# Giant Cell Arteritis (GCA): An international, multicentre, longitudinal evaluation of clinical, laboratory and ultrasound parameters in the diagnosis, prognosis and monitoring of GCA.

**Alwin Udayakanth RAJAH SEBASTIAN**

A thesis submitted for the degree of PhD in Musculoskeletal Practice

Department/School of Sport, Rehabilitation & Exercise Sciences

University of Essex

Date of submission for examination: 15th January 2023

Date of Re-submission: 03rd September 2023

**Academic Supervisors: Prof. Jo Jackson & Dr Sue Innes**

**Clinical Supervisor: Prof. Bhaskar Dasgupta**

Special Thanks to my wife, **Dr Manomi Perera, f**or her support throughout this PhD journey.

## IMPACT OF COVID-19

COVID global pandemic put the research on hold from mid-March to July 2020. The National Institute of Health Research, UK (NIHR) had advised pausing the study for the safety of participants and researchers. We restarted our recruitment process in July 2020. As a result, we have to extend the recruitment phase till the end of June 2021 to have adequate participants. During this period of pause, we couldn't recruit new patients as the recruitment required face-to-face appointments and ultrasound scans on each participant. We also lost some of the participants' follow-up appointments and new participants during this time. Participants also, understandably, had great anxiety coming for the scheduled visits. Therefore, some participants withdrew their consent, and some recruited participants passed away due to COVID. Consequently, we lost some participants in our study. We have to open new recruitment centres to recruit adequate participants for the study. Despite this, we were still short of control participants. This all-process interruption affected the recruitment and completion of the study on time and the organising of the thesis writing. Therefore, we have extended the PhD with the university's permission to finish writing the thesis.

# TABLE OF CONTENTS

**ABBREVIATIONS**

| | |
|---|---|
| ACR | American College of Rheumatology |
| AION | Anterior ischemic optic neuritis |
| CRP | C-Reactive protein |
| CTA | Computer Tomography angiogram |
| DC | Dendritic cell |
| DMARD | Disease-modifying anti-rheumatic drugs |
| ESR | Erythrocyte sedimentation rate |
| EULAR | European League Against Rheumatism |
| GCA | Giant cell arteritis |
| GC | Glucocorticoids |
| GPSD | Giant cell arteritis, Polymyalgia rheumatica Spectrum disorders |
| HS | Halo Score |
| IMT | Intimal medial thickness |
| MRA | Magnetic resonance angiogram |
| OMERACT | Outcome Measures for Arthritis Clinical Trials |
| PET-CT | Positron Emission Tomography- Computed Tomography |
| PMR | Polymyalgia Rheumatica |
| TAB | Temporal artery biopsy |
| US | Ultrasound |
| 18F FDG PET-CT | 18F Fluorodeoxyglucose Positron Emission Tomography- Computed Tomography |

## ABSTRACT/SUMMARY

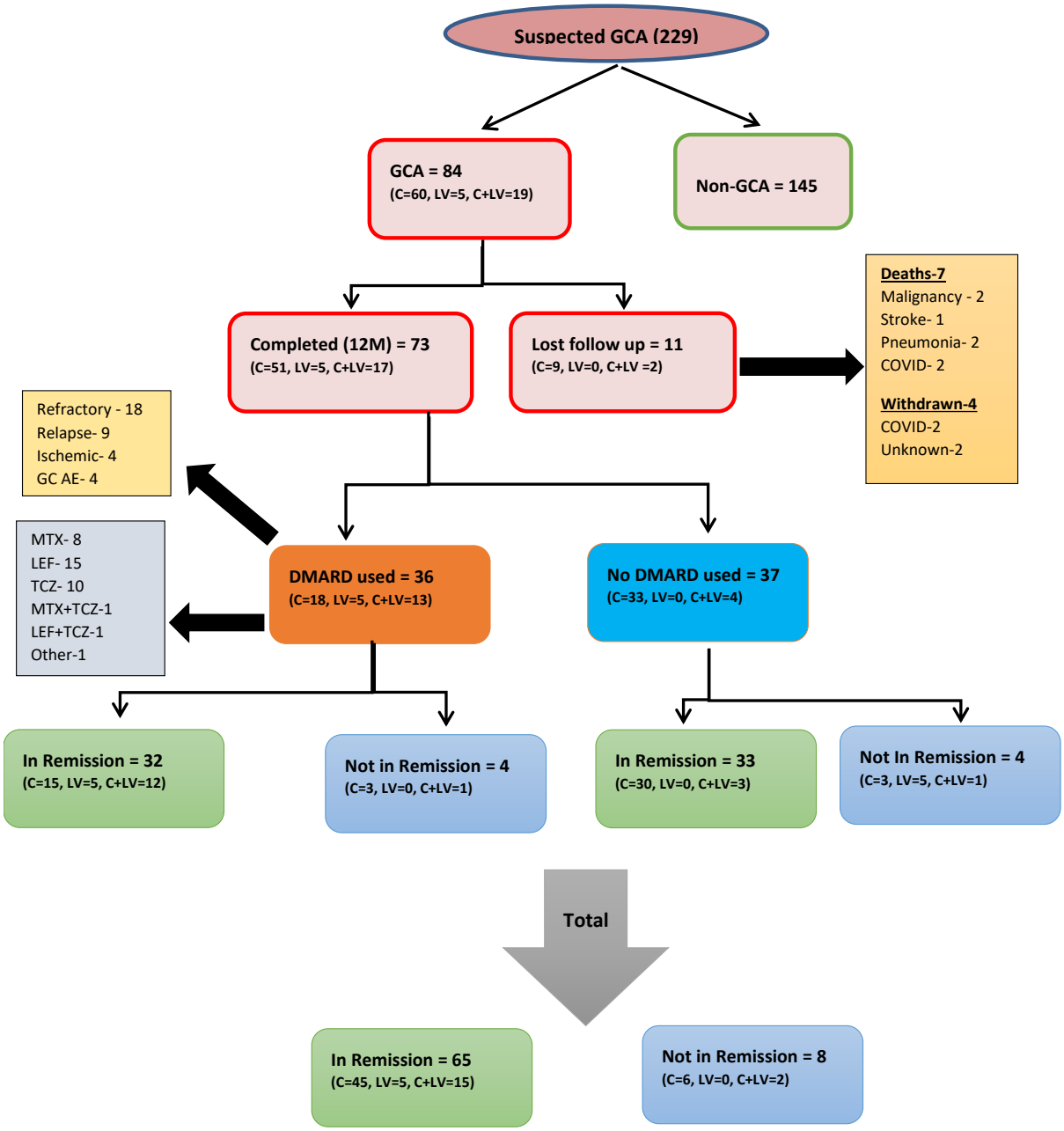
**Background:** Giant cell arteritis (GCA) is a vasculitis, varies in extent, severity and outcomes, hence requires disease stratification for targeted management. Ultrasound (US) non-compressible halo is currently categorised in a dichotomous pattern. We developed a US scoring system to quantify the extent of vascular inflammation and investigated its diagnostic accuracy and association with clinical factors in GCA.

**Methods:** HAS GCA is a prospective study recruited from 7 European GCA fast-track clinics. Southend probability score (GCAPS) risk-stratified patients into 3 categories. Temporal and axillary US Halo Scores (HS) were calculated from the halo thickness and extent in bilateral temporal arteries, parietal and frontal branches (TAHS) and axillary arteries (AAHS). These scores were summed to generate a Total Halo Score (THS). GCA patients had US at baseline,1,3,6,12 months. Primary outcome was remission at 12 months (prednisolone ≤ 5mg).

**Results:** 229 participants (84 GCA) were included: 73 completed follow-ups, 11 lost to follow-up and 65 achieved remissions (figure). GCA median age was 75 years. GCAPS stratified GCA and controls to Low risk (0% vs 46%; Sn-undefined, Sp-99), Intermediate risk (21% vs 38%; Sn-83, Sp-98) and High risk (79% vs 16%; Sn-99, Sp-91). The optimal GCAPS cut-off point was ≥12 (Sn-89, Sp-78). Median THS was 21.5 in GCA and 8 in controls. Optimal cut-off Halo Score in diagnosis was TAHS ≥6 (Sn-86, Sp-92), AAHS ≥11 (Sn-52, Sp-75), THS ≥17 (Sn-76%, Sp-91%). At 12 months, median TAHS, AAHS and THS reduced from 13 to 3, 12 to 9 and 21.5 to 12, respectively.

**Conclusion:** Along with GCAPS, Halo Score successfully discriminates GCA from non-GCA. Extent of arterial inflammation in GCA can be quantified by ultrasound halo scoring.

*Figure: flow chart of all the suspected GCA patients who completed the follow-up, DMARD used, and the numbers in remission*




*Abbreviations: AE, Adverse events; C, Cranial; DMARD, Disease- modifying anti-rheumatic drugs; GCA, Giant cell arteritis; GC, Glucocorticoids; LEF, Leflunomide; LV, Large vessel; MTX, Methotrexate; TCZ, Tocilizumab*

# CHAPTER ONE: INTRODUCTION

Giant cell arteritis (GCA) is a granulomatous vasculitis, an autoimmune disease, causing inflammation affecting the middle to large-sized blood vessels affecting the cranial (Temporal artery and branches) and extracranial arteries (aorta and its branches). It usually happens in individuals aged more than 50 years. The most common symptom of GCA is temporal headaches, scalp tenderness, jaw claudication, constitutional symptoms, and permanent vision loss. Therefore, it is vital to carry out a timely diagnosis of GCA to minimise its drastic effects. Proper therapy is essential to prevent mortality and morbidity linked to the acute presentation of the disease and its long-term complications. For the last five decades, the treatment for GCA has remained glucocorticoids (GCs). Due to its prolonged use in GCA, GC-related side effects are frequent in GCA patients(1) However, recent advances in genetics have led to a greater understanding of the epidemiology and pathogenesis of this disease, thus, providing better treatment suggestions. Tocilizumab, an IL-6 inhibitor, was approved by the U.S. Food and Drug Administration to treat GCA in combination with a robotic tapering GC regimen(2) Temporal artery biopsy (TAB) remains the gold standard in making a histological diagnosis. However, it has low sensitivity(3). Doppler ultrasound (US) is becoming more popular in making instant bedside diagnoses. The European League Against Rheumatism (EULAR) recommends US as the first imaging modality in all suspected GCA patients(4) Positron emission tomography-computed tomography (PET- CT), computer tomographic angiography (CTA) and Magnetic resonance angiography (MRA) are emerging in diagnosing the large vessel GCA (LV-GCA).

This PhD aimed to prospectively assess the value of the US to determine whether the severity of vessel inflammation in temporal and axillary arteries as measured by a composite ultrasound Halo Score (HS) is of prognostic value in predicting severity and outcomes in GCA. Also, to

prospectively validate the role of the Southend probability score (GCAPS) and its vital application in the GCA fast track clinics to discriminate the GCA from the GCA mimics. We acknowledge the new concept of Giant cell arteritis and Polymyalgia spectrum disorders and the importance of stratifying the GCA suspects into the Low, Intermediate and High-risk categories. This allows the identification of the GCA who requires immediate treatment and the necessary additional tests for further confirmation. In this regard, this PhD project was structured with protocol-driven recruitment and follow-up in the multicentre (Southend, Poole,UK; Reggio Emilia,Milan and Siena,Italy; Santander,Spain and Groningen,Netherlands) setup from August 2019 to June 2022. The study protocol and the GCA probability-based algorithm were published in peer-reviewed journals during the PhD. Also, the results were presented at multiple international conferences at different timelines during the follow-up phase of the study (Appendix). The main emphasis was the role of GCAPS and ultrasound halo score in diagnosing GCA.

**The thesis included the following papers:**

1. **Sebastian A**, Coath F, Innes s, Jackson J, van der Geest KSM , Dasgupta B. Role of the 'halo sign' in the assessment of Giant Cell Arteritis (GCA): A systematic review and Meta-analysis. Rheumatology Advances in Practice, Volume 5, issue 3, 2021. https://doi.org/10.1093/rap/rkab059
2. **Sebastian A**, Tomelleri A, Dasgupta B. Current and Innovative therapeutic strategies for the treatment of giant cell arterits. Expert opinion on Orphan Drugs, *2021 May 31*. https://doi.org/10.1080/21678707.2021.1932458
3. **Sebastian A**, Tomelleri A, Kayani A, Prieto-Pena D, Ranasinghe C, Dasgupta B. Probability-based algorithm using ultrasound and additional tests for suspected GCA

in a fast-track clinic. *RMD Open. 2020 Sep;6(3): e001297. https://doi.org/10.1136/rmdopen-2020-001297*

4. **Sebastian A,** van der Geest KSM, Coath F, Gondo P, Kayani A, Mackerness C, Hadebe B, Innes S, Jackson J, Dasgupta B. Halo score (temporal artery, its branches and axillary artery) as a diagnostic, prognostic and disease monitoring tool for Giant Cell Arteritis (GCA). *BMC Rheumatol. 2020 Aug 18; 4:35. https://doi.org/10.1186/s41927-020-00136-5*

**Other articles published during PhD:**

1. Tomelleri A, van der Geest KSM, **Sebastian A,** Van Sleen Y, Schmidt WA, Dejaco C, Dasgupta B. Disease Stratification in giant cell arteritis to reduce relapses and prevent long-term vascular damage. The Lancet, Rheumatology 2021. DOI:https://doi.org/10.1016/S2665-9913(21)00277-0
2. Tomelleri A, Coath F, **Sebastian A**, Prieto-Pena D, Kayani A, Mo J, Dasgupta B. Long-Term Efficacy and Safety of Leflunomide in Large-Vessel Giant Cell Arteritis: A Single-Center, 10-Year Experience. Journal of Clinical Rheumatology. *2021 Jan 19. https://doi.org/10.1097/RHU.0000000000001703*.
3. Tomelleri A, **Sebastian A**, Dasgupta B. Diagnostic accuracy of ultrasound for detecting large-vessel giant cell arteritis using FDG PET/CT as the reference. *Rheumatology (Oxford). 2021 Feb 1;60(2): e66. https://doi.org/10.1093/rheumatology/keaa764*
4. **Sebastian A**, Kayani A, Prieto-Pena D, Tomelleri A, Whitlock M, Mo J, van der Geest N, Dasgupta B. Efficacy and safety of tocilizumab in giant cell arteritis: a single centre NHS experience using imaging (ultrasound and PET-CT) as a diagnostic and monitoring tool. *RMD Open. 2020 Nov;6(3):e001417. https://doi.org/10.1136/rmdopen-2020-001417*

5. van der Geest KSM, Wolfe K, Borg F, **Sebastian A**, Kayani A, Tomelleri A, Gondo P, Schmidt WA, Luqmani R, Dasgupta B. Ultrasonographic Halo Score in giant cell arteritis: association with intimal hyperplasia and ischaemic sight loss. *Rheumatology (Oxford). 2020 Dec 23: keaa806. https://doi.org/10.1093/rheumatology/keaa806.*

**Conferences attened with abstracts/posters/oral presentation during PhD:**

- **Oral Presentation: Probability based diagnostic algorithm in suspected Giant Cell Arteritis: A prospective, multicentre validity data from HAS GCA study,** American College of Rheumatology (ACR), 2022.
- **Poster Presentation:** Southend pre-test probability score and Halo Score as markers for diagnosis and monitoring of GCA: early results from the prospective HAS-GCA study. European League Against Rheumatism (EULAR), 2022
- **Poster Presentation:** Southend pre-test probability score and Halo Score as markers for diagnosis and monitoring of GCA: early results from the prospective HAS-GCA study. European League Against Rheumatism (EULAR), 2021
- **Oral Presentation:** Ultrasonographic Southend halo score is a novel marker for diagnosing and monitoring of disease activity in Giant cell arteritis. William Stokes award presentation, RCPI, 2021
- **Oral Presentation:** Southend pre-test probability score and halo score as markers for diagnosis and monitoring of GCA: Early results from the prospective HAS GCA study, European League Against Rheumatism (EULAR), 2021
- **Oral Presentation:** Prognostic value in Halo Score in GCA, 19$^{th}$ European Congress of Internal Medicine (ECIM), 2021.

