. transmural) have been correlated with specific clinical manifestations (e.g. typical cranial symptoms) (130). The presence of giant cells and calcifications on TAB have been correlated with the development of PVL (139). Giant cells have also been linked with a relapsing disease course (134–136).

In summary, TAB is a highly specific test to confirm a diagnosis of GCA (LoE 1b), however, diagnostic yield depends on timing after GC initiation and correct sampling. There is no consistent data supporting a prognostic role for TAB on disease course or outcome.

Fast-track clinics for the diagnosis of GCA

The SLR found two retrospective cohort studies (total number of patients n=189) comparing conventional clinical practice to a FTA (Table 2). (100,145) Compared to historical cohorts, the FTA has been associated with a significant reduction in the rates of PVL (100,145), costs (100) and TAB requirements (19) (LoE 2b).

Table 20. Retrospective cohort studies comparing a fast track diagnostic strategy for giant cell arteritis to conventional practice

Study ID	N	Variable assessed	FTA	Conventional practice	p value	NOS scale
Patil et al. (145)	113	Permanent visual impairment [n; (%)]	6 (9%)	17 (37%)	0.001	2
Diamantopoulos et al. (100)		Time from symptoms to diagnosis [median (range) days]	17.5 (0–206)	21.0 (1–196)	>0.2	
	75	Permanent visual impairment [n]	1 (1.3%)	6 (8%)	0.01#	2

Relative risk: 0.12 (95% CI: 0.01, 0.97)
FTA: fast-track approach; NOS: Newcastle-Ottawa risk of bias scale

Implications of disease activity, damage, comorbidities and complications on GCA

According to the SLR results, several observational studies have investigated the predictors of ischaemic complications in GCA. Transient visual ischemic symptoms (146,147), cerebrovascular accidents (148), jaw claudication (146,149), headache, temporal artery tenderness (146), and increased platelet count (146) have been reported as risk factors for visual complications. On the contrary, PMR, upper limb arterial involvement, systemic symptoms, elevated c-reactive protein (CRP) and low haemoglobin levels were associated with a reduced risk (48,146,150). Cerebrovascular accidents in GCA have been associated with the presence of comorbidities such as hypertension (151–153) and dyslipidaemia (151) but negatively correlated with anaemia and female sex (151,152).

Relapses are more frequent in the first year after diagnosis (154) and are more common amongst patients reporting scalp tenderness, PMR, and evidence of a strong inflammatory response (at least three of the following: fever >38°C, weight loss ≥4kg, haemoglobin <11g/L, and erythrocyte sedimentation rate (ESR) ≥85mm/h) (102,155,156).

The occurrence of vascular complications in GCA is high within the first year from diagnosis. The risk of development of aortic aneurysms/dissection increases over time, especially after 5 years from diagnosis, and occurs in 20-30% of patients. The aortic diameter (assessed by CT) increases over time and is more significant in the ascending and descending aorta, occurring mostly at the expense of patients with aortic structural damage at the first CT. Interestingly, the size of the aneurysm has not been associated with the risk of dissection/rupture in patients with GCA, with these complications potentially occurring at lower aneurysm sizes compared to atherosclerotic aneurysms (157).

Aortic involvement is associated with a 5-fold increase risk of death (157,158).

Overall, evidence suggests a prognostic role of specific disease-onset symptoms with ischaemic complications and poor outcome (LoE 3b). Comorbidities can influence GCA-related complications and their management should be integrated in the treatment of GCA (LoE 2b).

Biomarkers for GCA

The SLRs retrieved 24 observational studies that analysed biomarkers and their association with disease outcome. ESR and CRP are the most frequently used biomarkers to assess disease activity in GCA. A stronger inflammatory response has been associated with a decreased risk of ischemic events, (159,160) but higher risk of relapse (156,161). Rarely, GCA can present with normal inflammatory markers.

As Tocilizumab (TCZ) suppresses CRP production and indirectly ESR levels (e.g. secondary to fibrinogen and acute phase reactants reduction) these biomarkers may not accurately reflect disease activity in patients treated with TCZ and the search for alternative biomarkers is desirable.

Circulating levels of several cytokines (e.g. IL-6 and TNF-alpha) have been associated with a relapsing course of GCA (162–164). High IL-6 levels have been inversely associated with ischaemic events (165). Osteopontin has recently been proposed as a marker of active disease especially in patients treated with TCZ (166).

The association between antiphospholipid antibodies and ischaemic complications in GCA is controversial (167–170).

In summary, validated, reliable biomarkers for GCA are still not available. ESR and CRP are the most widely used and correlate with disease activity (LoE 3b). Nevertheless, the reliability of CRP in patients with GCA receiving TCZ still needs to be addressed.

Long term follow-up of patients including clinical assessment; physical therapy

The SLRs could not find evidence regarding the best timings/frequency of follow-up visits nor was there any data on the role of physical therapy.

Patient reported outcome measures and patient centred care in GCA

One prospective study assessed the efficacy of a patient education program for patients with different types of vasculitis (including nine patients affected by GCA). A significant increase in the awareness on the disease was confirmed after the training programme (171).

Treatment aspects

Glucocorticoids

The SLRs yielded four randomized controlled trials (RCTs) assessing the use of GC in patients with newly diagnosed GCA (172–175). Table 21. Of these, two RCTs studied the GC-sparing effect of high-dose pulse intravenous (i.v.) methylprednisolone induction therapy; one of these had a high RoB as the study was not blinded (175). Notably, both RCTs on the use of high-dose i.v. GC excluded patients with recent vision loss or ocular/vascular complications. The GC regimens used differed between the two studies: 15 mg/kg i.v. methylprednisolone for 3 days followed by 40 mg/day oral prednisone with rapid tapering (173), or 240 mg i.v. single pulse of methylprednisolone, followed by 0.5-0.7 mg/kg/day oral prednisone with rapid tapering, respectively (175). Only the first study met the primary end-point allowing a more rapid GC tapering in patients treated with 3 days of i.v. pulses at diagnosis, with 71% of patients reaching a prednisone dose ≤ 5 mg/day by week 36 compared to 15% for patients not receiving pulse i.v. methylprednisolone; p=0.003 and a reduction by 2224 mg in the cumulative prednisone dose (however, the dose of GC pulses was not considered) (173) .

One small RCT, including 7 patients in the active group and 5 in the control group, analysed the efficacy and safety of modified-release prednisone with immediate-release prednisolone in newly

diagnosed GCA suggesting a similar outcome profile, but with worse sleeping scores in the modified-release GC (172). The differential effect on bone mass loss of deflazacort versus prednisone was assessed in a RCT showing no difference between the two GC compounds (174).

Data on the most effective initial GC dose to treat GCA derive from uncontrolled observational studies with no conclusive evidence to be drawn and no apparent influence on the maintenance dose (176–178). In a retrospective review of 286 patients with GCA, a higher initial oral prednisone dose (> 40 mg/day) was associated with greater chances of reaching a low dose sooner and of discontinuing GC (154).