- **Oral Presentation:** Halo Score (Temporal Artery and Axillary Artery); Diagnostic and Prognostic Marker in GCA, The Role of Ultrasound in GCA, a Virtual International Course, 2021 and 2020.
- **Oral Presentation:** Probability-Based Diagnostic Algorithm or Suspected Giant Cell Arteritis, The Role of Ultrasound in GCA, a Virtual International Course, 2021 and 2020.
- **Poster Presentation:** Efficacy and Safety of Tocilizumab in Giant Cell Arteritis: Single-Centre NHS Experience Using Imaging (Ultrasound and PET CT) as a Diagnostic and Monitoring Tool, American College of Rheumatology (ACR), 2020.
- **Poster Presentation:** Ultrasonographic Halo Score as a Marker for Diagnosis and Monitoring of Disease Activity in GCA, ACR, 2020.
- Poster Presentation: Probability-Based Diagnostic Algorithm for Suspected GCA, EULAR, 2020.
- **Oral Presentation:** Efficacy and Safety of Tocilizumab in GCA: Multi-Centre Experience of NHS Clinical Practice, Rheumatology, BSR, 2020.- Best Research in Vasculitis award

# CHAPTER TWO: BACKGROUND

## 2.1 Giant cell arteritis

### 2.1.1 General aspects

GCA is a common vasculitis disease in older adults, with a probability of 7.4 per 10,000 women aged 70-79 years (5). This disease affects cranial or temporal and posterior ciliary arteries, aorta, and branches. Inflammation is the cause of ischemia and cytokine release, resulting in the ischemic eye, including ischemic option neuropathy or retinal artery occlusion. The most critical visual symptoms observed in patients with GCA are visual loss, amaurosis fugax, and diplopia (6). Van der Geest et al. divided GCA into three subsets based on clinical and immunological classifications. GCA is divided into systemic inflammation, large-systemic artery vasculitis, and polymyalgia rheumatica (7). Symptoms of GCA vary from person to person, as visual loss is higher in patients experiencing jaw claudication symptoms and those who do not face any temporal headache symptoms (8). Such variability leads to more specific diagnostic techniques improving the early diagnosis of patients with GCA. About an 8-week delay in diagnosis in patients that have cranial symptoms, and 18 weeks delay in patients with non-cranial symptoms were observed in a meta-analysis (9). Ophthalmic complications that led to the delayed diagnosis of GCA warrant more research to improve a prompt diagnosis of GCA. Introducing fast-track clinics in GCA diagnosis could reduce such a burden and help to have an instant diagnosis. However, as first-contact physicians, general practitioners have a major role in identifying and differentiating patients with GCA and non-GCA.

GCA features often overlap with Polymyalgia Rheumatica (PMR), as studies have shown that 16-21% of patients with PMR have GCA on temporal artery biopsy. Also, symptoms of PMR

are present in 40-60% of patients suffering from GCA (10). Therefore, we also believe GPSD exist, and it is more appropriate to look into this spectrum disorder as a whole rather than a single disease. John Hutchinson first described GCA in 1890, and he used 'Thrombotic arteritis of the aged' as the terminology to explain the condition. Horton et al.(11) reported a woman of 52 years and a man of 68 years in 1932, who were under observation at Mayo Clinic in 1931, having anaemia and scalp tenderness. The biopsies of the temporal arteries demonstrated chronic arteritis. In the mid-1940s, GCA was described as an auto-immune disease. Jennings (1938) and Wagener (1946) reported the visual loss as a complication of GCA. Soon it was observed that cranial arteries are not the only ones affected by GCA (12)(13). Sproul and Hawthorn found chronic inflammation of the aorta, iliac arteries, and carotid arteries post-mortem in 1937 (14). Shick reported that two patients of GCA were relieved with cortisone (15).

It was anticipated that using glucocorticoids (GC) for treating GCA reduce GCA-associated blindness; however, very little is known about whether this treatment has shortened the course of this complication. Furthermore, further studies contributed that after the treatment of GC, vascular inflammation persists. Since then, several studies have focused on adjuvant therapy as a steroid-sparing to check its usefulness in reducing vascular inflammation.

### 2.1.2 Nomenclature, Epidemiology, and classification

**A) Nomenclature:**

In 2012, Revised International Chapel Hill Consensus Conference, the nomenclature of vasculitis recognised as the GCA is a large and medium vessel vasculitis defined by arteritis, often granulomatous and usually affecting the aorta and its major branches with probable

involvement of carotid and vertebral arteries(16). There are various names for GCA, like Horton disease, temporal arteritis, granulomatous arteritis, and arteritis of ages.

**B) Epidemiology:**

GCA has unknown aetiology but is understood to be caused by the inflammation of the blood vessels and giant cells appearing during temporal arteries' biopsies. It usually happens in people having an age of more than 50 years. Studies from different sources have reported various statistics of global GCA incidence. Scandinavia said that 15 to 35 per 100,000 individuals over 50 years of age had GCA. Another study by Olmsted County and UK community showed similar results (17). The influence of this disease is greater in persons aged 80 years or above, and very few cases have been reported in persons less than 50 years of age. A Northern Europe report showed that females are influenced by GCA more than males in a ratio of 2.5:1. However, Southern European studies revealed that females have lower ratios in those countries. But the same results as of Northern Europe were observed in Spain, India, and Turkey. Studies conducted in Sweden revealed that GCA patients increased from 16.8 to 30.1 out of 1,00,000 persons (>50 years) between 1976 and 1995. Also, GCA was common in Caucasian persons more than non-Caucasians. However, little research on their comparison has been done (17). Texas and Tennessee studies have shown that there is less incidence of GCA in African Americans as well as Hispanics. Moreover, Japan has faced low prevalence than Europe (18).

Studying the epidemiology of a rare disease is a difficult task to achieve. The most challenging task epidemiologists consider in the epidemiology of GCA is its definition. American College of Rheumatology (ACR) (1990) has set up criteria for GCA, and these criteria were used in various studies (19). The age criteria, i.e., less than 50 years, means that persons younger than 50 years are least affected by GCA. ACR has not given biopsy a mandate; however, many

studies revealed biopsy-based hospitalisation of GCA patients. In addition, many cases were managed without biopsy. Thus, the cases remain uncertain of GCA.

Genetics can be an essential source of the development of this disease due to the predominance of HLA-DR4 allele expression(20). The inflammation of GCA is granulomatous, containing macrophages and T-lymphocytes inactive form. The T lymphocytes have CD4+ T cells in larger amounts. These CD4+ T cells occur due to external or autologous antigen-driven diseases. T lymphocytes and adventitial macrophages produce cytokines in higher quantities, which promotes inflammation and reaction, but no tissue damage is observed (21,22). Vessel walls are further injured because of the destruction of elastic laminae as a cause of metalloproteinases and oxygen radicals produced by macrophages in media. Cytokine patterns are correlated with clinical phenotypes of the disease. Therefore, higher cytokine levels are related to cranial symptoms. However, lower levels are associated with systemic symptoms only(23). Some growth factors stimulate hyperplasia; these factors are produced by multi-nucleated giant cells that are not only the debris removers but also secretory. The vascular pathology in GCA results from immunological injuries to the walls of the vessels and stromal response in the arterial wall. Systemic inflammation and inflammatory infiltration of the vessel wall are the major symptoms of GCA that result in luminal narrowing and end-organ ischemia. The most significant sign includes blindness and infarction of vessels(24).

Patients with GCA have a minor decrease in long-term survival compared to age- and sex-matched controls. The difference is due to excess mortality in the first two years and ten years after diagnosis(24).

**C) Classification:**

The signs of GCA include cranial arteritis (c-GCA), extracranial arteritis (LV-GCA), PMR, and systemic symptoms(25). Any of these could be present in the patient suffering from GCA.

The only test that provides authentic evidence of GCA is TAB. The US, as an imaging modality of the temporal artery, is also used in diagnosing GCA. No specific criterion can tell whether a person has GCA when his biopsy results are negative. In 1990, the ACR developed criteria for GCA classification (26) however, the classification does not mean complete diagnosis. This criteria mainly aimed to differentiate GCA from other vasculitic diseases. The diagnosis is made by histological, laboratory, imaging, and clinical findings.

ACR developed the criteria for classifying GCA based on comparing 214 GCA patients and 593 patients with another vasculitis. They classified GCA into traditional and classification tree groups. The conventional group had five categories, i.e., age >50 years at onset, new onset of localized headaches, temporal artery tenderness, elevated erythrocytes sedimentation rate of less than and equal to about 50 mm, and biopsy sample. The presence of any of the three criteria has a 91.2% specificity and 93.2% sensitivity of GCA. A recently validated ACR/EULAR classification criterion gives a sensitivity of 87% and specificity of 94.8% when applied the revised parameters (Table-1) (27)

**Table 1: 2022 ACR/EULAR classification criteria for Giant cell arteritis**

| Criteria | Score |
|---|---|
| **Absolute Requirement** | |
| Age ≥ 50 years at the time of diagnosis | |
| **Additional Clinical Criteria** | |
| Morning stiffness in shoulders/neck | +2 |
| Sudden visual loss | +3 |
| Jaw or tongue claudication | +2 |
| New temporal headache | +2 |
| Scalp tenderness | +2 |
| Abnormal examination of the temporal artery | +2 |
| **Laboratory, Imaging, and clinical criteria** | |
| Maximum ESR ≥ 50mm/Hour or maximum CRP ≥ 10 mg/L | +3 |
| Positive temporal artery biopsy or halo sign on temporal artery ultrasound | +5 |
| Bilateral axillary involvement | +2 |
| FDG-PET activity throughout the aorta | +2 |

***A score of ≥ 6 points, needed for the classification of Giant Cell Arteritis***

### 2.1.3 Disease subsets, phenotypical presentation, and Stratification

#### A. Disease stratification in GCA

GCA has several disease phenotypes with different outcomes (28). These phenotypes' possible disease management consequences may be addressed by recognising at least three domains of stratification in GCA, employing clinical, laboratory and imaging modalities.

##### a. Clinical stratification

Four major clinically interlinked disease phenotype subsets exist in GCA (**Figure 1**).

***Cranial subset.*** The main clinical features are new-onset headache, scalp tenderness, and jaw/tongue claudication(29). The inflammation mainly affects extra-cranial branches of carotid arteries (e.g., temporal, frontal, and parietal arteries) (30).

***Ischaemic GCA subset.*** The dreaded consequence of GCA relates to ischaemic permanent sight loss, seen in 10-25% of cases and mainly associated with arteritic ischaemic optic neuropathy (31). Sight loss in GCA seems to be associated with a less increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels (32,33). There is also a correlation between a higher Halo score and intimal hyperplasia on TAB (34,35). Binocular vision loss is usually preceded by unrecognised sight loss in one eye. Diplopia and amaurosis fugax can precede permanent vision loss in 8-28% of patients (36). Notably, headaches may not be prominent in the ischaemic group, and the absence of headaches may delay diagnosis and precipitate avoidable blindness (37). Therefore, ischaemic ocular symptoms should always be actively sought, even without cranial symptoms. Ultrasound-based fast-track pathways to heighten patient and professional awareness have effectively reduced sight loss (38).

***LV-GCA subset.*** LV-GCA is diagnosed when the aorta, especially its supradiaphragmatic sections and branches, are involved (39). Manifestations are low-grade fever, weight loss, fatigue, drenching sweats, and back pain (30). Patients with systemic symptoms have a more relapse-prone disease (40,41). Some

patients with extra-cranial vascular involvement may chiefly present with symptoms of polymyalgia. This clinical entity was recognized by Hamrin et al. decades ago, before sophisticated imaging methods, as *polymyalgia arteritica* (42)Finally, some patients may present with isolated aortitis, mainly fever, sweats and weight loss, and can develop aneurysms but rarely ischemia (43).

***PMR subset.*** PMR is also recognised as a manifestation of GCA (*see detailed Section on PMR stratification below (B)*).

These four subsets are not independent and mutually exclusive; patients often present a mix of features (44). Polymyalgic symptoms were observed in around 40% of patients diagnosed with GCA, either at disease onset or flare (45). Up to 80% of patients with GCA, including the classic "cranial" clinical phenotype, may have involvement of the aorta or its branches (46). Extra-cranial involvement is present in around 30% of isolated PMR (47).

Clinical features may predict disease course. For example, cranial symptoms prevail, and the risk of ocular ischaemic complications rises (48). In this scenario, the initial management target is rapid control of the inflammation with high-dose glucocorticoids with pulsed intravenous methylprednisolone where necessary (49). In the long term, such patients may have a lower need for glucocorticoids and DMARDs (50). As is true for the GCA disease subsets, patients with persistent systemic symptoms have a more relapse-prone disease (40,41). However, it is essential to underline that clinical features may not reflect the disease state, as disease activity with inflammation may be present in the absence of overt clinical symptoms.

### b. Laboratory and histological stratification

Vascular and non-vascular biomarkers can help with GCA stratification and monitoring (**Table 2**).

A solid systemic inflammatory response may identify patients with an unfavourable disease course. One study (51) reported that the presence of two or more of the following factors at diagnosis was

eventually associated with a relapsing disease course and high glucocorticoid requirement: fever, weight loss, ESR ≥ 85 mm/hr and haemoglobin < 11.0 g/dL. Another study (40) reported a similar finding that applies a slightly different set of clinical and laboratory parameters reflective of systemic inflammation; therefore, validation of the two composite scores for systemic inflammation is needed. Some studies (52–55) suggested that individual blood tests, such as ESR, CRP and haemoglobin, could have some prognostic value in GCA, without reporting actual cut-off values for these parameters. Other studies failed to find any prognostic value of these individual blood tests (56–59).

Several biomarkers measured at diagnosis and before initiation of treatment have shown a promising potential to predict the subsequent disease course in patients with GCA. For example, serum levels of the angiogenesis markers vascular endothelial growth factor (VEGF) and angiopoietin-1 have been linked to a relatively benign disease course (59) This was also observed for high serum levels of the tissue-degrading matrix metalloproteinase-2 (MMP2) (52,59). In contrast, high serum levels of YKL-40 (chitinase-3 like-1) and osteopontin (OPN), both involved in the angiogenesis and vascular remodelling of GCA, were associated with an unfavourable disease course (58,59).

Neutrophils seem to have a role in GCA pathogenesis, particularly those with an escaped pro-inflammatory phenotype exhibiting increased endothelial adhesion (60). Further translational studies regarding the utility of neutrophil phenotypes as biomarkers in GCA are required.

Several studies have evaluated the prognostic value of TAB findings in GCA. High IL-17 expression in TAB may associate with low glucocorticoid requirement, according to one study (41,61) in one-third of cases, TABs were collected after a median of one week of high-dose glucocorticoid treatment. High expression of the monocyte-attracting chemokine CCL2 in TABs, all of which were obtained before initiation of therapy, is also associated with an unfavourable disease course (62). Two studies, in which it was unclear to what extent TAB was obtained before initiation of treatment, linked high

TNF-alpha expression in TAB and increased numbers of infiltrating CD8 T cells, respectively, to a high glucocorticoid requirement (63,64).

Disease severity regarding ischaemic complications has been linked to a mild systemic inflammatory response. Several findings on TAB, including intimal hyperplasia, strong IL-1β and IFN-γ response, appear associated with ischaemic complications: (65). Serum levels of the glycolytic enzyme Pyruvate Kinase M2 (PKM2) also correlate with the inflammatory burden on FDG-PET/CT, as determined by semi-quantitative scoring methods (34,66) Unlike imaging findings (67), inflammation markers at diagnosis do not predict later occurrence of aortic aneurysms in GCA (68,69).

During patient follow-up, timely recognition and treatment of relapses are critical. CRP and ESR are typically serially followed as indicators of clinical disease, but their accuracy in detecting active disease is moderate during follow-up. Several other markers associated with disease activity have been reported, but these lack sensitivity and specificity for use as relapse markers in daily clinical practice (28). Serum angiopoietin-2 levels during clinical remission may predict future relapse (70,71); this biomarker has potential as a disease stratification aid during monitoring. The same has been suggested for serial measurements of serum IL-6 in patients treated with anti-IL-6R therapy: persistently high levels of serum IL-6 were associated with an increased risk of relapse following the withdrawal of anti-IL-6R therapy, whereas patients with gradually declining IL-6 levels were less likely to relapse after discontinuation of treatment (72).

### c. Imaging stratification

Imaging is now an accepted part of the diagnosis of GCA (73). Increasing evidence supports an unfavourable prognosis for extracranial involvement in GCA: Sugihara et al. found that baseline imaging documenting LV involvement was associated with worse treatment response in a retrospective multicentre cohort of 139 patients (74), and similar results were shown by other authors (47,75–77). In some of these studies, a comprehensive evaluation of all vascular sites at baseline was missing, and extracranial involvement was assessed only during follow-up in some cases. Two small, robust

prospective studies confirmed that patients with LV-GCA have a worse outcome associated with an increased risk of flares (78,79).

Patients with residual vascular FDG-PET/CT inflammation at follow-up seem to be at higher risk of clinical relapse, according to one study (80). This study proposes a novel score to quantify the extent and intensity of extra-cranial arterial involvement, the PET Vascular Activity Score (PETVAS). PETVAS is made of a simple arithmetic sum of the Meller score (from 0 to 3 per vascular bed according to the degree of uptake compared to the liver) in 4 aortic territories and 5 branch arteries (81) PETVAS does not include an assessment of the axillary arteries, a key vascular region in LV-GCA. Therefore, it has been suggested that PETVAS needs modification with the addition of axillary arteries (82).

FDG-PET/CT also seems able to predict the risk of long-term vascular complications. Four studies found that the presence of aortic inflammation at baseline is associated with a higher probability of developing aortic aneurysms (47,48,68,76). Baseline aortitis may be an essential stratification tool for meticulous follow-up and non-steroid therapy indications.