The incidence of visual loss with respect to early diagnosis and GC initiation compared to delayed treatment was assessed in a prospective longitudinal cohort study of 68 patients with GCA, suggesting the importance of prompt treatment in reducing the rate of permanent visual loss. This approach did not have any effect on the frequency of relapses (179). Further evidence from a retrospective, multi-centre study supports the concept that partial improvement of visual acuity is associated with the very early initiation of GC within 24 hours from the onset of visual symptoms, regardless of the route of administration (180).

The effect of the best route of administration of GC (i.v. versus oral) on visual loss in GCA was assessed in a retrospective longitudinal cohort study. Visual improvement only occurred in a very limited number of cases (only in 4% of eyes and only for overall visual acuity and not for central vision) with no differences in the route of GC administration. Earlier GC initiation was associated with a trend for greater likelihood of improvement (181). Another retrospective longitudinal study compared the route of GC administration during the first week of treatment on visual loss at presentation of GCA. Different i.v. schemes were used (i.v. methylprednisolone pulses 1000 mg per day, 250 mg 2-4 times per day, 500 mg 1-2 times per day for a median of 3 days [range 2–5 days]) compared to oral GC prednisolone (50-100 mg/day). There was an increased likelihood for improved

visual acuity in the group treated with i.v. GC (40%) compared to the oral route (13%); in all except for 4 patients, vision remained stable one month after presentation, supporting the idea that improvement only occurs in the very initial phases of the ischaemic process (182). Both studies were characterized by high RoB; different baseline characteristics of the two cohorts and different GC doses limited the comparability and possibility to achieve firm conclusions.

The most effective GC tapering scheme was not specifically assessed in any study included in the SLRs. In the trial of tocilizumab in GCA (GiACTA) (183) two standardised prednisone-taper protocols (52-week and 26-week taper) were tested in a RCT. Patients who enrolled in the placebo group with more rapid tapering protocol experienced more relapses (68% versus 49%) and a greater need for prednisone escape therapy (74% versus 55%).

The safety of GC treatment was reported by a large nested case-control analysis demonstrating a direct correlation between prednisone dose (average daily GC dose > 30 mg/day) and the development of diabetes, glaucoma, osteoporosis, fractures, serious infections and death (184). Similar concerns regarding the significant rate of GC-related adverse events (AE) were confirmed in a retrospective medical claims data analysis, reporting an increase in hazard ratio (HR) by 3% for every 1000 mg increase in prednisone-equivalent exposure (185).

Evidence for GC discontinuation and drug-free remission was evaluated in a retrospective cohort study reporting that a lower number of flares, lower cumulative GC dose at one year, lower duration of GC treatment, and more rapid achievement of low dose GC are associated with higher chances of obtaining long-term remission (186).

In summary, the prompt initiation of GC therapy is consistently associated with a better outcome, including permanent visual complications (LoE 4). Only low-moderate quality evidence with

conflicting results exists on the most appropriate initial dose and route of administration of GC (LoE 4). The best tapering scheme has not been established yet, with evidence from one high-quality RCT suggesting a higher risk of flares in more rapid tapering regimens (within 6 months from diagnosis) (LoE 1b). Nevertheless, safety concerns related to GC are dose-dependent (LoE 3b), underlying the need to optimize the dose and duration of GC treatment.

Table 21. Randomised controlled trials of glucocorticoids in giant cell arteritis

Study ID	Study design	GCA subtype	n	Intervention	Control	Primary outcome	Results (i)	Results (c)	p-value
Raine et al. 2017 (172)	Feasibility study, prospective, randomised, open-label, blinded evaluator	New	**12** 7 (i) vs 5 (c)	MR prednisolone	Prednisolone	Persistent clinical disease control week 26	6/7	4/5	na
Mazlumzadeh et al. 2006 (173)	Double-blind, placebo-controlled, randomised prospective controlled trial	New	**27** 14 (i) vs 13 (c)	GC i.v. 15 mg/kg/day for 3 days → 40 mg/day PRED p.o.	i.v. saline for 3 days + 40 mg/day PRED	GC ≤ 5 mg/day week 36	10/14 (71%)	2/13 (15%)	0.003
Cacoub et al. 2001 (174)	Double-blind, randomised prospective controlled trial	New	**74** 37 (i) vs 37 (c)	Prednisolone 0.7 mg/kg/day	Deflazacort (equivalent dose)	Bone mass loss (g/cm^2) month 12	0.026±0.007	0.03±0.005	ns
Chevalet et al. 2000 (175)	Randomised prospective controlled trial (not blinded)	New	**146** 61 (i) vs 53 (c2) vs 50 (c3)	GC i.v. 240 mg → 0.7 mg/kg/day PRED p.o.	(C2): 0.7 mg/kg/day PRED p.o. -(C3): GC i.v. 240 mg → 0.5 mg/kg/day PRED p.o.	Mean cumulative PRED dose (mg) mo 12	5777	5578 (c2); 5168 (c3)	0.38

New: newly diagnosed giant cell arteritis; GCA: giant cell arteritis; i: intervention; c: control; GC: methylprednisolone; PRED: prednisolone; i.v.: intravenous; p.o.: oral route; mo: month; MR: modified release

Methotrexate and other non-biologic immunosuppressive drugs

The SLR showed that the adjunctive role of methotrexate (MTX) for the treatment of newly diagnosed GCA has been tested in 4 RCTs (187–190). The fourth RCT enrolled a limited number of patients with GCA (n=6) and/or PMR and presented a significant RoB (190). Only one RCT had a low RoB (189). Just one trial met the primary endpoint (reduction in number of relapses and total cumulative dose of GC during follow-up) (188). In all studies, the dose of MTX was generally low, administered orally and differed significantly amongst the RCTs: maximum dose ranged 7.5-15 mg/week. Moreover, the concomitant GC dose was not standardised amongst the studies, nor was the GC duration and tapering scheme.

An individual patient-data meta-analysis pooling information from 161 patients enrolled in the 3 RCTs performed exclusively on GCA patients (187–189) re-evaluated the efficacy and safety of adjunctive low-dose MTX in newly diagnosed and relapsing patients with GCA (191). HRs compared to placebo for a first disease relapse are 0.65 (95% CI 0.44-0.98; p=0.004), for a second relapse: 0.49 (95%CI 0.44-0.98; p=0.02). Superiority of the treatment effect of MTX over placebo becomes apparent after 24-36 weeks, suggesting that the duration of follow-up might have influenced the possibility to reach the endpoint in the individual trials. Ne number needed to treat is at least 3.6 (95% CI 2.2-56.8) and 4.7 (95% CI 3.3-21.9) patients to prevent a first and second relapse, respectively. The adjunctive use of MTX resulted in a significant reduction in the cumulative GC dose by 842 mg within 48 weeks. Finally, MTX was associated with higher probability of reaching a sustained drug-free remission (HR 2.84; p<0.001). The overall incidence of adverse events was not significantly different between patients treated with MTX versus placebo.

The effectiveness and safety of MTX in real-life has been reported by one observational retrospective longitudinal study describing the role of long-term (up to 8.4 years) continuation of MTX in routine clinical practice for patients with GCA (both as first-line in newly diagnosed patients or as add-on treatment in relapsing cases) (192). In this study the maximum MTX dose was 15 mg/week, and the

drug proved to be safe and with low discontinuation rates due to inefficacy (incidence rate for discontinuation: 2.8/100 patient-years). However, the RoB is high due to study design and lack of a comparator group.

Cyclosporine was not efficacious and did not display a GC-sparing effect in two open RCT including newly diagnosed and refractory cases of GCA (193,194). Azathioprine (AZA) efficacy was tested in a RCT with significant methodological issues negatively influencing the results of the study (195). Dapsone was tested in an open, prospective randomised trial vs GC alone but did not demonstrate a GC-sparing effect. Dapsone toxicity often limits its use (196). A summary of the RCTs of non-biologic immunosuppressants in GCA is presented in Table 22.

Leflunomide (LEF) and cyclophosphamide (Cyc) effectiveness and safety were only assessed in retrospective cohort studies not allowing for definitive conclusions (197–201).

In summary, MTX reduces the risk of relapse and exposure to GC in patients with GCA (LoE 1a). There is no high-quality evidence supporting the efficacy of other csDMARDs (LoE4).

Table 22. Randomised controlled trials of non-biologic immunosuppressants in giant cell arteritis

Study ID	Study design	GCA subtype	n	Intervention	Control	Primary Outcome	Results (i)	Results (c)	p-value
Methotrexate									
Hoffman et al. 2002 (187)	Randomised, double-blind, placebo-controlled trial	New	**98** 51 (i) vs 48 (c)	PRED p.o. (1 mg/kg/day) + MTX p.o. (maximum 15 mg/week)	PRED + placebo	First disease relapse (6 mo)	68.9%	66.1%	0.31
Jover et al. 2001 (188)	Randomised, double-blind, placebo-controlled trial	New	**42** 21 (i) vs 21 (c)	PRED p.o. (60 mg/day) + MTX p.o. (10 mg/week)	PRED + placebo	Number of relapses Cumulative PRED dose (mg)	9 (45%) 4187±1529	16 (84.2%) 5489.5±1396	0.018 0.009
Spiera et al. 2001 (189)	Randomised, double-blind, placebo-controlled trial	New	**21** 12 (i) vs 9 (c)	PRED p.o. (1 mg/kg/day) + MTX p.o. (7.5 mg/week) when PRED dose of 30 mg/day	PRED + placebo	Cumulative GC dose (mg)	6469±2024	5908±2131	0.6
Van der Veen et al. 1996 (190)	Randomised, double-blind placebo-controlled trial	New PMR or GCA or both	**40** 20 (3 GCA) (i) vs 20 (3 GCA) (c)	PRED p.o (20 mg/day) + MTX p.o. (7.5 mg/day)	PRED + placebo	Time to remission (days)	48	45	ns
Cyclosporine									
Schaufelberger et al. 1998 (193)	Open-label, randomised controlled trial	Refractory	**22** 11 (i) vs 11 (c)	PRED (mean 11.8±10 mg/day) + CsA (2 mg/kg/day)	PRED (mean 11.1±7 mg/day)	Cumulative GC dose (g) 6 mo	1.41	1.44	ns
Schaufelberger et al. 2006 (194)	Open-label, randomised controlled trial	New	**59** 29 (i) vs 30 (c)	PRED (mean 40±11 mg/day) + CsA (2-3.5 mg/kg/day)	PRED (mean 40±12 mg/day)	Cumulative GC dose 12 mo	nsp	nsp	nsp
Dapsone									
Liozon et al. 1993 (196)	Open-label, randomised controlled trial	New	**47** 24 (i) vs 23 (c)	PRED (0.7 mg/kg/day-1 mg/kg/day if ocular) + Dapsone	PRED (0.7 mg/kg/day-1 mg/kg/day if ocular)	Total duration of GC	14 mo	13 mo	ns
Azathioprine									
De Silva et al. 1986 (195)	Randomised, double-blind, placebo-controlled trial	Established PMR/GCA	**31** 16 (i) vs 15 (c)	PREDNL maintenance dose p.o. (8.1 vs 7.4 mg/day) + AZA p.o. (100-150 mg/day)	placebo	GC dose 52 weeks (mg)	1.9±0.84	4.2±0.58	<0.05

I: intervention; c: control; New: newly diagnosed giant cell arteritis; GCA: giant cell arteritis; PMR: polymyalgia rheumatica; MTX: methotrexate; CsA: cyclosporine; AZA: azathioprine; mo: month; PRED: prednisone; PREDNL: prednisolone; GC: glucocorticoid; p.o.: oral route; nsp: non-specified; ns: non-significant

Biologic immunosuppressive drugs

The SLRs found two multi-centre double-blind, placebo-controlled RCTs on the use of TCZ for patients with GCA (newly diagnosed/relapsing/LV-GCA) (104,183). Table 23. One RCT (GIACTA) (n=251 patients) tested two different schemes of TCZ s.c. (162 mg every week or every other week) with two GC tapering protocols (26-weeks or 52-weeks). The second study (n=30 patients) assessed the use of i.v. TCZ (8 mg/kg/monthly). The primary outcome was met in both studies. In the larger GIACTA trial, sustained GC-free remission at week 52 was 56% (TCZ/weekly) and 53% (TCZ/every other week) versus 14% (26-week GC taper) or 18% (52-week GC taper); $p<0.001$ was demonstrated. The HR for relapses was 0.23 (99% CI 0.11-0.46) versus 0.28 (0.12-0.66); $p<0.001$ compared to patients receiving a 26-week taper (of GC alone). Sensitivity analyses excluding CRP normalization (given its scarce reliability during TCZ treatment) from the definition of remission confirmed the results. The weekly TCZ dose was more efficacious in preventing disease activity in relapsing disease. The cumulative median GC dose over 52 weeks was significantly lower for the group receiving TCZ (1862 mg) compared to both GC tapering schemes (3818 mg for the 52-week taper and 3296 for the 26-week taper); $p<0.001$ for both comparisons (183).

In the trial from Villiger et al. (104) complete remission was achieved by week 12 in 12/20 (85%) patients treated with TCZ (reaching a GC dose 0.1 mg/kg/day) versus 4/10 (40%) in the comparator group; risk difference was 45% (95% CI 11%-79%; $p=0.03$). The cumulative prednisolone dose after 52 weeks was 43 mg/kg in the TCZ group versus 110 mg/kg in the placebo group ($p=0.005$). There were no safety issues from the two RCTs. The RoB was low for both studies.

Effectiveness of TCZ was also confirmed in open-label observational studies (202–204) and case series (205,206). Few serious adverse events were reported (5 serious infections with 2 deaths, 1 tuberculosis infection). The RoB was high for all these studies.

The optimal duration of TCZ therapy to ensure sustained remission has not been clarified yet, with data on case series suggesting frequent relapses after TCZ discontinuation (202,207).