Imaging of non-aortic vascular territories is not only a valuable tool for monitoring long-term outcomes but can also quantify disease severity at presentation. This approach has been facilitated by the quantitative ultrasound Halo score calculated from 6 temporal arteries and 2 axillary artery segments (83). Higher Halo scores were associated with ocular ischaemia and intimal hyperplasia, a histologic feature associated with ischaemic sight loss (34,35).

**Figure 1: Four major clinically interlinked disease phenotype subsets in GCA**

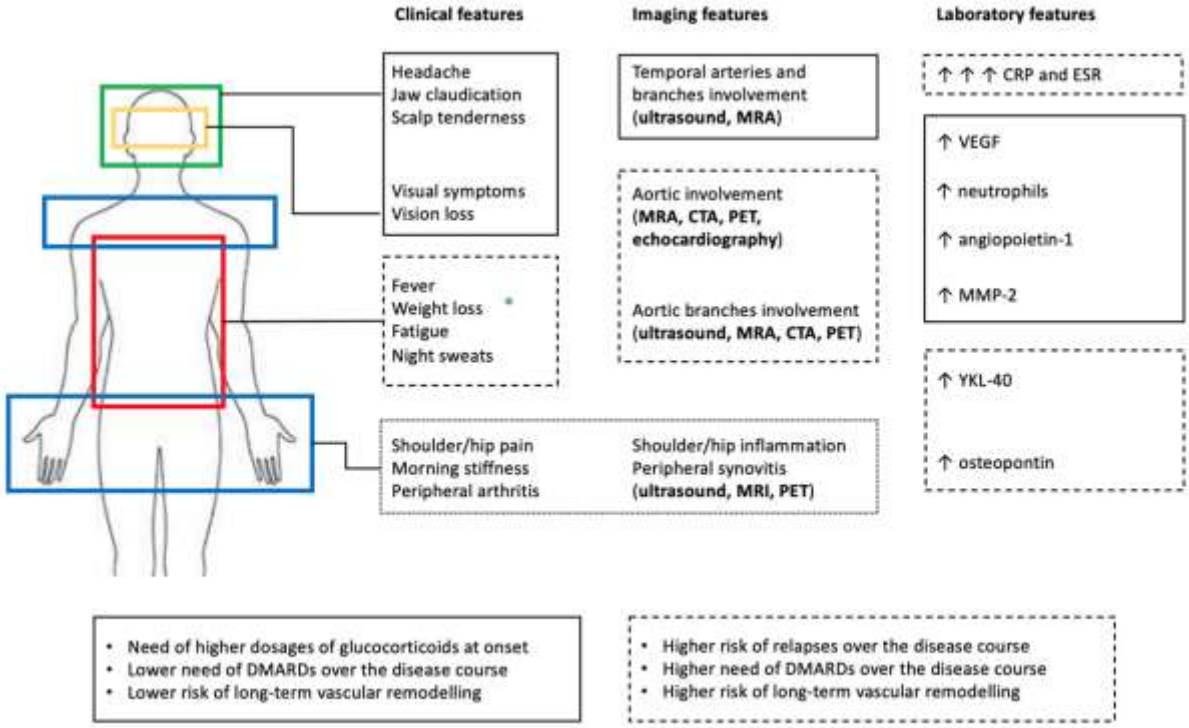



**Table 2.** Laboratory and histology findings associated with disease course in GCA and PMR. Unfavourable disease course: high number of relapses and/or high glucocorticoid requirement. Favourable disease course: low number of relapses and/or low glucocorticoid requirement.

| GPSD | Disease course | Factors at diagnosis associated with disease course |
|---|---|---|
| GCA | Unfavourable | Strong systemic inflammatory response |
| | | High serum YKL-40 |
| | | High serum osteopontin |
| | | High CCL2 expression in TAB |
| | | High TNFα expression in TAB |
| | | High number of infiltrating CD8 T cells in TAB |
| | Favourable | High serum VEGF |
| | | High serum angiopoietin-1 |
| | | High serum MMP-2 |
| | | High IL-17 expression in TAB |
| PMR | Unfavourable | High ESR |
| | | High serum angiopoietin-2 |
| | | High neutrophil to lymphocyte ratio |

## B. Disease stratification in PMR

Polymyalgia is a manifestation of GCA, but it may also present clinically as an isolated entity that can either remain as PMR or progress to overt GCA (44). For many years, PMR was dubbed 'little GCA', which has led to the loss of interest from specialists and relegation to non-specialist care. However, t polymyalgic syndrome is often complex, with many mimics and severity grades, and deserves specialist care (84).

### a. Clinical stratification

Twenty-to-fifty percent of patients with PMR complain of constitutional symptoms (85). In these cases, occult cancer and infections need to be excluded (86); however, these symptoms can also reflect severe inflammatory PMR or LV involvement (*polymyalgia arteritica*) (87). In addition to systemic symptoms, patients with pain localised over the back, pelvic girdle and/or lower limbs have a higher likelihood of having a positive FDG-PET/CT for LV-GCA (88,89). In around 20-25% of patients, distal manifestations such as peripheral synovitis can resemble rheumatoid arthritis (90). In some cases, extensor tendonitis and flexor tenosynovitis lead to remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) (91).

Response to low-dose glucocorticoid may help stratify PMR. Two inception cohort studies reported that complete response (>70% improvement in pain, stiffness and inflammatory markers) is seen in only 60% of cases (84,92). This may help stratify PMR into those who respond to low-dose glucocorticoids versus those who may need additional workup and non-steroid therapies.

According to a prospective study on 94 patients, the presence of systemic symptoms or peripheral arthritis did not influence the risk of clinical relapses (93). Conversely, another study showed that the duration of glucocorticoid therapy was longer and relapses higher in patients with PMR and peripheral arthritis compared to isolated ('pure') proximal disease (94). In the same study, the presence of RS3PE

was associated with a benign course (95). Another study compared the clinical outcomes of isolated PMR versus PMR with RS3PE syndrome. This study showed no differences between groups (96). Imaging of large vessels was not done in these studies since they were conducted prior to the area where our understanding toward the GPSD emerged (97). Recent data using imaging indicated that difficult-to-treat and relapse-prone PMR often reflects LV involvement (88).

Differentiation of PMR from other arthritides affecting the elderly, such as late-onset rheumatoid arthritis (LORA) and calcium pyrophosphate dihydrate crystal deposition (CPPD) disease, remains a challenge. Pease et al proposed that wrist synovitis and the involvement of either metacarpophalangeal or proximal interphalangeal joints helped to early identify LORA patients with polymyalgic onset (90). This differentiation has prognostic implications, as LORA can evolve towards erosive arthritis while PMR-associated synovitis does not cause articular damage. However, there may be a genuine overlap, as reflected by the 2012 EULAR/ACR PMR classification criteria, which performed well in differentiating PMR from non-inflammatory bilateral shoulder pain but less well in differentiating it from rheumatoid arthritis (92). The GPSD spectrum includes inflammatory arthritis and variants (such as RS3PE), since previous studies suggest the evolution of a section of PMR into rheumatoid arthritis on long-term follow-up, especially in patients with peripheral synovitis (90,98).

**b. Laboratory and histological/cellular infiltrates stratification**

Several studies have investigated the ability of blood biomarkers, as measured at diagnosis, to identify subsets of PMR with high versus low glucocorticoid requirements (**Table 2**). High ESR levels, defined as > 40 mm/hr by two studies and ≥ 74 mm/hr in another report, have been linked to a high glucocorticoid requirement (99–101). A fourth report did not identify any prognostic value of the ESR in patients with PMR (57).

Another easily applicable marker, the neutrophil-to-lymphocyte ratio, predicted glucocorticoid resistance in PMR (92). Data from two independent cohorts have indicated that a high ratio between

angiopoietin-2 and angiopoietin-1 in serum identifies PMR subsets with concomitant LV-GCA (99). In the absence of LV-GCA, a high ratio of these angiogenesis biomarkers also identifies a subset of patients with PMR with a high glucocorticoid requirement (100). Routine inflammation markers, such as CRP and ESR, show no relationship with disease extent on FDG-PET/CT (100,101).

Biopsy studies in PMR are still scarce but have become more feasible with the introduction of ultrasound-guided biopsy techniques (102,103). Studies linking histology to disease subsets, severity or extent are lacking. Recently, it has been shown in patients with RA that distinct pathotypes in synovial biopsies seem to predict the response to particularly targeted therapies (104,105). Investigation of such an approach in PMR would be of interest to future studies.

### c. Imaging stratification

Imaging as an aid to stratify different subsets in PMR is a subject of active ongoing research, and there is discordance in the data available so far.

The main imaging aids used in the evaluation of GPSD are ultrasound, magnetic resonance imaging (MRI), and FDG-PET/CT (106). The common lesions detected by ultrasound are subacromial/subdeltoid (SAD) bursitis, bicipital tenosynovitis, hip synovitis and trochanteric bursitis (107). MRI has higher resolution, particularly for the pelvic girdle (108), and provides a comprehensive evaluation with greater sensitivity and specificity for inflammation (109). FDG-PET/CT is usually performed in patients with atypical presentation or relapsing/refractory PMR, to exclude concomitant LV-involvement or other diagnoses (e.g., malignancies). A systematic literature review (SLR) highlighted that composite FDG-PET/CT scores provide a pooled sensitivity and specificity higher than ultrasound but also pointed out the need for standardized scoring systems and scanning protocols (110). The diagnostic accuracy and reported diagnostic cut-off value of one composite FDG-PET/CT score, the Leuven Score, was confirmed in a study comparing various scoring systems for PMR (111).

All three modalities have been evaluated for their role in defining prognosis in PMR. However, imaging as an aid to stratify PMR in different subsets is still a matter of ongoing research and data are discordant so far.

In the PMR classification study, PMR-specific lesions were found frequently in patients with a good response to glucocorticoids (92). However, subdeltoid bursitis and/or bicipital tenosynovitis on ultrasound at baseline was not a predictive marker of a 12-month response in a prospective study (112). A study evaluating total grey-scale (GS) scores derived from a semiquantitative assessment of bicipital tenosynovitis and SAD bursitis showed that patients with a higher score had a lower response to glucocorticoids (113). Also, the intensity of the power doppler (PD) signal at baseline may predict the risk of relapses (114). In the same study, the persistence of PD signal on follow-up was not associated with relapses (114).

The risk of relapses in PMR is higher when there is synovial hypertrophy in the shoulders on baseline MRI (109). MRI can also be used to evaluate sites other than the shoulders. In a prospective study, 22 patients with a clinical diagnosis of PMR underwent baseline whole-body gadolinium-enhanced MRI (115). Imaging may allow stratification into two main groups, according to the pattern of capsular involvement, i.e., ‘extracapsular’ versus ‘non-extracapsular’. Notably, symmetrical, extracapsular inflammation was associated with higher patient-reported responsiveness to glucocorticoids. This pattern was associated with higher pre-treatment levels of CRP and IL-6 (115).

Uptake in the acromioclavicular joints and higher global uptake disclosed by FDG-PET/CT at baseline may predict a lower steroid dependency (116).

### 2.1.4 Pathogenesis

GCA pathogenesis is affected by genetic substrate, immune and arterial systems alternations, and gender (117). GCA and PMR also show substantial overlap at a genetic level. The development of GCA has been mainly linked to the carriage of the HLA-DRB1*04 allele 120). The incidence of GCA in a particular geographical region correlates with the population's distribution of the HLA-DRB1*04 allele(118). A similar genetic association with HLA-DRB1*04 has been described in PMR (119), although this has not been confirmed in all studies (120,121).

An important role in the initiation phase of GCA has been attributed to dendritic cells that reside in the adventitia of the arterial wall. These dendritic cells can be activated via their pattern recognition receptors and might subsequently trigger an inflammatory cascade involving macrophages and T cells (122–124). Synovial macrophages and dendritic cells could theoretically play a similar role in the synovium, tendon sheaths and bursae of patients with PMR (125,126). The exact triggers that activate these tissue-residing immune cells are unknown but could include microbial products and damage-associated molecular patterns, possibly related to ageing or mechanical stress (127).

Shared immune pathways have been implicated in GCA and PMR. Similarities in the circulating immune cell compartment include a profound expansion of myeloid cells (i.e., monocytes and neutrophils) (57) and interleukin (IL)-17 producing T cells (i.e., T helper 17 cells and T cytotoxic 17 cells) (64,102,128). Data on the frequencies of circulating T helper 1 cells have not been consistent (102,128–130). Serum levels of IL-6 are substantially elevated in both conditions (131,132) and treatment with anti-IL-6 receptor therapy seems effective in GCA and PMR (133–135). GCA arteries are characterized by extensive infiltrates of T helper 1 and T helper 17 cells (128,130) as well as pro-inflammatory and tissue-degrading macrophages (136,137). Recent insights derived from the PMR Research On disease Mechanisms in Synovium (PROMIS) project, in which ultrasound-guided biopsies are obtained from the subacromial bursae of patients with PMR, indicate that macrophages also

predominate in PMR synovium (102,138) and produce IL-6 (103). However, the PROMIS project has also shown that T cell infiltrates relatively limited in PMR synovium, with most of these cells being T helper 1 cells (102,138). Intriguingly, an early study indicated that vascular dendritic cells are also activated in the temporal artery biopsies (TABs) of patients with isolated PMR. However, further signs of inflammation were absent in those biopsies (139). In an adaptive transfer animal model, T cells derived from engrafted GCA arterial lesions could migrate to TABs derived from PMR patients but not to TABs of control patients without PMR/GCA. These findings suggest that more specific T-cell activation is needed before full-blown inflammation develops in the activated arterial walls of patients with PMR.

Overall, the pathobiology of GCA and PMR shows substantial overlap, including a predominant IL-6 signature, although T-cell responses in tissues seem relatively limited in PMR. Within the GPSD spectrum, PMR might primarily reflect the autoinflammatory component of the disease, whereas the autoimmune component is more developed in GCA (140).

### 2.1.5 Treatment

Treatment guidelines address GCA as a monolithic disease, with high-dose glucocorticoids as the keystone therapy. EULAR and ACR guidelines agree on starting with 1 mg/kg/daily of prednisone-equivalent to be maintained until clinical remission (49,141). The tapering schedule for glucocorticoid monotherapy disregards baseline manifestations, severity, and extent. The target for reaching low acceptable doses of glucocorticoids (i.e., $\leq$ 5 mg daily of prednisolone equivalent) is arbitrarily set at 12 months. Still, most patients experience relapses, requiring dose increase, prolonged therapy and often the addition of disease-modifying antirheumatic drugs (DMARDs) (41).

Numerous DMARDs have been evaluated in steroid-dependent GCA 45). To date, the IL-6 receptor inhibitor tocilizumab is the only biologic DMARD licensed for GCA since its efficacy was demonstrated in a phase-3 randomized controlled trial, the GiACTA trial (133). However, therapies

exploiting different mechanisms of action have recently emerged as promising alternatives in phase-2 studies, including a small number of patients. Specifically, the fusion protein composed of the extracellular domain of CTLA-4 abatacept, the GM-CSF inhibitor mavrilimumab, and the IL-17A inhibitor secukinumab have all been demonstrated to be able to reduce the risk of relapse in the short-term (e.g., at 6 or 12 months) (142–144). Confirmation of these results in larger populations is required before witnessing their widespread use. In addition, the IL-23 inhibitor guselkumab and the JAK-1 inhibitor upadacitinib are currently under investigation (NCT04633447, NCT03725202).

Among conventional DMARDs, the use of methotrexate is supported by a meta-analysis of three randomised controlled trials (RCTs), which themselves show conflicting results (145–147). Nowadays, methotrexate is the only DMARD recommended by European and American Guidelines (49,141). There are promising data on leflunomide (148–150), but acquiring high-quality RCT evidence is hampered by scanty trial funding for testing a generic drug.

There is poor consensus about the role and position of DMARD therapy in managing GCA. According to ACR guidelines, tocilizumab should be started at diagnosis, irrespective of disease severity and extent, to achieve the lowest dose of glucocorticoids (141). Methotrexate and abatacept represent alternatives. The EULAR guidelines recommend using tocilizumab in patients experiencing a flare or with an increased risk of steroid-related adverse effects and propose methotrexate as a valid alternative (49). Prior disease stratification does not influence these decisions, except for susceptibility to steroid-related adverse events. The U.K. National Institute for Health and Care Excellence (NICE) funding approval for tocilizumab implies stratification with empirically developed eligibility criteria, recommending use in relapsing and refractory disease (151).

**Published article:**

The following review material in this chapter was published on 30th May 2021 during the PhD. This printed article summarised the innovative treatment strategies used in GCA and

highlights the ongoing clinical trials. The references in this article below is amended from the original publication to reflect the continuity of the PhD thesis references.


Review

Current and innovative therapeutic strategies for the treatment of giant cell arteritis

Alwin Sebastian, Alessandro Tomelleri & Bhaskar Dasgupta

Pages 161-173 | Received 26 Jan 2021, Accepted 18 May 2021, Accepted author version posted online: 19 May 2021, Published online: 30 May 2021

Download citation https://doi.org/10.1080/21678707.2021.1932658

**Abstract.**

**Introduction**. Glucocorticoids represent a highly effective treatment for giant cell arteritis (GCA); however, steroid-dependency frequently hinders an adequate dose reduction. This has led to flourishing interest in new therapeutic strategies.