The efficacy of i.v. abatacept (ABA) was assessed in a multi-centre, double-blind placebo-controlled RCT enrolling 41 newly diagnosed or relapsing patients with GCA or LV-GCA. After 12 weeks of treatment with ABA, patients were randomised to either continue with the active drug or with placebo (GC). The trial demonstrated a marginally significant reduction in the risk of relapse compared to GC alone (relapse-free survival rate at 12 months: 48% versus 31%; p=0.049) and a longer median duration of remission (9.9 months versus 3.9 months; p=0.023), without increased toxicity (105). The RoB was generally low.

The SLRs identified three multi-centre, double-blind placebo-controlled RCTs of TNF inhibitors (TNFi) – adalimumab (ADA), etanercept (ETA) and infliximab (IFX) for GCA (208–210). Efficacy in terms of GC-sparing effect, disease activity and GC withdrawal or reduction of GC cumulative doses and AE was not confirmed by any of the studies using TNFi. All studies, but the one on IFX (210), had a high RoB.

An open-label proof-of-concept study testing the GC-sparing effect of ustekinumab in 14 patients with refractory GCA was identified, showing promising results in terms of GC dose reduction from baseline to last follow-up (from 20 mg/day to 5 mg/day; p=0.001) (211).

In summary, TCZ significantly enhances the chances of achieving remission, preventing relapses and reducing GC requirements in newly diagnosed and relapsing patients with GCA (LoE 1b). The duration of treatment (beyond one year) and long-term safety should still be clarified by further studies.

Table 23. Randomised controlled trials of biologic immunosuppressants in giant cell arteritis

Study ID	Study design	GCA subtype	n	Intervention	Control	Primary outcome	Results (i)	Results (c)	p-value
Stone et al. 2017 (183)	Randomised, double-blind placebo-controlled trial	New/Relapse	**251** 100 (i1); 50 (i2) vs 50 (c1);	(i1): TCZ 162 mg/week s.c + 26-week GC taper (i2): TCZ 162 mg/2 weeks s.c. + 26-week GC taper	(c1): placebo + 26-week taper GC (c2): placebo + 52-week taper GC	Rate of sustained GC-free remission week 52 vs placebo + 26-week GC taper	56%(i1) 53% (i2)	14% (c1) 18% (c2)	<0.001
Villiger et al. 2016 (104)	Phase 2, randomised, double-blind, placebo-controlled trial	New/Relapse	**30** 20 (i) vs 10 (c)	i.v. TCZ 8 mg/kg/4 weeks + PREDNL 1 mg/kg p.o.	placebo	Complete remission at a PREDNL 0.1 mg/kg/day week 12	17 (85%)	4 (40%)	0.0301
Langford et al. 2017 (105)	Randomised, double-blind placebo-controlled trial	New/Relapse	**41** 20 (i) vs 21 (c)	i.v. ABA 10 mg/kg on day 1,15, 29 and week 8 + GC 40-60 mg/day with 28-week taper	GC 40-60 mg/day with 28-week taper+ placebo	Duration of remission (relapse-free survival rate) mo 12	46%	31%	0.049
Seror et al. 2014 (208)	Randomised, double-blind placebo-controlled trial	New	**70** 34 (i) vs 36 (c)	ADA s.c. 40 mg/2 weeks + PRED 0.7 mg/kg/day	PRED 0.7 mg/kg/day + placebo	Percentage of patients in remission with < 0.1 mg/kg/day PRED week 26	20 (58.9%)	18 (50%)	0.46
Martinez-Taboada et al. 2008 (209)	Randomised, double-blind placebo-controlled trial	Established with AE to GC	**17** 8 (i) vs 9 (c)	PRED ≥ 10 mg/day + ETA 25 mg /twice week s.c.	PRED ≥ 10 mg/day + placebo	Ability to withdraw GC and control disease mo 12	50%	22.2%	ns
Hoffman et al. 2007 (210)	Randomised, double-blind placebo-controlled trial	New in remission	**44** 28 (i) vs 16 (c)	IFX (5 mg/kg) weeks 0,2,6 then every 8 weeks + GC	GC + placebo	Relapse-free rate through week 22	43%	50%	0.65

I: intervention; c: control; TCZ: tocilizumab; GC: glucocorticoids; PREDNL: prednisolone; PRED: prednisone; ABA: abatacept; ADA: adalimumab; AE: adverse events; ETA: etanercept; IFX: infliximab; p.o.: oral route; i.v.: intravenous; mo: month

Surgical procedures

The treatment of aortic aneurysms (and/or dissection) in GCA was assessed by two retrospective studies (212,213). The surgical outcome and short-term survival were good, but with the need for frequent surveillance and occasional requirement for repeated intervention (8%-10% of cases).

There were no studies addressing the role of preventive medical treatment or timing for screening for aortic complications.

One retrospective case series (n=10 LV-GCA patients) described the outcome of percutaneous transluminal balloon angioplasty (PTA) in combination with GC, csDMARDs and anti-platelet agents for symptomatic upper limb stenosis/occlusion resistant to medical treatment. The rate of restenosis was high (primary patency rate 65.2%), but repeated PTA was effective (secondary patency rate 82.6%) (214).

A retrospective case-series including 10 patients with LV-GCA or Takayasu arteritis (TAK) analysed the safety and effectiveness of PTA for occlusive arterial disease in LVV, which were in accord with previous evidence. Technical success was good for stenotic lesions and moderate for occlusive lesions; the cumulative primary clinical success rate was 67.6%. There is an important risk of arterial injury during PTA, reported in 36% of patients (215).

Overall, we found only limited and low-quality data to guide revascularization procedures in patients with GCA (LoE 4).

Adjunctive therapy and prophylaxis

The SLRs identified six retrospective longitudinal cohorts studies investigating the role of anti-platelet agents to prevent ischaemic complications in GCA (153,216–220). The results of the studies are controversial, with some suggesting no effect of acetylsalicylic acid (ASA) in preventing ischaemic events when prescribed before or at the time of GCA diagnosis (216,217); and one

suggesting an association with increased risk for severe cranial ischaemic events (221). By contrast, two studies reported that antiplatelet/anticoagulation therapy might reduce ischaemic complications at diagnosis and during follow-up without any increased risk of bleeding (218,222). There have been no RCTs assessing the use of low-dose ASA for GCA (223). A meta-analysis of six retrospective studies (including 914 patients) concluded that established antiplatelet/anticoagulants given prior to diagnosis do not reduce the risk of ischaemic events. The heterogeneity of the studies was moderate/high.

The role of statins in GCA is unclear. Contradictory results were obtained from two population-based incident cases cohorts (224,225) and two retrospective longitudinal cohorts (226,227). The first two studies (characterized by a lower RoB) reported that statin therapy, given prior to (226,227) or within one year from the diagnosis of GCA (228) was associated with reduced hospitalization due to cardiovascular events in GCA (HR 0.993; 95% CI 0.986-0.999; p=0.0467).

Concomitant treatment with angiotensin receptor blockers (ARB) but not with angiotensin-converting enzyme inhibitors (ACEI) was associated with lower relapse rate and more prolonged disease-free survival in GCA in a single prospective, open-label controlled study (adjusted HR for relapses with ARB 0.32; 95% CI 0.12-0.81; p=0.017) (229). Of the 106 patients included, only 36 received ACEI and 14 were treated with ARB. Although patients had been followed-up prospectively, data were analysed retrospectively. Finally, duration, dose and type of ARB treatment were heterogenous. Therefore, these results need confirmation by further studies.

The SLRs identified two studies assessing the role of prophylaxis against *Pneumocystis jiroveci* pneumonia (PJP). In one prospective cohort of 62 patients treated with GC (20-50 mg/day) combined with MTX (15-20 mg/week), there were 4 (6%) cases of PJP. The main risk factor identified for PJP infection was the presence of lymphopenia. The other study was a retrospective case-series (7 patients) reporting 29% mortality in patients with GCA who developed PJP infections (230,231)

.Although both studies raised the issue of infection screening and the risk of infection in these elderly patients treated with intensive immunosuppressive regimens, they did not provide any clear evidence on the modality or timing of antibiotic prophylaxis to prevent infectious complications.

The prevention and treatment of osteoporosis, the management of medium to high-dose GC therapy and vaccinations have not been assessed specifically for GCA. International consensus recommendations on the management of osteoporosis and vaccinations in rheumatic diseases in general have been published (232,233).

In summary, there is no consistent evidence that anti-platelet agents given at the time of GCA diagnosis prevent future ischaemic events (LoE 2a). Treatment should be decided on an individual basis. There is no strong evidence on other adjunctive or prophylactic therapies specifically designed for GCA.

4.3.2 Update of the European recommendations

Based on the results of the data from the SLRs presented above and the expert panel meeting and voting, the following recommendations were produced to guide the management of LVV in clinical practice (110). The expert panel agreed on the consensus definitions for disease activity states in GCA and other LVV (Table 24) to be applied when referring to the recommendations. Three overarching principles were defined (Table 25). The complete set of updated EULAR recommendations are presented in Table 26.

Table 24. Consensus definitions of disease activity states based on the EULAR recommendations for the management of large vessel vasculitis (110)

Activity state	EULAR consensus definition
Active disease	1. The presence of typical symptoms of active LVV. 2. At least one of the following: a. Current activity on imaging or biopsy. b. Ischaemic complications attributed to LVV. c. Persistently elevated inflammatory markers (after other causes have been excluded).
Flare	EULAR recommends against the use of this term.
Relapse	EULAR recommends use of the terms major or minor relapse.
Major relapse	1. Recurrence of active disease with either of the following: a. Clinical features of ischaemia (including jaw claudication, visual symptoms, visual loss attributable to GCA, scalp necrosis, stroke, limb claudication). b. Evidence of active aortic inflammation resulting in progressive aortic or large vessel dilatation, stenosis or dissection.
Minor relapse	Recurrence of active disease, not fulfilling the criteria for a major relapse.
Refractory	Inability to induce remission (with evidence of reactivation of disease, as defined in "active disease") despite the use of standard care therapy.
Remission	Absence of all clinical signs and symptoms attributable to active LVV and normalisation of ESR and CRP; in addition, for patients with extracranial diseases there should be no evidence of progressive vessel narrowing or dilatation (frequency of repeat imaging to be decided on an individual basis)
Sustained remission	1. Remission for at least 6 months. 2. Achievement of the individual target glucocorticoid dose.
Glucocorticoid-free remission	1. Sustained remission 2. Discontinued glucocorticoid therapy (but could still be receiving other immunosuppressive therapy)

Table 25. Overarching principles from the update of the EULAR recommendations on the management of large vessel vasculitis (110).

	LoE	SoR	FV (%)	LoA (0-10)
OVERARCHING PRINCIPLES				
Patients with LVV should be offered best care which must be based on a shared decision between the patient and the rheumatologist, considering efficacy, safety and costs	n.a.	n.a.	n.a.	9.7±0.7
Patients should have access to education focusing on the impact of LVV, it's key warning symptoms and its treatment (including treatment-related complications	n.a.	n.a.	n.a.	9.7±0.7
Patients with LVV should be screened for treatment-related and cardiovascular comorbidities. We recommend prophylaxis and life-style advice to reduce cardiovascular risk and treatment-related complications	n.a.	n.a.	n.a.	9.8±0.7

The LoE was determined for different parts of each recommendation (referred to with different signs such as * or §). The level of agreement was computed on a 0–10 scale. FV, final vote (% of expert panel members that agreed to the recommendation); LVV, large vessel vasculitis; LoA, level of agreement; LoE, level of evidence; NA, not applicable; SoR, strength of recommendation.

The task force has identified a series of unmet needs that have been added to a research agenda for the future years. Amongst the unresolved issues, it will be necessary to develop data-driven classification and diagnostic criteria for LVV. This process is underway and the new classification criteria for LVV will soon be available. Data driven definitions for shared disease activity states (remission, response, relapse) in order to standardize outcome measures to be used in RCT is another important step in the improvement of the management of the disease. Disease subtypes should be better be defined. Another crucial aspect in the management of GCA is the identification of reliable biomarkers and the risk stratification of patients at diagnosis and the monitoring during biological treatments. The role of imaging in the follow-up of these patients still needs further clarification. In terms of treatment, new therapeutic options based on the pathogenetic knowledge of the disease will expand the available options to treat the disease. Further evidence to support the correct use and tapering of GC is also advisable. Furthermore, the exact effects of MTX or TCZ on long term outcomes and the duration of treatment should be clarified (110).

Table 26. Set of recommendation statements from the update of the EULAR recommendations on the management of large vessel vasculitis (110).

	LoE	SoR	FV (%)	LoA (0-10)
RECOMMENDATIONS				
All patients presenting with signs and symptoms suggestive of GCA should be urgently referred to a specialist team for further multidisciplinary diagnostic work-up and management	2b	C	91	9.2±2.1
All patients presenting with signs and symptoms suggestive of TAK should be referred to a specialist team for multidisciplinary diagnostic work-up and management	5	D	100	9.6±0.9
A suspected diagnosis of LVV should be confirmed by imaging (ultrasound* or MRI§ for temporal or other cranial arteries, ultrasound, CT, PET-CT or MRI for the aorta/extracranial arteries#) or histology (TAB*)	*1b §2b #3	*A §B #C	*100 §100 #100	9.5±0.9 9.3±1.2 9.6±0.8
High dose glucocorticoid (GC) therapy (40–60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active GCA& or TAK+ Once disease is controlled, we recommend tapering the GC dose to a target dose of 15–20 mg/day within 2–3 months and after 1 year to ≤5 mg/day (for GCA) and to ≤10 mg/day (for TAK)	&4 +5 5	&C +D D	&100 +100 87	9.8±0.6 9.8±0.5 9.5±0.9
Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using tocilizumab**. Methotrexate may be used as an alternative§§	**1b §§1a-	**A §§A	**100 §§100	9.4±0.8 9.4±0.8
Non-biologic disease modifying agents should be given in combination with GC in all patients with TAK#. Tocilizumab or TNF-inhibitors can be considered in case of relapsing or refractory disease despite conventional DMARD therapy#	4	C	100	9.4±1.2
In case of major relapse (either with signs or symptoms of ischaemia or progressive vascular inflammation) we recommend reinstitution or dose escalation of GC therapy as recommended for new onset disease.## For minor relapses we recommend an increase in GC dose at least to the last effective dose.* Initiation or modification of adjunctive therapy should be considered particularly after recurrent disease relapses&&	##2b &&1b	##C &&A	##95 &&95	9.5±1.0 9.6±1.0
Antiplatelet or anticoagulant therapy should not be routinely used for treatment of LVV unless it is indicated for other reasons (eg, coronary heart disease or cerebrovascular disease etc). In special situations such as vascular ischaemic complications or high risk of cardiovascular disease, these might be considered on an individual basis	4	C	100	9.4±0.8
In LVV, elective endovascular interventions or reconstructive surgery should be performed in phases of stable remission. However, arterial vessel dissection or critical vascular ischaemia requires urgent referral to a vascular team	4	C	95	9.8±0.5
Regular follow-up and monitoring of disease activity in patients with LVV is recommended, primarily based on symptoms, clinical findings and ESR/CRP levels	3b	C	100	9.6±0.6