**Areas covered**. An analysis of the main treatments for GCA was conducted. The work is structured in four sections: data supporting the use of glucocorticoids are summarised; uncertainty regarding the use of antithrombotic agents is discussed; studies on different conventional steroid-sparing agents are reported; controlled trials with biologic agents already available and the design of those still ongoing are presented. The basis for this review is a literature search on PubMed of studies published until 31st December 2020 pertaining to GCA treatment.

**Expert opinion**. Every new GCA patient should be stratified, and the therapeutic management should be tailored accordingly. High-risk patients should be early treated with steroid-sparing agents, but the currently available evidence only supports the use of tocilizumab, with conflicting data on methotrexate. Soon, the results of controlled trials evaluating other agents, such as mavrilimumab, will be released and, hopefully, this will lead to their inclusion as alternatives to tocilizumab. Even if biologic drugs seem highly effective, their use could be limited by high costs; hence, clinical research should not forget about less expensive conventional agents, such as leflunomide.

**Keywords.**

bDMARDs; csDMARDs; biologic therapy; clinical trials; giant cell arteritis; glucocorticoids; large-vessel vasculitis; therapy

**Article highlights.**

- High-dose glucocorticoids represent the mainstay of new-onset GCA treatment, as they allow to rapidly suppress systemic inflammation and to prevent ischaemic complications.
- Gradual and controlled glucocorticoids reduction is imperative, to limit the risk of metabolic side effects related to their use; however, a significant proportion of GCA patients experience disease relapses upon glucocorticoids tapering.
- Hence, there is the need for effective and safe steroid-sparing agents, to be introduced early in patients at increasing risk for glucocorticoids-related side effects or with particularly aggressive disease and later in those experiencing disease relapses or incipient damage.
- Among the numerous conventional disease-modifying drugs available, methotrexate is the only one partially supported by controlled studies and therefore the most commonly used; however, although non-controlled, increasing evidence supporting the use of leflunomide have been published.
- In the last years, a better knowledge of the molecular mechanisms implicated in GCA pathogenesis has encouraged the use of biologic agents targeting the main inflammatory cytokines involved in the vasculitis process.
- To date, only the IL-6 receptor antagonist tocilizumab has been definitely proven to be effective in preventing disease relapse and reducing the use of glucocorticoids.
- The positive preliminary results of a phase II placebo-controlled study with the GM-CSF inhibitor mavrilimumab have been recently released.

The use of other agents, such as abatacept, ustekinumab, guselkumab, secukinumab, and the JAK inhibitors, is still under investigation.

# 1. Introduction

Giant cell arteritis (GCA), also known as temporal arteritis, is a critically ischaemic large vessel vasculitis usually diagnosed in adults over the age group of 50 years, mainly affecting the aorta and its cranial and extra-cranial branches (152). In its acute presentation, GCA can be responsible of ischaemic and irreversible events (i.e., sight loss, ischaemic stroke), whereas its chronic evolution can lead to significant vascular damage (i.e., stenosis, occlusions, aneurysms) (61,153,154). From the clinical point of view, GCA patients can experience a wide range of symptoms, that can be classified into four non-mutually exclusive groups: cranial, ischaemic, constitutional, and polymyalgic. New-onset headache is the most typical cranial symptom, along with scalp tenderness and jaw claudication. Constitutional symptoms are mainly represented by fever, weight loss, and drenching night sweats. Finally, about 50% of GCA patients complain of bilateral shoulder and/or hip pain and stiffness, expression of polymyalgia rheumatica (155). The common ischaemic symptoms are jaw and tongue claudication and visual manifestations such as diplopia, blurred vision and amaurosis fugax. The most feared acute ischaemic complication of GCA, permanent blindness, occurs in about 15% - 25% of patients at disease onset and it's mainly related to anterior ischaemic optic neuropathy or central retinal artery occlusion (38).

Originally, GCA was considered as an inflammatory disease confined to the cranial arteries; however, the increasing use of extensive vascular imaging investigations over the years has made clear that a significant proportion of GCA patients have evidence of involvement of large-vessel extra-cranial vessels, particularly thoracic aorta and supra-aortic trunks (156–158). These patients are generally younger at disease onset and diagnosed with a higher delay, probably due to the fact that, in this subset, cranial manifestations are often absent and

constitutional symptoms prevail (48,159,160). Interestingly, even if GCA patients with cranial-restricted and with large-vessel phenotypes have different demographic, clinical and prognostic features, they apparently share a common HLA-DRB1 association (i.e., HLA-DRB1*04:01 allele) (161).

Early diagnosis and prompt treatment initiation are required to improve symptoms and prevent both acute events and chronic complications (162,163). The most common treatment option is high-dose glucocorticoids (GC), which is recommended as soon as GCA is suspected (164). However, considering the elderly age group, co-morbidities and long duration of therapy, GC-related serious side effects are frequent (165); for this reason, the use of steroid-sparing agents, either conventional (c-) and biologic (b-) disease modifying anti-rheumatic drugs (DMARDs), is progressively emerging. The efficacy of some of these agents has already been demonstrated, whereas others are still under evaluation.

## 2. Treatment of giant cell arteritis

### 2.1. Glucocorticoids

Immediate high-dose GC represents the cornerstone of the treatment of new GCA (166). The exact starting dose, route of administration and duration of therapy remains a matter of debate and may need to be individualised. A starting dose of 40-60 mg daily of oral prednisolone-equivalent is suggested by current recommendations, followed by a tapering regime customised according to the individual circumstances, such as adverse events, tolerance and comorbidities (49,164). GC monotherapy should be administered for at least 9-12 months but in most of the cases a longer interval is needed in order to maintain remission and prevent relapses (167)owever, after the publication of the GiACTA trial, when concomitant tocilizumab is administered a shorter 6-month GC tapering scheme is advised, as it is associated with a reduced cumulative steroid dose (168). The efficacy of GC in GCA is so strong that if there is

no symptomatic improvement within 1-2 days within GC start, GCA diagnosis should be revised (169).

In patients with neurological or evolving visual symptoms, higher dose of GC in the form of intravenous methylprednisolone boluses (1 gram per day for 3 days) are usually recommended (164,169,170). Intravenous GC is widely administered with ischaemic complications, although strong evidence supporting their superiority to the oral route is lacking and their use mainly relies on retrospective studies (171). On the other hand, the use of intravenous GC in patients with no ischaemic features is not recommended, as it has not been shown to reduce the long-term cumulative dose of GC and GC-related side effects (172).

Timing is more important when dealing with patients with ischaemic complications: an improvement of sight has been observed in up to 58% of patients started on GC within 24 hours from the visual symptom onset, compared to only 6% if administration of GC was delayed (173). Another study found an incidence of vision loss of 60% in GCA patients erroneously not started on GC (174). A population-based cohort study of 136 patients with biopsy-proven GCA with visual manifestations over 17 years showed 19% of patients developing permanent visual loss, a result in line with other studies that have evaluated GC use as a treatment for GCA (154). However, it is worth pointing out that in the last decades, a considerable decline in the incidence of GCA-related visual ischaemic complications has been observed (175,176). This is probably a consequence of a growing awareness of this disease among physicians. Another possible explanation is the fact that an increasing number of rheumatologic centres are equipped with fast-track services, allowing an easier and faster referral of patients with a GCA suspect (38).

Rate of visual loss is generally lower in patients with involvement of the aorta and its major branches (48). Conversely, in these patients, GCA has typically a more aggressive course, with higher tendency to relapse and need of GC, and a greater risk of developing long-term vascular

complications, such as aortic aneurysms (48,177,178). For these reasons, increasing evidence suggesting an early addition of DMARDs to standard GC therapy in this population of patients is cumulating (160,179).

GCA usually requires prolonged use of GC (more than 12 months), thus it is associated with significant treatment-related complications and adverse effects. These include hypertension, hyperglycemia, osteoporosis, cushingoid changes, infections, mood disturbance and electrolyte imbalance, but this is not the full list (180,181). A decade long study showed that 58% of GCA patients developed at least one serious GC related side effect during the course of the treatment (182). A GCA cohort study showed a significant risk of adverse rates for every 1 g increase in the cumulative GC dose (odds ratio 1.17) (183). Notably, as GCA is exclusively in elderly population, they are susceptible to have at least one or more pre-existing co-morbidities such as hypertension, diabetes mellitus, ischaemic heart disease or osteoporosis. GC is an added risk factor in this population and, therefore, GC related risk of harm is often patient specific (184). In an evidence-based consensus European League Against Rheumatism (EULAR) task force statement in chronic rheumatic diseases, the long-term level of harm with GC use was deemed to be dose dependent. Doses ≤ 5mg/day may be acceptable with low level of harm, except in cardiac diseases needing preventative measures; with doses ≥ 10 mg/day the risk of harm is definitely increased and between 5-10 mg/day harm versus benefit remains dependent on individual patient specific risk factors and behaviours (185).

Alternative treatments are the need of the hour for GCA, considering these serious side effects of long-term GC. Even though many studies have been conducted, finding treatment options that completely exclude glucocorticoids has been elusive (186) .

### 2.2. Anti-thrombotic agents

Aspirin is an antiplatelet drug which inhibits the formation of thrombosis by reducing platelet aggregation. There is no clear evidence that vascular thrombosis is associated with GCA although a small case series showed histologically proven thrombus formation in the vertebral arteries in GCA patients (187). A retrospective study found that patients taking aspirin reported fewer GCA-related cranial ischemic complications (188). Another study found that patients taking an anti-thrombotic agent had a protecting effect against ischemic complications and did not show an increase in bleeding events (189). In both trials, all patients were on a prednisone regimen after GCA diagnosis (190).

Other studies found no benefit in preventing ischaemic complications when patients were already on aspirin at the time of diagnosis of GCA (191,192). A meta-analysis showed that being on antiplatelet or anticoagulant therapy before the diagnosis of GCA was not associated with a reduction in severe ischemic complications (193). A Cochrane database review found no reports of randomised controlled trials (RCT) with aspirin as adjuvant treatment for GCA (194). British Society of Rheumatology (BSR) and EULAR guidelines do not recommend routine use of antiplatelet or anticoagulants in GCA unless there are other cerebrovascular, cardiovascular or peripheral vascular indications (49,164).

### 2.3. Conventional disease-modifying anti-rheumatic drugs

The only effective treatment for GCA-related ischaemic complications is the start of GC as quickly as possible, upon the onset of the disease. However, GC therapy is often of a long duration, and this has led to many immunosuppressive therapies being tried for GCA, with the aim of allowing a quicker steroid tapering regimen, reducing GC related adverse events and helping reduce disease activity. However, studies have been limited, and not conclusive (165).

Immunosuppressants play a vital role in the case of patients with a high-risk of GC-related adverse effects, such as concomitant high blood pressure, diabetes mellitus and severe osteoporosis. Adding an immunosuppressive agent at the onset of disease may allow a faster tapering regimen of glucocorticoids (165). Many synthetic immunosuppressants such as methotrexate, azathioprine, mycophenolate mofetil, leflunomide, cyclophosphamide and hydroxychloroquine have been tested on patients with GCA. Although evidence shows some efficacy, the reports are limited in sample size and to case series (186).

### *2.3.1. Methotrexate*

Methotrexate (MTX) is a dihydrofolate reductase inhibitor (195,196) which inhibits the enzymes involved in purine metabolism, with consequent adenosine accumulation. Hence, its use leads to selective B cells downregulation, methyltransferase activity inhibition, and increasing CD95 sensitivity of activated T cells leading to increased apoptosis of T cells (197,198). Another fundamental mechanism of action of MTX is the inhibition of the binding of IL1-beta to its cell surface receptor (199). MTX has been the anchor drug in the management of inflammatory arthritides and a range of systemic inflammatory diseases; hence it is a natural candidate for use in GCA. Despite this promise, there is conflicting evidence on its efficacy in GCA (186).

Among three studies conducted on small patient groups, only one showed some promise with the use of MTX where patients reported a reduced relapse rate and use of lower doses of steroids. The other two studies showed no significant effects of MTX (146,200,201). Another large retrospective, single-institution, case-control study in North America, evaluated the real-world efficacy of MTX in GCA patients. Results showed that patients treated with MTX along with glucocorticoids had a nearly 2-fold reduction in relapse than in the group of

patients who were treated with glucocorticoids alone (202). A meta-analysis of 3 randomised control trials showed modest efficacy when given 7.5 mg to 15 mg dose of MTX as an adjunct therapy once a week but found a 842 mg reduction of cumulative GC in 48 weeks follow up (203). EULAR recommends that MTX should be considered in selected patients with refractory or relapsing GCA (49)Similarly, BSR also recommends considering MTX in the treatment of the patients having refractory disease or risk of high GC toxicity (164).

### *2.3.2. Azathioprine*

Azathioprine, as a steroid-sparing agent, is frequently used in the treatment of vasculitides and connective tissue diseases. Evidence supporting the use of azathioprine in GCA is limited. One non-randomised double-blind study (31 patients) using azathioprine 150 mg in patients with GCA, showed significant reduction in average steroid use, over 52 weeks (204). Another more robust trial using azathioprine on patients with GCA showed a steroid-sparring effect during the glucocorticoid taper. However, this became statistically significant only one year after treatment, demonstrating the slow mode of action of azathioprine (190). In view of small sample sizes, high dropouts, there is no clear evidence for its efficacy in GCA.

### *2.3.3. Leflunomide*

Leflunomide is commonly prescribed as an alternative to MTX in patients with rheumatoid and psoriatic arthritis, where its use is licensed and supported by international guidelines (205,206). However, in the last years, leflunomide has been also proposed as a potential steroid-sparing agent in GCA patients. Even if no controlled trials have been published to date, some interesting data are available.

After the publication of two small case series (207,208), the first open-label trial was conducted. In this study, 30 GCA patients started on leflunomide 10 mg daily at week 12 were prospectively compared to 46 patients treated only with GC. After a 48-week follow-up, patients who relapsed were significantly lower in the leflunomide-treated group than in the comparator group (13.3% *versus* 39.1%, p = 0.02); in addition, leflunomide allowed a significant reduction of the GC cumulative dose (209). In another retrospective study, 27 leflunomide-treated patients were compared to 24 patients receiving MTX; interestingly, disease remission was achieved earlier in those from the former group with high baseline disease activity (210). Lastly, our group recently showed that leflunomide can be an effective aid also in GCA patients with extra-cranial large-vessel involvement, a difficult-to-treat disease subset with high relapse rates (148). All these experiences should support a more extensive use of leflunomide in GCA and, above all, should prompt towards future developments of highly needed randomized-controlled trials.

### *2.3.4. Mycophenolate mofetil*

There is only one study which showed the potential benefit of the use of mycophenolate mofetil in elderly patients with giant cell arteritis (211). Currently, there is no data or sufficient evidence available for the use of mycophenolate mofetil in patients with GCA. Therefore, the use of mycophenolate mofetil is not recommended in treating of GCA (49,164).

### *2.3.5. Cyclophosphamide*

In a retrospective study of refractory GCA in a group of 35 patients, 90.3% of patients responded to the treatment with cyclophosphamide with reduction of disease activity and sustained decrease in prednisolone dose (212). In a case series and systematic review of GCA patients treated with cyclophosphamide, 84% were responsive, where it was used along with

other immunosuppressive agents such as MTX as a part of maintenance treatment (213). Use of cyclophosphamide is limited in GCA by to its side effects, especially in older groups of patients and due to lack of prospective or RCT data.

### *2.3.6. Hydroxychloroquine*

Hydroxychloroquine is a well-tolerated immunomodulatory drug widely used in rheumatoid arthritis and connective tissue diseases. However, a double-blind, randomised controlled trial of hydroxychloroquine failed to show any benefit as a steroid-sparing agent in GCA (214).

### *2.3.7. Cyclosporin A*

Two Scandinavian studies tried cyclosporin A as a steroid-sparing agent in GCA. Neither of them showed any steroid-sparing potency due to its poor tolerability and adverse events (215,216).

## 2.4. Biologic therapy

The treatment of systemic rheumatic disease has been revolutionised by biologic agents, as they have provided an effective treatment option to patients with previously intractable conditions. Most importantly, biologics have been able to reduce disability and improve quality of life for such patients.

See **Table 3** for a summary of the main clinical trials with biologic agents for the treatment of GCA patients.

### *2.4.1. Tumour Necrosis Factor-alpha inhibitors*

Tumour Necrosis Factor (TNF) is a proinflammatory cytokine that has been successfully targeted in inflammatory arthritis and may also have a place in the pathogenesis of GCA. The exact role of TNF in the pathogenesis of GCA is still not known. Temporal artery biopsy specimens confirm TNF is abundantly present in patients with GCA (217). Raised TNF levels

in both serum and tissue are associated with active GCA (218). There is also a need to study the role of anti-TNF in the treatment of GCA. Anti-TNF therapy has been considered in patients with refractory cases of GCA or having corticosteroid dependence. Currently, there are five types of anti-TNF approved for use in rheumatoid diseases. These include three anti-TNF-alpha immunoglobulin G1 (IgG1) antibodies (infliximab, golimumab and adalimumab), an Fc-fusion protein (etanercept), and one pegylated antibody fragment (certolizumab pegol). However, TNF blockade is not recommended by national and international guidelines in GCA (164,219) because of absence of efficacy as discussed below. Additionally, there have been new GCA cases diagnosed in patients already treated with adalimumab (220) and etanercept (221) for RA.