The LoE was determined for different parts of each recommendation (referred to with different signs such as * or §). The level of agreement was computed on a 0–10 scale. DMARD, disease modifying anti-rheumatic drug; FV, final vote (% of expert panel members that agreed to the recommendation); LVV, large vessel vasculitis; LoA, level of agreement; LoE, level of evidence; NA, not applicable; SoR, strength of recommendation; TAB, temporal artery biopsy; TAK, Takayasu arteritis; TNF, tumour necrosis factor.

5. Discussion

Over the course of the past three-year PhD activity in Experimental Medicine I have focused on three main projects with the aim of investigating the optimal management of GCA and contributing to the improvement of its management. The projects comprised the analysis of the impact that a dedicated, fast track path can have on a rheumatological emergency such as GCA, particularly on ischaemic complications and long-term outcome improvement (*in press*); we then assessed if the quantitative (rather than only qualitative "positive/negative") ultrasonographic findings detected at the time of GCA diagnosis in the context of the fast track clinic would have an impact on the diagnostic certainty and on the clinical outcome of the disease (107). Finally, I was responsible for a systematic literature review (114) and contributed to the update of the European recommendations on the management of LVV which included the indication to urgently refer the patient to a specialised team, and to use ultrasound as the first confirmatory diagnostic tool in centres with the adequate expertise in the management of this systemic vasculitis (110).

Our data confirm that FTA including CDS assessment is an innovative disease-modifying strategy leading to a significant reduction of PVL and related disability. The effectiveness of the FTA approach has been further highlighted in our cohort by the significant increase in diagnostic delay and occurrence of PVL, including the previously unreported bilateral blindness, observed during the COVID-19 pandemic. The rate of severe complications seen during COVID-19 has probably been caused by the patients', and possibly care givers' fear of seeking medical attention and attending the hospital.

The introduction of CDS for the diagnosis of GCA has brought further improvements in the management of the disease. In Centres with the adequate expertise and machine equipment and settings, ultrasound has replaced TAB for the diagnosis of patients with suspected GCA and a highly suggestive clinical picture (90,101,234). This is an important step for patients, by reducing the need for invasive procedures, and for the medical community, by significantly reducing costs and

inpatients needs. As demonstrated by the change of practice in our two cohorts, the need for TAB reduced by 93% since the use of CDS as part of the FTA clinic. CDS has the advantage of being a quick, repeatable, low-cost procedure that allows to assess the whole length of the temporal artery (reducing false negatives related to the skipped nature of GCA inflammation) and to extend the examination to other cranial or extra-cranial arteries, optimizing the diagnostic yield (235,236). CDS has been demonstrated to be more sensitive compared to TAB in the diagnosis of GCA (90), as confirmed by our study [CDS sensitivity 82.5% (95% C.I. 70.9%-91.0%) versus TAB sensitivity 53.2% (95% C.I. 38.1%-67.9%)].

The implementation of CDS into FTA clinics allowing for a prompt and direct assessment and interpretation of imaging findings by the treating physician has led to the demonstration that very early diagnosis with the aid of CDS can significantly reduce the risk of PVL in patients with GCA (100,145). Our data highlight the importance of early diagnostic assessment and treatment initiation through FTA. The burden imposed by COVID-19 pandemic on hospital resources and patients' perception of the risk associated with attending hospital clinics have demonstrated once more that early diagnosis and prompt treatment initiation to prevent ischaemic complications needs to be associated with early referral through the prompt recognition of prodrome symptoms possibly preceding the occurrence of PVL in GCA. Blindness has been described in 15-30% of patients with GCA and usually occurs at the early stages of the disease, often being the presenting symptom leading to the diagnosis (237). Nevertheless, up to 28% of patients with PVL report premonitory reversible transient visual symptoms that can prompt the urgent referral if properly investigated and recognized (237). Some general systemic symptoms associated with rheumatological disease can be overlooked, particularly at the time of COVID-19 pandemic and a high degree of attention for other conditions needs to be reintroduced to avoid further indirect morbidity caused by the virus (238). Visual loss is usually irreversible in GCA, however, early initiation of GC, particularly if initiated within the first 24 hours of visual symptoms has been reported as the sole prognostic factor for a partial improvement of visual loss (110,239). Diagnostic delay is known to be associated with the occurrence of bilateral

PVL as confirmed by our data unfortunately observed during COVID-19 outbreak due to a delayed referral despite a regularly operating FTA service (239).

Clinical suspicion avoiding over-reliance on temporal headache alone is key to the early recognition of GCA. To further improve the outcome of LVV, the expedited process allowing for early access to specialist evaluation and confirmatory investigational tests obtained with FTA should be paralleled by educational programmes to increase the awareness of the disease. Moreover, clear recommendations for fast track referral offered to primary care and other relevant specialists will be needed to further reduced the symptom latency period (240,241). An improvement of the general public awareness of GCA could also be beneficial to reduce the diagnostic delay.

During the COVID-19 pandemic several medical emergencies, including acute coronary syndromes, have recorded an unusual decrease in hospitalization and increased out-of-hospital mortality as a result of avoidance or delay in seeking medical attention out of fear of contracting the virus (242,243). Similarly, we have observed a significant increase in the rate of ischaemic complications (with 40% of PVL), including bilateral blindness with two new cases over a period of two months, compared to only one case over the previous 4-year activity of the FTA (244). The duration of symptom prior to the first evaluation for suspected GCA has increased during the COVID-19 outbreak despite a regularly operating fast track clinic. The negative outcome of newly diagnosed patients with GCA observed during SARS-CoV-2 outbreak confirms once more that urgent referral and FTA are key in the management of LVV with a significant change in visual prognosis.

Nonetheless, despite the clear early benefit of an early diagnosis, our data suggest that FTA does not impact the long-term outcomes and relapse-risk. Our findings are in line with previous reports suggesting that early diagnosis of GCA does not seem to significantly improve the future risk of relapse (179). Predictors of relapse in LVV are poorly understood. Our data confirm that markers of inflammation, baseline anaemia, and LV-GCA are associated with a higher risk of relapse (102,103,164,245). Increasing interest is emerging to find different predictors of relapse or future disease complications as part of the FTA approach, including quantitative analysis of CDS findings

suggestive of more extensive or more severe vascular involvement at disease onset (107); the results of such analysis will be described later in this section. Nevertheless, to date, no reliable imaging biomarker has been identified to predict the risk of relapse or future ischaemic complications during follow-up (247,248).

The unmodified disease course despite the FTA and early diagnosis strategies in GCA suggest that a change in therapeutic strategy should be applied since the early stages of the disease to significantly modify the long-term outcome. Available evidence demonstrated a glucocorticoid-sparing effect and efficacy in reducing the risk of relapse in newly diagnosed or relapsing patients with GCA treated with methotrexate or tocilizumab (183,191). Nevertheless, in clinical practice patient-tailored evaluations of safety and cost-effectiveness issues are often taken into consideration in this elderly population group treated with concomitant high-dose GC. Current recommendations suggest to reserve adjunctive therapy to selected patients with refractory or relapsing disease or with the presence or increased risk of GC related adverse events and complications. A risk stratification process to select patients with poor prognosis to be treated more intensively upfront still requires further research. Data obtained from the FTA clinics suggest that the window of opportunity to obtain long-term modifications of the disease process in GCA is exceedingly short and should probably be associated with an optimization of the disease awareness to further accelerate referral and with a tailored therapeutic approach to potentiate treatment in patients at higher risk of relapse and complications.

In order to assess the diagnostic and prognostic value of quantitative data obtained at the first CDS assessment of a patient with GCA, we have conducted the first study to assess the role of quantitative information on the localization and degree of vascular involvement detected by CDS in patients with GCA.

Our study demonstrates that a comprehensive analysis of specific CDS quantitative findings rather than a simple binary (positive/negative) approach can add value to the diagnostic role of ultrasound in the assessment of GCA.

In this study we identified the most useful CDS and clinical characteristics to identify patients with a positive TAB. Ultrasonographic, clinical and laboratoristic features were combined to obtain a comprehensive GCA-US score to assess the probability of a positive biopsy. The same imaging and clinical models were not able to discriminate the clinical outcome (ischaemic complications and need for higher doses of GC and/or adjunctive immunosuppressants) at 6 months.

The gold standard for the diagnosis of GCA is the presence of characteristic histologic findings on TAB, (249) however, the unsatisfactory sensitivity of this test prompted the search for more reliable, rapid and less invasive diagnostic tools. TABUL was the first study to systematically compare the role of CDS versus TAB in a large prospective, multi-centre cohort study (90). The TABUL study demonstrated that ultrasound has a higher sensitivity (but lower specificity) compared to TAB. The sensitivity of CDS was indeed higher than that of TAB to provide evidence for a diagnosis of GCA, with a fair level of agreement between the two tests (30% discordance). Our study analysed this association more in detail by exploring the role of specific quantitative CDS findings and not just the presence/absence of a halo. We demonstrated that several CDS parameters representing the extent of vascular involvement (total number of sites with halo, number of halos at the TA, bilateral TA halos) and the degree of vessel wall inflammation (maximum IMT at the TA) are strongly associated with a TAB consistent with GCA. We developed a score to estimate with a certain percentage of probability the positivity of histology. The increase in specificity up to 100% in the presence of bilateral TA halos has been previously reported, (250) however, the association in terms of number and size of halos is new. Our findings suggest that having more widespread vessel involvement with a higher number of sites with halos and having a more prominent halo at the level of the TA correlate with the histologic diagnosis of GCA. An increasing interest in the size of IMT and its potential role in the diagnosis and/or monitoring of disease is emerging. Recently, cut-off values to distinguish IMT

of patients with GCA from matched controls without vasculitis have been formally addressed in a prospective study demonstrating that halo thickness can be useful in distinguishing pathologic cases from normal findings (99). IMT of TA and AX has been analysed to identify the cut-off value ensuring the best diagnostic performance (using clinical diagnosis as the reference standard) finding IMT sizes in line with the values used in our study (≥ 0.7 mm for TA and ≥ 1.2 mm for AX) (251).

The evidence obtained from our study further clarifies the association between CDS and TAB and supports the current practice of avoiding TAB in patients with a clinically suggestive picture and a positive ultrasound (252). Based on the association of the ultrasound models and several clinical and laboratory findings, we have identified a comprehensive score that best fitted with the outcome of a positive TAB. The comprehensive GCA-US SCORE, by combining the maximum IMT size and bilaterality of halos at the level of the TA and AX with relevant clinical or laboratoristic variables (raised inflammatory markers, headache, ischaemic symptoms, PMR) provides a computable estimate of the probability of a positive histology, supporting the use of CDS as a surrogate diagnostic tool to replace TAB.

In the management of GCA we are in urgent need of clinical, laboratory or imaging prognostic biomarkers that would predict, at the time of diagnosis, the subsequent outcome of disease. In our study, we did not identify any baseline CDS or clinical parameter that could predict a worse outcome at 6 months (visual sequelae and/or the need for more intensive treatment). In line with our findings, Schmidt et al. (248) had previously assessed a large cohort of consecutive patients with GCA and found no statistically significant association between number of pathological TA segments, presence of stenoses or bilateral findings and ophthalmic complications. We did not confirm the findings from Czihal et al. (92) who had reported a poorer response to treatment after a mean follow-up of over 2 years in 43 GCA patients with extra-cranial large vessel involvement. The shorter follow-up in our two cohorts might explain the different results. It is possible that the long-term consequence of higher degree of disease extent at baseline only become apparent after a longer follow-up, once the dose of GC has been significantly reduced. Nonetheless, these results might also suggest that CDS findings

do not fully capture the complexity and severity of disease and, until further evidence is collected, underscore the need to always correlate imaging findings with clinical picture and clinicians' judgment.

Our study has some limitations. Some baseline characteristics of the two cohorts (TABUL and independent cohort) are different, particularly concerning the frequency of female patients and the number of days on GC treatment at the time of CDS assessment. However, the independent cohort reflects common clinical practice and represents the setting in which to apply the evidence gathered from standardised clinical studies. The need for more intensive treatment at the end of follow-up as a measure of worse prognosis can be considered a reliable indicator of a higher GC-dependent disease or more relapsing disease, but may also be biased by the treating physician's practice; nevertheless, the inclusion of patients enrolled in TABUL and of an independent cohort applying the same methodology should have limited too much variability. Finally, the short-term follow-up (6 months) might have precluded the recognition of some potential associations between ultrasound findings and long-term outcome which will need to be addressed by further studies. This might limit prognostic ability of our tool based on a combined endpoint of ischaemic complications or need for intensified treatment.

The diagnostic and therapeutic options for the management of LVV have gone through paradigmatic changes in the past few years. This has prompted the need to update the previously available European recommendations published in 2009 (109) to integrate them with the most recent evidence, including the standardised use of CDS and the indications for new biologic drugs such as TCZ.