*Infliximab*

Infliximab is a chimeric murine-human monoclonal antibody that binds to TNF alpha blocking its interaction with the TNF alpha receptor. Infliximab is administered intravenously with a dose of 5mg/kg at 0, 2 and 6 weeks, followed by every eight weeks. To minimise the formation of human anti-chimeric antibodies and to increase the efficacy, infliximab is usually given in combination with MTX weekly (222). A small case series reported that infliximab showed excellent results in patients who had not tolerated tapering of prednisolone doses lower than 7.5-12.5 mg/day (223). However, international multi-centre RCTs have not shown efficacy of infliximab in the maintenance of glucocorticoid induced remission inpatients with newly diagnosed GCA (224,225).

*Adalimumab*

Adalimumab is a humanised IgG1 monoclonal antibody that binds TNF-alpha, and 40 mg dose once in every two weeks administered subcutaneously. A double-blind, randomised control trial evaluated the addition of 10 weeks of adalimumab versus placebo with GC taper to

standard treatment in 70 patients with newly diagnosed GCA. This trial failed to show any benefit either in preventing relapse or showing GC sparing effect at 26 and 52 weeks (219).

*Etanercept*

Etanercept is a soluble TNF-receptor fusion protein and binds TNF alpha. 25-50 mg weekly dose is administered subcutaneously. A double-blind placebo-controlled trial showed some promising results in the etanercept group by achieving GC free remission at 12 months. However, this did not reach statistical significance (226).

*Certolizumab pegol and golimumab*

They have not been studied in GCA, since their efficacy is expected to be limited like other TNF alpha inhibitors.

### *2.4.2. Interleukin-6 inhibitors*

Interleukin-6 is a proinflammatory cytokine and plays a vital role in the pathophysiology of GCA. Patients with active GCA generally exhibit elevated serum IL-6 levels with increased expression of IL-6 mRNA by inflamed temporal arteries. It has been shown that IL-6 concentration is significantly elevated in the serum of untreated GCA patients (227,228) and found in GCA histology specimens (229). Additional research has revealed that IL-6 also plays a potential role as effector cytokine in the TH17 pathway.

*Tocilizumab*

Tocilizumab, a monoclonal antibody acting against the interleukin-6 receptor, is widely used in the treatment of rheumatoid arthritis. This has emerged as a very promising and attractive therapeutic agent in GCA treatment as well (230,231). It can be administered as intravenous 8mg/kg monthly or 162 mg subcutaneous weekly. Randomised controlled studies have shown

very encouraging data in reducing cumulative steroid dose and in relapse rate. In a phase II study, as high as 85% of patients were able to achieve relapse-free survival after 52 weeks of treatment with tocilizumab as opposed to 20% in the placebo group. Crucially, patients with a tocilizumab regimen were able to reduce their cumulative glucocorticoid dose by 52 weeks (43 mg/kg) as compared to the group without tocilizumab (110mg/kg) (232). In the GiACTA phase III study in 251 patients with either new or relapsing GCA, patients on tocilizumab treatment plus a 6-month prednisone taper showed sustained remission rates at 52 weeks (53-56%), compared to 14-17% in patients treated with 6 months or 12 months GC monotherapy. The cumulative GC dose was reduced by 50% in the tocilizumab arms (233). Recently, part two of the GiACTA trial has been published (234). Here, authors observed two-year remission maintenance in 42% of the 59 patients who were tocilizumab- and GC-free after one year of treatment. In addition, they reported an excellent ability of tocilizumab to restore remission in those who experienced a relapse (234).

Since the first case series in 2011 (235), there have been many confirmatory reports of long-term efficacy and safety of tocilizumab in the real-word (236). In a retrospective comparative study conducted in 40 different centres in Spain, it emerged that GCA patients started on tocilizumab were older, with a longer disease duration and more frequently already treated with a conventional DMARD than those recruited in the GiACTA study (237). Nevertheless, the number of patients achieving sustained remission was comparable, thus confirming the efficacy of this biological agent outside clinical trials. Conversely, a tendency to a higher incidence of serious infections was noticed, a result that could be read as a consequence of the older age of included patients, but also probably related to a less tighten clinical monitoring. In a more recent work from the same Spanish group, Authors investigated the advantage provided by the addition of a conventional DMARD (mainly, MTX) to tocilizumab therapy (238). Interestingly, even if patients who received the combination therapy had a more aggressive disease (i.e.,

higher prevalence of large vessel involvement, higher levels of acute-phase reactants, longer disease course), they had a higher rate of prolonged remission (238). In another real-world study evaluating 60 GCA patients, Unizony *et al.* confirmed the ability of tocilizumab to substantially reduce disease flares also in selected subpopulations, such as patients with visual manifestations and patients with PMR symptoms at disease onset (239). The number of patients who experienced a relapse after tocilizumab discontinuation was in line with the results of the extension phase of the GiACTA trial in a French multicentre retrospective study (62%) (240). Moreover, in this work, Authors identified four factors associated with relapse: introduction of tocilizumab after more than 6 months after diagnosis, a relapse rate >0.8/year before tocilizumab introduction, incapacity to reduce GC below 5 mg daily, and absence of ischaemic features at disease onset (240). In a recently published work including only GCA patients with extra-cranial large-vessel involvement, Schönau et *al.* did not find any significant differences between patients treated with GC monotherapy and patients treated either with tocilizumab or MTX at baseline regarding reduction of vascular inflammation as determined by the PETVAS score. However, in those treated with tocilizumab, imaging response was faster and GC cumulative dose was significantly lower (241).

To date, tocilizumab is the only biologic treatment approved for GCA, with limited availability in different countries due to local restrictions. In the UK, it is approved only in relapsing or refractory GCA to use a maximum of 12 months (242).

The positive results achieved with the use of first-in-class IL-6 receptor antagonist tocilizumab (233), opened the path to clinical trials investigating other biologic agents with similar mechanisms of action.

*Sirukumab*

Sirukumab is a selective, high-affinity human IL-6 monoclonal antibody initially developed for the treatment of rheumatoid arthritis (243,244). Its efficacy and safety in GCA have been

investigated in a randomised, double-blind, placebo-controlled, phase III trial (NCT02531633), whose results have been recently published (245). In this study, GCA patients were randomised to 5 different groups of treatment where they could receive placebo or sirukumab (100 mg every-2-week or 50 mg every-4-week) along with prednisone tapering according to three different regimens. The primary endpoint was the proportion of patients reaching sustained remission at week 52. However, due to the Sponsor's decision to terminate the study early, only 28 of the 161 randomised patients completed week 52, limiting the statistical interpretation of the results (246).

Nevertheless, it's worth noticing that all the 6 patients who achieved the primary endpoint were receiving sirukumab and that disease flares were observed in a proportion numerically higher in the placebo groups. Additionally, among the three sirukumab arms, the highest proportion of disease recrudescence between weeks 2-12 was experienced by patients tapering prednisone over a 3-month regimen, suggesting the unsuitableness of this extremely short prednisone taper in clinical practice. GCA-related visual disturbances were observed in two patients, both receiving sirukumab (246).

*Sarilumab*

Another IL-6 receptor antagonist, sarilumab (247), is currently under evaluation utilising a randomised, double-blind, placebo-controlled, phase III trial (NCT03600805). Results are not available yet. The study was designed to investigate both the 150 mg and the 200 mg doses of sarilumab and the total number of patients to enrol was originally estimated to be 360. Unfortunately, the study had to be suspended early due to the Covid-19 pandemic.

### *2.4.3. T-cells activation modulator*

*Abatacept*

In GCA pathogenesis, antigen-driven triggering of macrophages and T lymphocytes by vascular-resident dendritic cells is deemed to be a key-step in arterial wall inflammation (248–250). This observation leads to the hypothesis that a strategy aimed at blocking this exuberant T lymphocytes activation might have therapeutic activity in GCA. As with IL-6 inhibition, a biologic agent with this mechanism of action is already available, and widely employed for the treatment of rheumatoid arthritis. Abatacept is a fusion protein combining the Fc region of the immunoglobulin IgG1 with the extra-cellular domain of CTLA-4, a negative modulator of T cell co-stimulation (251–253). To date, only one study evaluating the efficacy and safety of abatacept in GCA has been published (254). The trial was designed with an initial open-label stage, followed by a double-blind 1:1 randomisation to abatacept or placebo of patients achieving remission at week 12. Abatacept was administered intravenously at a dose of 10 mg/kg on days 1, 15, and 29 and then monthly and all patients tapered prednisone according to a standard regimen within week 28. Three of the 49 enrolled patients did not achieve remission at weeks 12, and 24 had a relapse. Relapse was experienced by 12 patients receiving abatacept (2 in the open-label phase and 10 after randomisation) and by 14 patients receiving placebo. Notably, the 12-month relapse-free survival of patients who entered the double-blinded randomisation was significantly higher among those in the abatacept arm (48%, versus 31% for those in the placebo arm, p=0.049). Additionally, abatacept-treated patients-maintained remission for a significantly longer time (median, 9.9 *versus* 3.9 months, p=0.023). Among the 26 relapses observed, one was a cranial ischaemic complication in a patient on double-blind abatacept, and another one was new large-vessel stenosis in a patient on placebo. In most of the cases, relapses were mirrored by an elevation of acute-phase reactants, a helpful information missed in patients treated with biologic agents inhibiting the IL-6 pathway. No

significant differences in the rate of adverse events were observed between the two groups, a result that confirms the excellent profile of safety of abatacept (255).

Although this study achieved the primary endpoint, abatacept is still not included as a steroid-sparing agent in the recently published Guidelines for the management of GCA elaborated by the EULAR (49) and its use has not been officially approved by Regulatory Agencies either in Europe or in the United States. Additional studies including a greater number of patients are strongly warranted and, if the results of this preliminary trial are confirmed, the use of abatacept in refractory/relapsing GCA will be an addition to the therapeutic armamentarium.

### *2.4.4. IL-12/23 inhibitors*

*Ustekinumab*

Antigen presentation by dendritic cells in the vascular wall induces naïve T lymphocytes to differentiate into two different clusters, namely Th1 and Th17 (249,256). IL-1β, IL-6, IL-21, and IL-23 are the main inducers of the Th17 cluster, which is highly represented in early and untreated GCA and is rapidly suppressed by systemic glucocorticoids (63,257). On the other hand, IL-18 and IL-12 are mainly involved in the shift towards the Th1 cluster (258), which is more refractory to glucocorticoids and predominantly responsible for the chronic, vaso-destructive smouldering disease (257). Starting from these pre-clinical observations, the opportunity to interfere with both these clusters at the same time would certainly be an intriguing therapeutic strategy. Ustekinumab is a biologic agent which hypothetically could achieve this target since it binds to the common p40 subunit shared by both the IL-12 and IL-23 cytokines (259,260). The results of two prospective, single-arm, open-label trials investigating the use of ustekinumab in GCA are currently available (261,262).

The first one included 25 patients who had an initial response to high-dose glucocorticoids but were unable to taper glucocorticoids due to disease recurrence (median disease duration, 29

[IQR, 11.5-36.5] months) (263). Subcutaneous ustekinumab was initially given at a dose of 90 mg at week 0, week 4 and then every 12 weeks, but in six patients the interval of administration had to be reduced to every 8 weeks to achieve better control of constitutional symptoms and systemic inflammation. Clinical features at the last relapse before ustekinumab start were homogeneously distributed between cranial, constitutional, and polymyalgic symptoms and, after 52 weeks, no patients experienced a clinical relapse. In addition, median daily prednisone dose decreased from 15 (IQR, 5-20) mg to 5 (IQR, 2.5-5) mg ($p<0.001$) and 6 patients (24%) definitively stopped it. All the 8 patients with signs of large-vessel vasculitis on CT angiography at ustekinumab start with repeat imaging evaluation at follow-up (after a median of 8 [IQR, 6-14] months) had an improvement of arterial wall thickening (263).

The positive results of this preliminary study were not confirmed by a second pilot trial which evaluated both new-onset (n=5) and relapsing (n=8) disease, for a total of 13 GCA patients enrolled (264). In this study, after the first two doses, ustekinumab was administered every 8 weeks, and all the patients followed the same prednisone 6-month tapering regimen. Only 3 patients achieved a 52-week steroid-free remission, the primary outcome of the study. The other 10 patients experienced a clinical relapse (n=7) or had an elevation of inflammatory markers at week 52.

In both these studies, ustekinumab was well tolerated. Infectious events were exclusively mild and experienced only by a small fraction of patients, and no other relevant adverse events emerged (263,264).

The non-concordant results of these two preliminary trials, their non-randomised design, and the low number of patients included make ustekinumab currently non-indicated for the treatment of new-onset or relapsing GCA patients. However, since the rationale behind its use is plausible, data from more robust studies are necessary before labelling it as ineffective.

*Guselkumab*

Selective inhibition of IL-23 can be achieved through the use of another monoclonal antibody, guselkumab, currently approved for the treatment of plaque psoriasis (265). Even if no data on guselkumab in GCA are available to date, a randomised, double-blind, placebo-controlled, phase II proof-of-concept trial is currently recruiting patients (NCT04633447).

### *2.4.5. IL-17 inhibitors*

*Secukinumab*

The selective inhibition of IL-17A through the use of the monoclonal antibody secukinumab offers another fascinating therapeutic approach for GCA patients (266). IL-17 is one of the main effector cytokines released by Th17 lymphocytes after their differentiation, primarily responsible for neutrophils and macrophages recruitment and endothelial cells, vascular smooth muscle cells and fibroblasts proliferation (249,267). Hence, its effects encompass not only the reinforcement of the inflammatory process but also the remodelling of the vascular wall.

To date, available data on the use of secukinumab in GCA are limited to a single report describing the case of a woman with a diagnosis of cranial and large-vessel disease superimposed on a previous history of psoriatic arthritis (268). Once GCA remission was obtained with the addition of leflunomide and tocilizumab to the standard steroid therapy, she experienced a severe arthritis flare. The consequent replacement of leflunomide and tocilizumab with secukinumab monotherapy (300 mg weekly for 5 weeks and then every 4 weeks) led to arthritis remission and, notably, allowed to keep GCA steroid-free remission at 12-month follow-up (269).

The positive experience with a single patient must be only interpreted as a starting point for the design of controlled studies. A randomised, double-blind, placebo-controlled, phase II trial (NCT03765788) has recently completed patients' recruitment and, hopefully, first results will

be soon available. The results of this study will be crucial to understand if secukinumab represents a suitable therapy for GCA.

### *2.4.6. GM-CSF inhibitors*

*Mavrilimumab*

Another pioneering therapeutic approach for GCA patients is grounded in the use of mavrilimumab, a human monoclonal antibody that inhibits the receptor of the granulocyte-macrophage colony-stimulating factor receptor (GM-CSF), originally developed for the treatment of rheumatoid arthritis (270,271). GM-CSF is a pleiotropic cytokine, involved in the pathogenesis of GCA at various levels. First, it promotes the expansion and differentiation of myeloid cells in the context of inflammatory processes and facilitates their gathering into giant cells (272). Second, it stimulates dendritic cells to favour naïve CD4 maturation into Th1 and Th17 phenotypes (273). Finally, GM-CSF drives inflammation-induced angiogenesis by triggering the proliferation of vascular endothelial cells (273). Consistent with these observations is the fact that both GM-CSF and its receptor are highly expressed in temporal artery tissue samples obtained from GCA patients (274).

Mavrilimumab use in GCA has been recently investigated in a randomised, phase II trial. In this trial, 70 GCA patients were assigned in a 3:2 ratio to mavrilimumab 150 mg or placebo, administered subcutaneously every 2 weeks for 26 weeks, along with 26-week prednisone taper. Interestingly, at baseline randomization, patients were stratified according to disease type (new-onset *vs* relapsing/refractory disease). The study achieved both the primary and secondary efficacy endpoints according to preliminary reports (275). Specifically, there was a significant reduction in the time-to-first GCA flare in the mavrilimumab group, with a 62% lower risk of flare compared to placebo recipients. The patient receiving mavrilimumab also had a higher sustained remission rate at week 26 (83.2% *vs* 49.9%, p=0.0038). In addition, the

drug was well-tolerated, and no drug-related serious adverse events emerged. The phase II results form an excellent basis for a more definitive phase III trial in the future.