The update of the recommendations went through a thorough review of the available literature through two SLRs.

The SLRs provided more evidence than ever before they were conducted from inception of all available literature to ensure a more systematic assessment of the evidence in LVV which had not been performed for the previous version of the guidelines. All study designs (except for case reports

of less than 2 patients) were included in the SLRs, in order to offer a comprehensive overview of all available evidence to support clinical decisions in a field of rare diseases with very limited numbers of RCTs/high LoE studies. The inclusion of observational studies reflecting routine care improves the generalizability of our results but introduces a higher risk of bias and confounding elements that need to be taken into account when interpreting the result of our study.

The SLR on the general management and monitoring demonstrated the presence of different disease patterns of GCA, predominantly separated into cranial and LV-GCA, supported by clinical and imaging features, but with potential overlap. These disease patterns have implications in terms of epidemiology, clinical presentation and disease course, however, high-quality evidence on the role of disease phenotypes is still lacking. The increasingly recognised role of imaging, especially CDS, in the diagnosis of GCA has been incorporated into the recently published EULAR recommendations on imaging of LVV (101) and should allow earlier diagnosis and better characterization of disease patterns in the future. A fast track diagnostic approach including the use of ultrasound significantly reduced visual loss and the need for TAB compared to historical cohorts (19,100,145). When a TAB is performed, the SLR confirmed the need for prompt and accurate tissue sampling to optimize the diagnostic yield (90). The most widely used biomarkers for GCA remain ESR and CRP levels, with some limitations in their use, especially during follow-up (159,160). Ongoing research is exploring the role of novel biomarkers, particularly needed in the setting of TCZ treatment. Clinical predictors of ischaemic complications were identified such as transient visual symptoms, jaw claudication, temporal artery tenderness, thrombocytosis and cerebrovascular accidents. A relapsing course of disease has been associated with higher ESR levels, anaemia and constitutional symptoms (102,103,159). Nevertheless, the optimal monitoring timings and tools to detect relapses still need to be defined.

The SLR focusing on treatment confirmed the urgent nature of GCA and the need to promptly initiate GC therapy as soon as the diagnosis of GCA is suspected. Initiation of GC within 24 hours from disease onset has been reported as the only predictor of visual improvement (179,180). There are

conflicting data on the optimal starting dose and route of administration of GC. There is limited observational evidence supporting the use of a higher initial GC dose (> 40 mg/day) to ensure a more rapid tapering and subsequent withdrawal of GC treatment (154). No consistent data on the need for initial i.v. high-dose GC in patients with visual loss have been published, but this practice is still recommended on the basis of common practice and uncertainty of the available evidence (173,180,181).

The optimal tapering strategy or timing for stopping GC is still unclear. Data from the GIACTA trial suggested a higher rate of relapses in patients undergoing very rapid (26-weeks schemes) GC reduction and withdrawal. A high rate of GC-dependent AE was confirmed, underlying the need to optimize future studies to define the minimum effective initial dose and a safe reduction approach for managing GCA with GC (183). Our conclusions support the use of GC, particularly in the very early stages of disease, but highlight how the mostly used and recognized cornerstone of GCA treatment still lacks high LoE studies addressing the optimal starting dose, route of administration and monitoring strategy in the management of GCA.

The treatment challenge of GC-dependent or refractory/relapsing disease remains, particularly when reaching lower-to-medium doses of GC (10-15 mg/day). The RCTs conducted to assess the role of MTX in newly diagnosed patients with GCA have been criticized since they applied variable endpoints (time to first relapse, reduction of relapses or influence on cumulative GC dose), have used different drug doses (maximum 15 mg/week) for a variable period of time, and with heterogeneous adjunctive GC doses and tapering schemes. None of them had reached their primary end-point. However, a meta-analysis on individual-patient data assessed the role of MTX in preventing the first and subsequent relapse, confirming the efficacy and safety of MTX in both disease states and highlighting the relatively slow-action of the drug within 2 to 3 months. MTX was confirmed to reduce the cumulative GC dose (191). Therefore, MTX represents a valuable treatment option in patients with relapsing disease or with contraindications/high risk of adverse events related to GC.

Low-quality evidence is available for other standard immunosuppressive agents (AZA, LEF, Cyc, and dapsone) (193,195,197,198,201).

The main novel therapeutic option for GCA in recent years has been TCZ, approved for the treatment of the disease based on the data published in two multi-centre, double-blinded RCTs, prompted by a series of observational reports confirming the efficacy of inhibiting the IL-6 pathway (104,183). The efficacy of TCZ applies to newly diagnosed and relapsing patients and is demonstrated for the reduction of the risk of relapse and the GC-sparing effects. There were no safety concerns arising from the two RCTs. Continuous surveillance and future studies are needed to assess the optimal dose, duration of treatment and tapering speed of GC when prescribed concomitantly to TCZ. Further studies are also needed to find a reliable biomarker of disease activity during treatment with TCZ which makes CRP unreliable.

Monitoring and treatment of disease complications, mainly aortic aneurysms and peripheral vessels stenosis have only been assessed in observational studies, with no clear evidence on the screening timing, modalities and surgical approach to be recommended (213). Similarly, the evidence supporting the role for anti-platelet agents in reducing ischaemic complications of GCA is controversial and should be decided on an individual basis (253). Further preventive strategies to reduce the cardiovascular risk in GCA such as statins might be useful, although there is no evidence of any effect on the course of disease or need for GC (225,227). There are no conclusive data regarding the use of prophylactic strategies to prevent infectious complications in GCA, including any benefit from PCP prophylaxis or other screening strategies for infection. A high level of attention is warranted in these elderly patients treated with high-dose GC especially when combined with other immunosuppressants.

6. Conclusions

The management of GCA has gone through paradigmatic changes in the last few years. With our studies we have contributed to clarify the role of novel diagnostic approaches to the disease as part of fast track clinics and supported the role of ultrasound as a reliable diagnostic tool. FTA including CDS evaluation contributed to a substantial reduction of the permanent blindness in GCA by shortening the time to diagnosis and treatment initiation. Relapse rate and LV-complications did not change upon FTA introduction, highlighting the need for better disease activity monitoring strategies and risk stratification at disease onset that would predict the occurrence of relapse. These findings will require further confirmation once the length of follow up increases for the recently introduced FTA cohort. We have demonstrated that the quantitative analysis of CDS findings (bilaterality of halos, IMT size) provides important information which can be used to support the diagnosis of patients with GCA and predict the probability of a diagnostic biopsy. A simple score combining ultrasonographic and clinical information allows for a predictable risk assessment supports the role of CDS as a surrogate diagnostic tool. The prognostic role of FTA and quantitative CDS findings need to be addressed by long-term studies. Changes in diagnostic and therapeutic approaches to GCA were systematically reviewed and contributed to the update of the European recommendations on the management of LVV. The review highlighted some unresolved issues in terms of the prognostic stratification, optimal monitoring tests, ability to detect complications and prophylactic treatment to prevent ischaemic, cardiovascular or infectious events in patients with LVV which will need to be addressed by further studies.

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