### *2.4.7. Janus-kinase (JAK)-inhibitors*

*Baricitinib, tofacitinib, upadacitinib*

Extra-cellular binding of the inflammatory cytokines to their receptors finally affects target gene expression and cellular responses. One of the main signalling pathways responsible for information transfer from the extracellular space to the nucleus is the Janus kinase-signal transducer of activators of transcription (JAK-STAT) complex, which is employed by various interleukins (IL-6, IL-2, IL-4, IL-7, IL-9, IL-10, IL-13, IL-15), stimulating factors (G-CSF, GM-CSF), and interferons (IFN-α, IFN-β, IFN-γ) (276,277). Once one of these cytokines binds to its cell-surface receptor, receptor-associated cytoplasmic JAKs come to proximity and activate each other through transphosphorylation. This process leads to the second phosphorylation of the receptors' tyrosine residues, activation of two STAT proteins which combine to form homo- and heterodimers, and finally transfer of these dimers to the cell nucleus to induce transcription of target genes (278).

Selective pharmacological inhibition of this pathway through the use of small molecules has been recently introduced in the clinical practice as a new effective therapy for autoimmune diseases, not only in the rheumatologic field (279). Additionally, preclinical evidence suggests a potential application of this strategy also in patients affected by GCA. In their experimental work, Zhang *et al.* evaluated the effects of the JAK 1-3 inhibitor tofacitinib in a murine model of large-vessel vasculitis developed through engraftment of immunodeficient mice with human arteries and then reconstitution with T cells and monocytes from GCA patients (280). In this model, tofacitinib reduced the number of tissue-resident memory T cells and suppressed the

production of the main effector inflammatory molecules. In addition, its use affected the vascular remodelling by impairing adventitial angiogenesis and intimal hyperplasia (281).

To date, the only experiences with the use of JAK inhibitors for the management of large-vessel vasculitis involved patients with Takayasu's arteritis treated with tofacitinib, with promising but still inconclusive results (282–286). Even if no reports on the clinical use of JAK inhibitors in GCA patients are available yet, two trials currently ongoing will provide robust data soon. Drugs under evaluation in these two trials are the JAK 1-2 inhibitor baricinitib (NCT03026504) and the selective JAK 1 inhibitor upadacitinib (NCT03725202).

## 3. Role of imaging in monitoring response to therapy

There is great interest in using imaging not only as a diagnosing tool, but also as an aid to monitor GCA activity. 'Halo sign' is a recognised sign in ultrasound assessment to appreciate the vessel wall inflammation. A recent study showed halo sign in temporal arteries was 82.5% sensitive in diagnosing GCA; however, this lowered to 60% when patients were on high dose GC (> 30 mg/day). This study also found that 42.9% of the patients had halo sign recurrence when the disease relapsed (287). Our group showed a marked improvement of halo sign after treatment with tocilizumab (82). Currently we are assessing the role of halo score in diagnosis and prognosis in GCA (288).

Although positron emission tomography (PET) is extremely useful in diagnosing large vessel GCA, its efficacy is limited after GC start. A study highlighted that its sensitivity is very high if performed within 3 days after high-dose GC start and then it progressively decreases, becoming inadequate after 10 days (289). A larger study reported a correlation between high

fluorodeoxyglucose (FDG) uptake and clinical relapses during follow-up (290). However, in two different studies, PET failed to predict the risk of relapse (55,291)

Data on computed tomography angiography (CTA) and magnetic resonance angiography (MRA) in follow up studies are lacking. A study with CTA found that after 12-month GC treatment 68% of patients had persistence of thickened vessel wall, whereas in 94% contrast enhancement resolved (292). In a small trial with tocilizumab, even if all patients reached complete clinical and laboratory remission at week 52, vessel wall signal on MRA was still present in 33% of treated patients (293).

Due to lack of evidence in the role of imaging in follow up studies, there is an unmet need for further prospective studies in this field.

## 4. Conclusion

Treatment of GCA has been a challenging field of research due to the critical nature of the disease and low availability of effective and safe treatment options. Although many drug combinations have been studied, the mainstay in treating GCA has been GC that can cause many steroid-related adverse effects. Conventional immunosuppressants exhibit a steroid-sparing effect in patients with GCA but have not been highly influential in remission. MTX has been currently used as steroid-sparing therapy in GCA although the RCTs failed to promise any significance. Azathioprine has shown some positive results but appears very slow acting. Leflunomide has some efficacy data in PMR and GCA but needs RCTs.

Current research has led to the use of biologics such as tocilizumab which is an IL-6 inhibitor and has shown promise in remission as well as reduction of steroid dependence in patients with GCA. Some newer biologics such as abatacept and mavrilumab and small molecules are showing promise of efficacy and may emerge in the treatment of GCA soon. There is an unmet

need for more research in this field to validate the efficacy of biologics actively, but they offer much-needed reduction in steroid side effects in the treatment of GCA.

## 5. Expert opinion

GC still constitute the cornerstone of GCA treatment in the acute setting, as they represent the only pharmacological approach that has been proven to extinguish the systemic inflammatory process, to resolve main clinical symptoms and, above all, to prevent irreversible ischaemic complications. For all these reasons, it is difficult to consider treating a GCA patient without including GC. However, a significant proportion of GCA patients tend to lose sensitivity upon GC tapering, leading to a chronic use with consequent high cumulative doses. As a consequence, these patients are exposed to a wide number of adverse events, such as osteoporosis, type II diabetes mellitus, arterial hypertension, hyperlipidaemia, whose negative impact is further worsened by the old age of the population affected. The best strategy to minimise the devastating effects of a long-term GC therapy is represented by a reasonable use of steroid-sparing agents. According to the EULAR recommendations, these agents should be introduced since the beginning when there is evidence of increased risk of GC-related adverse effects or during the disease course in patients with relapsing or refractory disease (49).

We agree with these recommendations, but we firmly believe that an early steroid-sparing introduction strategy should be pursued also in patients with high-risk disease features at onset (294). Vascular imaging has a pivotal role in defining who these patients are. Through the use of vascular ultrasound, but also with other imaging techniques such as FDG-PET scan, it is possible to identify signs of extra-cranial arteries involvement, known to be risk factors for a more relapsing course of the disease (48). In addition, quantitative approaches, such as the

Southend ultrasound HAS GCA score developed by our group (295), allows to recognize patients with a greater disease burden and at higher risk for ischaemic complications (34); we are currently prospectively evaluating if a higher HAS-GCA score is also associated with a more tendency to relapse, thereby helping with disease stratification (288).

The choice of the best steroid-sparing agent to be introduced is another crucial matter of discussion. To date, the strongest data available advice against the use of anti-TNF agents and support the use of the IL-6 receptor antagonist tocilizumab; conflicting but at least modestly positive is the evidence favouring MTX with reasonable reduction of cumulative GC. The main limits related to tocilizumab are three: its high costs, the invariable suppression of the acute phase markers which limits their use in disease monitoring, and the high relapse rate observed after its discontinuation. For these reasons, a large number of other compounds have been preliminary evaluated or are currently under investigation as alternative steroid-sparing agents for GCA patients. Among these, it's worth citing the T-cells activation modulator abatacept and the GM-CSF inhibitor mavrilimumab, which showed significant relapse-reduction activity in small prospective studies. Additionally, although no results are available yet, their innovative mechanism of action makes the JAK-inhibitors particularly appealing. Last, clinicians and researchers should consider leflunomide, a conventional steroid-sparing agent which showed promising results in non-controlled studies and which, in our opinion, deserves an appropriate randomised controlled evaluation.

| Mechanism of action | Agent | Study details | Study population | Sample size (n) | Study duration | Primary end-point | Main result | Reference |
|---|---|---|---|---|---|---|---|---|
| IL-6 receptor inhibition | Tocilizumab | Randomized, multi-centre, double-blinded | New onset or refractory active GCA | 251 | 52 weeks | Rate of sustained glucocorticoid-free remission at week 52 | Sustained remission 53-56% (TCZ) vs 14-18% (PBO), p< 0.0001 | [14] |
| | Sarilumab | Randomized, multi-centre, double-blinded | New onset or refractory active GCA | 360 | 52 weeks | Rate of sustained remission at week 52 | *Not yet available* | NCT03600805 |
| IL-6 inhibition | Sirukumab | Randomized, multi-centre, double-blinded | Active GCA | 161 | 52 weeks | Rate of sustained remission at week 52 | *Early termination (sponsor decision)* | [83] |
| CTLA-4 Ig | Abatacept | Randomized, multi-centre, double-blinded | New onset or relapsing GCA | 49 | 52 weeks | Relapse-free survival rate | Relapse-free survival: 48% (ABA) *vs* 31% (PBO) p=0.049 | [91] |
| IL-12/23 inhibition | Ustekinumab | Open-label, single-centre | Refractory GCA | 25 | 52 weeks | Glucocorticoid dose at baseline and at 52 weeks | Median daily prednisolone dose from 20 to 5 mg, p<0.001 | [97] |
| | Ustekinumab | Open-label, single-centre | New onset or relapsing GCA | 13 | 52 weeks | Prednisone-free clinical & laboratory remission | 10 patients (77%) failed to achieve remission | [98] |
| IL-23 inhibition | Guselkumab | Randomized, multi-centre, double-blinded | New onset or relapsing GCA | 60 | 52 weeks | GC-free remission at week 28 | *Not yet available* | NCT04633447 |
| IL-17 inhibition | Secukinumab | Randomized, multi-centre, double-blinded | New onset or relapsing GCA | 52 | 52 weeks | Rate of sustained remission at week 28 | *Not yet available* | NCT03765788 |
| JAK-inhibition | Baricitinib | Open-label, single-centre | Relapsing GCA | 15 | 52 weeks | Rate of patients experiencing adverse events at week 52 | *Not yet available* | NCT03026504 |
| | Upadacitinib | Randomized, multi-centre, double-blinded | New onset or relapsing GCA | 420 | 52 weeks | Rate of sustained remission at week 52 | *Not yet available* | NCT03725202 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| GM-CSF receptor inhibition | Mavrilimumab | Randomized, multi-centre, double-blinded | New onset or relapsing/ refractory GCA | 70 | 26 weeks | Time to flare by week 26 | Preliminary report: 62% lower risk of flare in the treatment group | NCT03827018 |

**Table 3. Main clinical trials of biologic agents for the treatment of giant cell arteritis**

ABA, abatacept; CTLA, cytotoxic T-lymphocyte antigen; GCA, giant cell arteritis; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; JAK, janus kinase; PBO, placebo; TCZ, tocilizumab

---------END OF THE ARTICLE------

### 2.1.6 Prognosis and Economic Implications

There are significant economic drivers for disease stratification of GPSD, to reduce steroid toxicity, and relapse rates and to detect early vascular involvement so that expensive consequences of vascular damage are prevented. Fast-track strategies have demonstrated the cost-effectiveness of early diagnosis, prevention of ischaemic disease in GCA, and reduction of hospitalisation of PMR (38,296).

Direct and indirect costs include healthcare utilisation costs, which rapidly increase for refractory/relapsing disease. Here, disease stratification may better direct the frequency of screening for complications, potentially reducing the disease duration by a better choice of therapies and reducing follow-up healthcare utilisation. With PMR, disease stratification will reduce costs by the wiser choice of who to screen, identify early incomplete disease response and unfavourable disease courses and facilitate early specialist referral.

As GPSD affects older people, work disability generally is not as great a factor in the economic equation, but there is a negative financial impact on caregivers. In a study of caregivers of patients with systemic vasculitis, 28% reported a loss of income due to caregiving commitments, including assistance with hospital visits (297). There are major costs attached to avoidable complications of uncontrolled disease, such as vision loss, stroke, aortic aneurysms/dissections, and glucocorticoid-related complications. These costs are expected to rise with ageing populations (298).

Sight loss results in high costs for personal, healthcare, and social care. The introduction of ‘Fast Track Pathways’ aiding prompt diagnosis and treatment has reduced its incidence, but unfortunately, this is not a universal practice (38,162,296). De Smit and colleagues estimate that GCA-related visual impairment costs will exceed $76 billion by 2050 (298). In addition, glucocorticoids increase the risk of cataracts, ocular hypertension, and open-angle glaucoma (299).

Patients in the LV-GCA cohort are at increased risk of aortic aneurysm and dissection (300). In addition, inflammatory aneurysm surgery carries a high rate of complications, operative mortality, and costs, with an increased risk of limb stenosis, persistent inflammation, peri-vascular fibrosis, and further interventions (301). Hence, preventing aneurysms with early diagnosis and disease stratification is clinically and economically advantageous.

Patients with the refractory disease require higher and prolonged courses of glucocorticoids. For every 1,000 mg cumulative increase in glucocorticoid dose, the adverse event hazard ratio increases by 3% (302). In a large UK retrospective study, the average cumulative prednisone use over the first two years was 8,600 mg; however, 33.4% received over 10,000 mg and 3.3% more than 25,000 mg (303). A review by Manson et al. estimates the annual excess cost of treating glucocorticoid-related effects at least an extra £84.2 million per year to the NHS (304).

Up to a 4-fold increased frequency of hyperglycaemia and diabetes has been observed with glucocorticoid use (299), rising by 5% for every cumulative 1,000 mg increase (302) GiACTA baseline data showed that relapsing patients were heavier than those with newly diagnosed disease by 5.2 kg (305). The higher weight, diabetes and hypertension in relapsing patients in GiACTA trial are striking because of their overall adverse health effects, especially cardiovascular and cerebrovascular implications (306).

There is a dose dependent increased risk of osteoporotic fracture with long-term glucocorticoids. The relative risk of hip fracture is 2.21 higher in patients on prednisolone doses of >7.5 mg per day and rises to 3.13 for doses above 30 mg (307). The average cost of care for a hip fracture is estimated at £10,761 (308).

### 2.1.7 GCA fast track clinic

The feared complication of delayed treatment of GCA is permanent vision loss. On the other hand, overdiagnosing the condition may pave the way to unnecessary exposure to GCs, which may cause GC-related adverse events such as hyperglycemia, hypertension, osteoporosis and bone fractures. Therefore, It is vital to see an expert in the field for an early diagnosis or exclude the mimics. Different strategies for early diagnosis of GCA have been used in the last decade to reduce the devastating complication of permanent blindness. GCA fast-track clinics (FTC) around the globe are becoming a successful way to deal with this issue. The relative risk of permanent blindness in GCA patients diagnosed through FTC is 88% lower, and it also reduced the mean hospital stay by 3 days(309)Althoug traditionally, TAB is considered a gold standard method to diagnose GCA, due to the delay in getting the biopsy, a TAB does not detect extracranial large vessel vasculitis; its use is valuable only in selected cases. Doppler US has been used as a diagnostic tool in temporal arteries and large extracranial vessels (310). US is readily available at the bedside and is recommended as a first-line imaging modality in all suspected GCA. Incorporating US in the FTC has shown significant reduction in permanent vision loss in two retrospective studies (311)(309).

The Southend team had developed a GCA probability score (GCAPS) to risk stratify the GCA suspected patients (312). It has a scoring system based on the clinical history, examination and laboratory values. An arbitrary cut-off value of 9.5 and above determines the high risk of having GCA. This score is integrated with the FTC (Figure 2).

The same group has also developed a probability-based diagnostic algorithm for suspected GCA patients applying the GCAPS. This risk stratifies the patients into Low, Intermediate and High-risk groups (313). This algorithm is now externally validated in many centres and

successfully integrated into the FTC (314,315). The development of this algorithm is discussed in detail later in this chapter (Section 2.2.2).

**Figure 2: Southend giant cell arteritis (GCA) probability score (adapted from Laskou et al 2019).**

**Table I.** GCA probability score [GCAPS] proforma.

| Weightage | -3 | 0 | +1 | +2 | +3 |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age (years) | | ≤49 | 50-60 | 61-65 | ≥66 |
| Sex | | | M | F | |
| Duration | | | | | |
| Onset of symptoms | | >24 weeks | 12-24 weeks | 6-12 weeks | <6 weeks |
| Laboratory | | | | | |
| CRP | | 0-5 mg/L | 6-10 mg/L | 11-25 mg/L | ≥25 mg/L |
| Symptoms | | | | | |
| Headache | | N | Y | | |
| Polymyalgic | | N | | Y | |
| Constitutional | | N | Single | | Combination |
| Ischaemic | | N | | | Y |
| Signs | | | | | |
| Visual (AION, CRAO, Field loss, RAPD) | | N | | | Y |
| TA abnormality | | N | Tenderness | Thickening | Pulse loss |
| Extra-cranial artery abnormality | | N | Thickening | Bruit | Pulse loss |
| Cranial nerve paisy | | N | | | Y |
| Alternative | | | | | |
| Infection | Y | | | | |
| Cancer | Y | | | | |
| Systemic Rheumatic diseases | Y | | | | |
| Head and neck pathology | Y | | | | |
| Other | Y | | | | |
| Total score | | | | | |

## 2.2 GCA diagnosis

GCA presentation and clinical manifestation are protean. There are several arguments in declaring which method is more suitable for diagnosing GCA. All methods have their own merits and demerits. The conclusion to all the studies and statements is that there is no independent and specific gold standard diagnostic tool for GCA. Diagnosis of GCA depends on several factors, such as the clinician's assessment, laboratory findings, TAB results and medical imaging.

### *2.2.1 Clinical diagnosis and Reference standard*

1. Clinical history and Physical Examination:

   Physical examination is the scalpel of a physician. Scalp tenderness, palpation of the temporal arteries, appreciation of the TA thickness or pulsation, visual field assessement, listening to any bruits in subclavian and axillary arteries, check for any differences in radial artery pulsation are the common physical exam findings would lead to a clinical diagnosis of GCA (316). ACR 1990 criteria were used as a clinical reference Standard for the last three decades (Table 4). According to the criteria, at least three out of five criteria must be present to classify as GCA. Recently ACR and EULAR updated the criteria (Table 1) (27).

**Table 4.**

| | |
|---|---|
| Age of the patient | Developing the disease signs at the age of 50 or more |
| Headache | Recent onset of the localised headache |
| Abnormal temporal artery | Reduced pulsation in the temporal artery or tenderness of the temporal artery when it is palpated |
| Increased erythrocyte sedimentation rate | ESR more than 50mm/h |
| Abnormal temporal artery biopsy | Micrographs of the biopsy specimens showing the signs of the infiltration of the inflammation site predominantly with the mononuclear cell and giant cells as well |

2. Laboratory Tests:

   Traditionally ESR was included in the 1990 ACR classification criteria. Raised ESR suggests an inflammatory process. ACR/EULAR 2022 criteria now include CRP and/or ESR as valid inflammatory markers (27). Low haemoglobin level, raised Liver enzymes and low albumin level in the blood also suggests some disease activity.

3. Temporal artery biopsy:

   TAB is a sensitive test to diagnose GCA. However, it has low specificity. This is to assess the histology of the artery for giant cell infiltration (317)

   A recent publication showed TAB directly correlates with the novel US halo score (318). TAB is discussed in detail later in this section 2.2.3.

4. Diagnostic Imaging:

   Colour Doppler US, MRA, PET-CT and CTA are considered to be imaging modalities used to help in diagnosing (319). Role of imaging will be discussed in detail later in this section 2.2.4.

### *2.2.2 Southend pre-test probability score and diagnostic algorithm*

**Published article:**

The following material in this chapter was published in October 2020 during the PhD. This published article explained the development of the probability score algorithm in suspected GCA. This algorithm helps to stratify the patients into Low (<9), Intermediate (9-12) and High (>12) risk groups according to the GCAPS. This has been externally validated in many centres and used in their routine practice in GCA FTC. Prospective results from HAS GCA study was presented at the ACR annual conference oral plenary session in November 2022 at Philadelphia. This outcome is discussed in the Results Chapter in this thesis. In the following material, the content is unchanged. The references, table and figure numbers in this article below are amended from the original publication to reflect the continuity of the PhD thesis references, Tables and figures.


## A probability-based algorithm using ultrasound and additional tests for suspected GCA in a fast-track clinic

**Authors:**

Alwin Sebastian[1]
Alessandro Tomelleri[1,2]
Abdul Kayani[1]
Diana Prieto-Pena[1,3]
Chavini Ranasinghe[1]
Bhaskar Dasgupta[1]

(1) Rheumatology Department, Mid and South Essex University Hospital Groups, Southend University Hospital, Westcliff-On-Sea, UK
(2) Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Milan, Italy
(3) Rheumatology Department, Marques de Valdecilla University Hospital, Santander, Spain

**Correspondence to:**
Professor Bhaskar Dasgupta, Mid and South Essex University Hospitals NHS Foundation Trust, Southend University Hospital
Rheumatology Department, Prittlewell Chase, Westcliff-On-Sea, Essex, SS0 0RY, UK

Email: bhaskar.dasgupta@southend.nhs.uk

**Word count:** 3012

## ABSTRACT

### Objectives

Clinical presentations of giant cell arteritis (GCA) are protean, and it is vital to make a secure diagnosis and exclude mimics for urgent referrals with suspected GCA. The main objective was to develop a joined-up, end to end, fast track confirmatory/exclusionary, algorithmic process based on a probability score triage to drive subsequent investigations with ultrasound and any appropriate additional tests as required.

### Methods

The algorithm was initiated with stratifying patients to Low (LRC), Intermediate (IRC) and High-risk categories (HRC). Retrospective data was extracted from case records. The Southend Pre-test probability score (PTPS) overall showed a median score of 9 and a 75$^{th}$ percentile score of 12. We, therefore, classified LRC as PTPS <9, IC 9-12 and HRC >12. GCA diagnosis was made by a combination of clinical, ultrasound findings and C-reactive protein >5 mg/L. The algorithm was assessed in all referrals seen in 2018-2019 to test the diagnostic performance of ultrasound overall and in individual categories.

**Results**

Of 354 referrals, 89 had GCA with cases categorised as LRC (151), IRC (137) and HRC (66). 250 had ultrasound whereas 104 did not (score <7, and/or high probability of alternative diagnoses). In HRC, ultrasound showed sensitivity 94%, specificity 85%, accuracy 92%, GCA prevalence 80%. In LRC, ultrasound showed sensitivity undefined (0/0), specificity 98%, accuracy 98%, GCA prevalence 0%. In IC, ultrasound showed sensitivity 100%, specificity 97%, accuracy 98% and GCA prevalence 26%. In the total population, ultrasound showed sensitivity 97%, specificity 97% and accuracy 97%. Prevalence of GCA overall was 25%

**Conclusions**

The Southend PTPS successfully stratifies Fast track clinic referrals and excludes mimics. The algorithm interprets ultrasound in context, clarifies a diagnostic approach, and identifies uncertainty, need for re-evaluation and alternative tests. Test performance of ultrasound is significantly enhanced with PTPS.

**Keywords:** Giant cell arteritis; Pre-test probability score; Diagnostic algorithm; Fast track clinic; Ultrasound

**Key Messages**

1. *What is already known about the study?*
    - Vascular ultrasound is recommended as a first-line investigation in GCA and pre-test probability score (PTPS) is useful in stratifying the GCA referral patients into different categories.

*2. What does the study add?*
    - The Southend PTPS successfully stratifies Fast Track Clinic GCA referral patients into Low, Intermediate and High probability categories.
    - The diagnostic algorithm includes ultrasound and additional tests, which help in the diagnostic approach. PTPS enhances test performance of US.
    - Diagnostic uncertainty of GCA is identified as well as identifying which cases need further clinical re-evaluation and helps choose additional tests.

3. *How might this impact on clinical practice or future developments?*
    - This new diagnostic algorithm approach will allow having a faster and reliable triage and assessment of GCA referral patients (remote versus face to face review) and ongoing multicentre HAS GCA study will prospectively validate this algorithm.

**INTRODUCTION**

Giant cell arteritis (GCA) is a critically ischemic organ-threatening disease(320)(321), particularly at the onset. Hence, it is vital to make a secure diagnosis urgently, not only to confirm GCA but also to exclude GCA mimics(322)(323). Several mimics, such as infection, cancer, head and neck pathology and systemic rheumatological diseases, are equally serious

conditions with similar challenges for early diagnosis and treatment(324). In other less serious, chronic conditions such as non-specific headaches, migraine, fibromyalgia, neuralgia and spondylosis, it is important to avoid inappropriate empirical glucocorticoids (GC) and minimise GC side effects while offering symptom alleviation, appropriate advice and therapy(1)(325)((326). Unfortunately, clinical presentations of GCA are protean(327), and they are often characterised by a mix of constitutional, cranial, ischemic and polymyalgic symptoms combined with raised inflammatory markers, a clinical scenario that can be difficult to distinguish from symptoms and presenting features of other conditions(328). In particular, headache is a common but often misleading symptom experienced in GCA(329). Recent onset of headache, along with the presence of scalp tenderness and/or jaw claudication, may increase the likelihood of GCA(330). A non-specific response to empirical GC may compound this diagnostic conundrum, resulting in many patients with steroid-responsive headaches being mis-labelled as GCA(331). American College of Rheumatology (ACR) 1990 GCA classification criteria(332) are often mistakenly used to diagnose GCA, but in clinical practice, they have low sensitivity and poor positive predictive value (PPV)(333)(334).

Fast track GCA clinics (FTC) are gaining popularity to provide rapid specialist clinical assessment along with temporal and/or axillary ultrasound (US)(323)(309). In GCA, they have been shown to reduce permanent sight loss(323)(309). EULAR recommendations support US as the first-choice diagnostic test, provided there are adequate expertise and equipment(4). Also, EULAR recommends using US or other cross-sectional imaging (e.g.PET-CT) to confirm the diagnosis of large vessel vasculitis in suspected GCA(335) A logistical difficulty for FTC is the misconception of GCA as a ‘headache disease’, leading to the challenge of reducing non-specific headache referrals and enriching referrals of high-risk cases(323). We have previously reported a pre-test probability score (PTPS) that shows promise to stratify patients into low (LRC), intermediate (IRC) and high-risk (HRC) categories when first

seen(312). Herein, we analyse our experience over 2 years (2018-2019) of pre-test probability triage (with a primary US test and additional tests [AT] to follow), with the objective of describing a probability-based secure diagnostic algorithm that works in clinical practice.

**METHODS.**

The main objective was to develop a joined-up, end-to-end, fast-track confirmatory/exclusionary, algorithmic process based on a probability score triage (PTPS) to drive subsequent investigations with ultrasound and any appropriate additional tests as required.

Data records of all the patients referred to Southend Hospital FTC between 1st January 2018 and 31st December 2019 were retrospectively reviewed. For all the patients, the main clinical and laboratory features at referral were evaluated, and a PTPS score was consequently generated (**Figure 2**). PTPS in FTC was categorised into Low (LRC), Intermediate (IRC) and High (HRC) risk categories based on the three quartiles (Q1, Q2, Q3). After that, vascular US results, if performed, were reviewed (a vast majority of US were done within 1-2 working days, but glucocorticoid treatment up to 1 week prior to ultrasound was allowed for this study). The application of the PTPS and the US results led us to categorise patients into 4 different categories ('GCA unlikely', 'GCA uncertain', 'Treat as GCA with AT', 'Treat as GCA') which formed part of the diagnostic algorithm.

Final GCA diagnosis was confirmed after 6 months follow-up and was made by fulfilling clinical criteria similar to GiACTA criteria (168) (*see below*). All GCA patients underwent at least one imaging evaluation – US and/or PET-CT – or a temporal artery biopsy (TAB) to confirm clinical suspect. Majority of the patients were seen in the FTC on the same day as the referral or the next working day. Most of them were commenced on 40 – 60 mg oral

prednisolone by their general practitioners at the time of the referral. The non-GCA diagnoses were all confirmed at 6 months.

***Clinical Criteria***

- Age ≥50 years
- Erythrocyte sedimentation rate (ESR) >30 mm/h *OR* C-reactive protein (CRP) >5 mg/L[**]
- Unequivocal cranial symptoms of GCA *OR* symptoms of polymyalgia rheumatica (PMR)[*]
- Abnormal temporal artery (US or biopsy) or evidence of large-vessel vasculitis by ultrasound or cross-sectional imaging (e.g. PET-CT, CTA)

*(Cranial symptoms defined as new, localised head pain, generalised scalp tenderness, tender temporal artery, ischemic optic neuropathy, jaw claudication or tongue claudication. PMR symptoms defined as morning stiffness >1 hour with bilateral shoulder pain and/or bilateral hip pain or stiffness)

[**] CRP and ESR measurements before the treatment

***Imaging of temporal and axillary arteries***

US scans were performed or supervised by an experienced ultrasonographer (BD) with an Esaote MyLabTwice US machine. A linear probe (LA435) with grey-scale frequency of 18 MHz or 22 MHz and colour doppler frequency of 9 MHz was used. The pulse repetition frequency was 2–3 kHz (4). The common superficial temporal arteries (TA) and their parietal and frontal branches, and/or the axillary arteries (AA) were examined in the long and short axis. Halo was measured at the point of maximum thickness in the longitudinal plane. A halo sign was morphologically defined as a US finding of a dark hypoechoic, non-compressible area around the vessel lumen (336)(337)(338)(339). An abnormal vessel wall thickness was defined as >0.29 – 0.42 mm in TA segments and >1.0 mm in AA (340). The TA halo score was

determined, as recently described (341). In addition, a provisional AA halo score was determined.

***Data analysis***

The results were expressed as the means ± standard deviation or as percentages. Descriptive statistics for test performance, Categorical variables are presented as frequency and percentage (%). Quantitative variables were compared between groups using Mann–Whitney *U* test (eg-CRP levels). Categorical variables were compared between two groups using the Two-tailed Fisher's exact test and between three groups using the Kruskal-Wallis test. Intraobserver and interobserver agreement was assessed using Intraclass correlation coefficient. All calculations were performed using SPSS statistical software. A p-value < 0.05 was considered statistically significant. Sensitivity, specificity, positive and negative predictive values, likelihood ratios, prevalence and accuracy, were calculated.

**RESULTS**

***Demographics***

Between 1st January 2018 and 31st December 2019, 371 consecutive patients were evaluated in Southend GCA FTC. Seventeen patients were excluded due to incomplete data (tertiary referrals from other Hospitals). Of the remaining 354 patients with complete data available, 89 (25%) eventually received a diagnosis of GCA. Mean age of the patients at the time of referral was 71.6 ± 0.81 years, and 69% were females.

***Pre-test probability score and algorithm***

PTPS in FTC patients overall showed a median (Q2) score of 9 and a 75th percentile (Q3) score of 12. Based on this (and on previous PTPS reported cut-off of 9.5 (312)), LRC was classified as PTPS <9, IRC as PTPS 9-12, and HRC as PTPS >12 (**Figure 3**). After the application of the PTPS, patients were categorised as LRC (151, 43%), IRC (137, 39%) and HRC (66, 18%). In

our algorithm, PTPS along with US results allowed us to further categorise referred cases in to 4 different groups: 'GCA unlikely' (233), 'GCA uncertain' (24), 'treat as GCA with AT'(23) and 'treat as GCA'(74) (additional tests not necessary) (Figure 3).

The 'GCA unlikely' group (Figure S1) represented cases with negative US (or US not done) and for whom no other additional test was considered necessary. The 'treat as GCA' group (Figure S2) included patients in HRC (45) or IRC (29) who had an unequivocal positive US. We identified 2 groups with diagnostic uncertainty (i.e., the groups 'GCA uncertain' and 'treat as GCA with AT and/or clinical re-evaluation') (Figure S3, S4). The former group 'GCA uncertain' (24 cases) came from US-negative IRC (11), US positive (1) IRC but also from US-positive (3) and US-negative/Not done (6) LRC, and from a few US-negative (3) HRC. The group 'Treat as GCA with AT' came entirely from the HRC (12) and IRC (11) groups.

***Clinical features***

**Table 5** shows the main clinical features at the time of referral. Interestingly, the generalised, non-localised headache was higher in LRC patients, whereas temporal headache (unilateral or bilateral) was more common in HRC patients. Not surprisingly, CRP level and frequency of scalp tenderness, jaw claudication, polymyalgic symptoms and constitutional symptoms (e.g., night sweats, weight loss, fever) were significantly higher in HRC patients and then in those eventually diagnosed with GCA. Notably, the blurred vision was the most common visual disturbance among the HRC patients. Overall, all the GCA symptoms and signs showed an increase through LRC, IRC to HRC, except for a generalised headache.

***Ultrasound results***

US of the TA and/or AA were performed in a total of 250 patients (71%), and the results were positive in 3/151 LRC (2%), in 39/137 IRC (29%), and 52/66 HRC (79%) patients. Overall, in the totality of the FTC population, US sensitivity was 97%, specificity 97% and accuracy 97%.

### A. High-risk category (HRC)

Of the 52 US positive HRC patients, 45 were treated as GCA without the need of AT, while 7 were investigated with AT while receiving treatment for GCA. Of these, only 2 patients were eventually diagnosed as non-GCA. Of the 10 US negative HRC patients, 3 (30%) were subsequently diagnosed with GCA but only after AT (PET-CT, 2; TAB, 1). In 4 patients, the clinical presentation was so typical of PMR without GCA and urgent for therapy that delays for US or AT to confirm the diagnosis was considered inappropriate. The total number of GCA and non-GCA in this category was 53 and 13, respectively. As a consequence, the sensitivity of US in HRC was 94%, specificity was 85%, and accuracy was 92% (see **Tables 6-7** for details).

### B. Intermediate-risk category (IRC)

US was positive in 39 IRC patients and of these 39, 27 (69%) were diagnosed without the need of AT. Twelve patients had AT and in only 3 of them (8%) GCA diagnosis was not confirmed after AT. Interestingly, none of the 68 IRC patients with the negative US was subsequently diagnosed as GCA (13 of them required AT). The total number of GCA and non-GCA in this category was 36 and 101, respectively. Regarding the performance of the US in IRC, sensitivity was 100%, specificity 97% and accuracy 98%.

### C. Low-risk Category (LRC)

Only 3 LRC patients had the positive US. However, they weren't treated as GCA but subsequently underwent AT, which pointed to other diagnoses. In 70 LRC patients, US was not done because the suspicion of GCA was too low. In total, GCA prevalence in this group was 0%. Therefore, in LRC patients, US had extremely high specificity (98%) and accuracy (98%) (see **Tables 6-7** for details).

**Table 5. Main clinical signs and symptoms at GCA fast track clinic referral**

| | Total n°354 (%) | LRC n°151 (%) | IRC n°137 (%) | HRC n°66 (%) | p-value | Not GCA n°265 (%) | GCA n°89 (%) | p-value |
|---|---|---|---|---|---|---|---|---|
| **Headache** | | | | | | | | |
| **Generalised** | 56 (15.8) | 31 (20.5) | 21 (15.3) | 4 (6.1) | 0.02 | 53 (20) | 3 (3.4) | 0.002 |
| **Temporal, unilateral** | 110 (31.1) | 41 (27.2) | 43 (31.4) | 26 (39.4) | 0.2 | 73 (27.5) | 37 (41.6) | 0.01 |
| **Temporal, bilateral** | 73 (20.6) | 20 (13.2) | 31 (22.6) | 22 (33.3) | 0.003 | 38 (14.3) | 35 (39.3) | <0.001 |
| **Scalp tenderness** | | | | | | | | |
| **Unilateral** | 53 (15) | 14 (9.3) | 19 (13.9) | 20 (30.3) | 0.001 | 26 (9.8) | 27 (30.3) | <0.001 |
| **Bilateral** | 51 (14.4) | 11 (7.3) | 16 (11.7) | 22 (33.3) | <0.001 | 22 (8.3) | 29 (32.6) | <0.001 |
| **Jaw claudication** | 70 (19.8) | 11 (7.3) | 25 (18.2) | 34 (51.5) | <0.001 | 23 (8.7) | 47 (52.8) | <0.001 |
| **PMR symptoms** | 134 (37.9) | 38 (25.2) | 61 (44.5) | 35 (53) | <0.001 | 93 (35.1) | 41 (46.1) | 0.043 |
| **Constitutional symptoms** | | | | | | | | |
| **Single** | 63 (17.8) | 18 (11.9) | 24 (17.5) | 21 (31.8) | 0.003 | 37 (14) | 26 (29.2) | 0.001 |
| **Combination** | 50 (14.1) | 6 (4) | 22 (16.1) | 23 (34.8) | <0.001 | 25 (9.4) | 26 (29.2) | <0.001 |
| **Visual disturbances** | | | | | | | | |
| **Blurred vision** | 62 (17.5) | 19 (12.6) | 23 (16.8) | 20 (30.3) | 0.008 | 36 (13.6) | 26 (29.2) | 0.001 |
| **Double vision** | 17 (4.8) | 5 (3.3) | 7 (5.1) | 5 (7.6) | 0.352 | 9 (3.4) | 8 (9) | <0.001 |
| **Amaurosis** | 22 (6.2) | 4 (2.6) | 9 (6.6) | 9 (13.6) | 0.01 | 8 (3) | 14 (15.7) | <0.001 |
| **Vision loss type** | | | | | | | | |
| **AION** | 16 (4.5) | 1 (0.7) | 5 (3.6) | 10 (15.1) | <0.001 | 2 (0.8) | 14 (15.7) | <0.001 |
| **CRAO** | 8 (2.3) | 1 (0.7) | 4 (2.9) | 3 (4.5) | 0.126 | 3 (1.1) | 5 (5.6) | 0.026 |
| **AION + CRAO** | 3 (0.8) | 0 | 2 (1.5) | 1 (1.5) | 0.308 | 0 | 3 (3.4) | 0.015 |
| **Mean CRP level (mg/L)** | 38 (± 51) | 15 (± 25) | 42 (± 50) | 82 (± 64) | <0.001 | 28 (±45) | 68 (± 56) | <0.001 |

*AION, anterior ischemic optic neuritis; CRAO, central retinal artery occlusion; CRP, C-reactive protein; GCA, Giant cell arteritis; HRC, high category; IRC, intermediate category; LRC, low category; PMR, polymyalgia rheumatica.* Categorical variables are presented as frequency and percentage (%). Quantitative variables were compared between groups using Mann–Whitney *U* test (eg- CRP levels). Categorical variables were compared between two groups using the Two-tailed Fisher's exact test and between three groups using the Kruskal-Wallis test

**Table 6. Categories, ultrasound findings and statistics**

| GCA Risk category (n) | Vascular US | Final diagnosis | | Sensitivity (%) [95% CI] | Specificity (%) [95% CI] | PPV (%) [95% CI] | NPV (%) [95% CI] | Prevalence (%) [95% CI] | Accuracy (%) [95% CI] | LR+ [95% CI] | LR- [95% CI] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | GCA (n) | Non-GCA (n) | | | | | | | | |
| **High (66)** | Positive | 50 | 2 | 50/53 (94) [84,99] | 11/13 (85) [55,98] | 50/52 (96) [87,99] | 11/14 (79) [54,92] | 53/66 (80) [69,89] | (50+11)/66 (92) [83,97] | 6.13 [1.71,21.98] | 0.07 [0.02,0.21] |
| | Negative/ND | 3 (3/0) | 11 (7/4) | | | | | | | | |
| **Intermediate (137)** | Positive | 36 | 3 | 36/36 (100) [90,100] | 98/101 (97) [92,99] | 36/39 (92) [80,97] | 98/98 (100) [-] | 36/137 (26) [19,34] | (36+98)/137 (98) [94,100] | 33.67 [11.04,102.64] | 0.00 |
| | Negative/ND | 0 (0/0) | 98 (68/30) | | | | | | | | |
| **Low (151)** | Positive | 0 | 3 | 0/0 (*undefined*) [-] | 148/151(98) [94,100] | 0/3 (0) [-] | 148/148 (100) [-] | 0/151(0) [0.00,2.41] | (0+148)/151 (98) [-] | - | - |
| | Negative/ND | 0 (0/0) | 148 (78/70) | | | | | | | | |
| **Total (354)** | Positive | 86 | 8 | 86/89 (97) [90,99] | 257/265 (97) [94,99] | 86/94 (91) [84,96] | 257/260 (99) [97,100] | 89/354 (25) [21,30] | (86+257)/354 (97) [95,98] | 32.01 [16.16,63.40] | 0.03 [0.01,0.11] |
| | Negative/ND | 3 (3/0) | 257 (153/104) | | | | | | | | |

*GCA, Giant cell arteritis; ND, not done; LR+, Positive likelihood ratio; LR-, Negative likelihood ratio NPV, negative predictive value; PPV, positive predictive value; US, ultrasound*

**Table 7. Ultrasound results, additional tests and final diagnosis in each category**

| GCA Risk category (n) | Vascular ultrasound | | | N° of AT (%) | Type of AT | Final Diagnosis |
|---|---|---|---|---|---|---|
| | Positive (%) | Not Done (%) | Negative (%) | | | |
| **Low (151)** | 3 (2) | 70 (46) | 78 (52) | 8 (5) | 1 x TAB (-), CTB (-) | Fibromyalgia |
| | | | | | 1 x TAB (-), MRA (-) | Tongue cancer |
| | | | | | 1 x CTA (+) | Stroke |
| | | | | | 1 x CTA (-) | Inflammatory arthritis |
| | | | | | 1 x PET (-) | PMR |
| | | | | | 2 x TAB (-) | Non-arteritic AION |
| | | | | | 1 x PET (-) | Stroke |
| **Intermediate (137)** | 39 (28) | 30 (22) | 68 (50) | 23 (17) | 1 x TAB (-), MRA (+) | Stroke |
| | | | | | 1 x PET (+) | Lymphoma |
| | | | | | 11 x TAB (-)<br>3 x PET (-) | No definite diagnosis |
| | | | | | 1x TAB (+)<br>6 x PET (+) | GCA |
| **High (66)** | 52 (79) | 4 (6) | 10 (15) | 15 (23) | 1 x TAB (-) | Non-arteritic AION |
| | | | | | 1 x PET (+) | Breast Cancer |
| | | | | | 3 x PET (-)<br>2 x TAB (-) | No definite diagnosis |
| | | | | | 2 x PET (+)<br>1 x TAB (+)<br>1 x CTA (+)<br>1 x MRA (+)<br>1 x PET (-)<br>1 x TAB (-)<br>1 x CT CAP (-) | GCA |

*AION, anterior ischemic optic neuritis; AT, additional tests; CTA, computed tomography angiography; CTB, computed tomography of brain; CT CAP, computed tomography of chest, abdomen and pelvis; GCA, giant cell arteritis; MRA, magnetic resonance angiography; PET, position emission tomography; TAB, temporal artery biopsy; UTI, urinary tract infection; the symbols +/- refers to test positivity or negativity to respectively include or exclude the final diagnosis*

## DISCUSSION

This single-centre 2-year cohort study of referrals to the FTC suggests that cases with suspected GCA represent a continuum of probability for GCA and that the Southend PTPS successfully stratifies them to HRC, IRC and LRC. This allows the diagnostic algorithm (with the US as the initial test and AT as required) to confirm GCA and securely exclude non-GCA. The overall prevalence of GCA over two years was 25%. However, the prevalence of GCA rose satisfactorily through the various pre-test probability groups (LRC, 0%; IRC, 24%; HRC, 80%). We, therefore, feel that this algorithm successfully stratifies suspected GCA referrals for the US and AT, and simplifies the diagnostic approach. It also validates our cut-offs for the 3 probability groups categorised based on probability scores obtained overall for the entire 2-year referrals(312). Any score above Q3 (>75$^{th}$ percentile, i.e. >12) was HRC, between Q2-Q3 (50$^{th}$- 75$^{th}$ percentile, i.e. 9-12) was IRC, and less than Q2 (<50$^{th}$ percentile, i.e. <9) was LRC. We have considered in future of adding a very low category below Q1 (< 25$^{th}$ percentile, i.e. score <7) but this is not the subject of the current study. We are pleased our current definitions fit well with the cut-off of 9.5, dividing LRC from IRC and HRC (i.e., LRC is < 9) reported from the original study(312).

The test performance of US in GCA was considerably enhanced with this Bayesian probability-based approach, as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of US overall and in all categories were much higher than previously reported (sensitivity in LC was undefined since there were no false negatives)(342). We feel such a pre-test Bayesian approach markedly augments the diagnostic performance of a test such as US and forms the rational basis for planning AT based on progress through the algorithm. Such an approach could be successfully implemented in other rheumatological areas such as in Early Arthritis clinics, where the assessment of pre-test probability of Early

Inflammatory Arthritis (EIA) referrals may allow better planning of the assessment/investigative approach using US and ancillary tests(343).

We are aware that in this study, the result of US was dichotomous (i.e., 'halo sign positive' vs 'halo sign negative'). Currently, we are investigating the use of a quantitative US score (i.e., Southend Halo Score (341)) in a prospective study (the 'HAS-GCA study' (344)), to see whether a quantitative approach that ascertains extent and severity of US GCA lesions may further enhance the test performance of US. There is preliminary evidence that indeed this is so. This too has implications for the use of musculoskeletal US in inflammatory arthritis. There is evidence that using a quantitative analysis of doppler US along with clinical features may potentially replace the necessity of TAB in GCA especially in the current pandemic environment where invasive tests in a hospital environment may not be popular with patients (345).

In the 151 cases in LRC, the prevalence of GCA was 0%, and 70 cases did not even require the US. Of the 81 cases that had the US, 78 were negative. Although 3 were interpreted as US positive, they were not started on steroids, and further investigations failed to confirm the diagnosis. Based on our results, we feel that the LRC may not require a face to face review in a specialist clinic, provided the probability score is accurately computed by a trained assessor. This could be performed by a trained clinician (a doctor or a nurse) through a telephone clinic. In the current climate of a global viral pandemic, this approach with prior ascertainment of pre-test probability of a referral will significantly weight the decision to proceed with remote consultation, assessment and advice given to the patient and referring physician versus the need for a face to face consultation.

We acknowledge that not all the patients had the US at the initial evaluation, and they were included in the US negative/Not done category. This may give a potential bias (i.e; HRC

specificity drops from 85% to 78% with only a slight drop in IRC and LRC). Supplementary table-1 outlines these figures in detail. Nevertheless, these patients remained non-GCA after 6 months.

With respect to the 4 diagnostic categories (GCA Unlikely, GCA uncertain, treat as GCA with AT and treat as GCA), the 'GCA unlikely 'group (Figure S1) reduces follow-up where a structured clinical assessment and PTPS, along with the point of care US, lead to a rapid and definitive decision to allow patient and physician education, reassurance and search for alternative pathology. The 'treat as GCA' group (Figure S2) was also populated as a one stop decision (i.e., patients in HRC or IRC who had an unequivocal positive US). We are currently working on what that unequivocal positive US is; whether quantitative Halo Score (Southend halo score) gives better test performance to decide on immediate treatment. There is evidence that larger and more extensive halos may be associated with more severe disease such as ocular ischemia(341).Our algorithm also allows precise identification of uncertainty (i.e., 'GCA uncertain' and 'treat as GCA with AT and/or clinical re-evaluation) (Figure S3 &S4). 'GCA uncertain' group requires AT such as PET-CT, TAB, or investigations for other pathology while withholding GC for GCA. We feel the quantitative Southend Halo Score would have reduced this uncertainty which arose not only related to the post-test probability of GCA but also to the probability of alternative pathology and individual safety of GC therapy in view of demographics, patient-specific factors, risks and co-morbidities. The algorithm again contributes to the patient management and review strategy (face to face versus remote reviews). The 'Treat as GCA with AT' group emphasises that the priorities about urgently treating GCA were balanced against individual patient factors, US findings and the probability of an alternative diagnosis. This group mostly generated the AT, such as TAB in suspected cranial GCA and PET-CT in suspected large-vessel GCA. Overall, only 9 TAB were requested over these 2 years, perhaps reinforcing the success of this approach.

A major objective of the FTC is that it speedily diagnoses non-GCA serious pathology too. Hence our probability score can allow inclusion of other serious mimics of GCA (as alternative diagnosis) which are rapidly confirmed with appropriate AT if US is negative, equivocal or discordant with clinical clues. Making a diagnosis in the HRC of GCA in 80% of patients with related US specificity of 85% reflects the fact that our keenness to make a correct diagnosis of GCA in this group is matched by an equal desire not to miss a non-GCA serious mimic such as head and neck cancer, infection or systemic rheumatological disease.

We feel that this probability-based approach for GCA diagnosis can be successfully considered in other areas of rheumatology. In particular, it should apply very well to EIA clinics. The critical aspect of the Southend PTPS is the negative weightage for alternative causative factors and in a score for an EIA clinic this should include other causes of musculoskeletal pain, such as osteoarthritis, fibromyalgia, and systemic connective tissue diseases. The role of targeted point of care US also becomes enhanced with higher diagnostic test performance, and the inclusion of quantitative musculoskeletal US assessments(346) should have an enhancing effect. The EIA algorithm will then allow us to arrive at analogous decision points (i.e., 'EIA unlikely', 'EIA uncertain', 'treat as EIA' or 'treat as EIA with AT').

This approach should be more cost-effective since it reduces the requests for invasive and expensive tests, such as TAB and PET-CT, respectively. The skill required to perform a TAB, the disincentive of an invasive test and the cost and waiting time of a PET-CT is currently an ongoing challenge in the UK. It makes the diagnosis of alternative pathology more rapid and should enable higher patient satisfaction, education, reassurance as well as immediate treatment of GCA after speedy diagnostic confirmation.

A similar approach could also be used for follow-up of GCA patients. It would be extremely useful for clinicians to have a score which comprises both clinical and laboratory findings and

that can help them to adequately categorise patients already diagnosed with GCA and to guide them in their management (e.g., reduction/increase of GC, the addition of steroid-sparing agents, request of diagnostic tests). We are currently working on a GCA clinical activity proforma and, in order to maintain a homogeneous approach, we think that this activity score should be used to assign GCA patients to the same four categories of the Southend PTPS (i.e., 'active GCA unlikely', 'active GCA uncertain', 'treat as active GCA', 'treat as active GCA with AT'). This novel scoring system would be helpful to guide clinicians not only in their daily practice but also when treating patients in the setting of clinical trials, as it would guarantee more uniform management between different centres. Our ongoing multicentre HAS GCA study with forming a halo score based on the intimal medial thickness measurement of the temporal and axillary arteries will further support our diagnostic algorithm.

We feel our novel approach to GCA is fully validated by our 2-year experience, although we acknowledge that this is indeed a single centre, open experience. Be that as it may, there may be an even greater need for rapidly adopting this approach across other diseases, especially during the current global viral pandemic crisis, since it arrives quickly at the decision between face to face versus remote review.

**Acknowledgement:** All authors would like to thank the Research and Development department at Southend University Hospital

**Contribution:** AS, AT and BD contributed to the conception or design of the work. AT, AK, DPP, CR and BD contributed to acquisition of data including ultrasound scans which were all done or personally supervised by BD. AS, AT and BD contributed to the analysis or the interpretation of data. All authors were involved in drafting the work or revising it critically for relevant intellectual content. All authors provided final approval of the version published

**Funding:** AS received an international educational (Bresnihan-Molloy) fellowship grant from the Royal College of Physicians of Ireland

**Competing interest:** BD reports grants and personal fees from Roche, personal fees from GSK, BMS, Sanofi and Abbie, outside the submitted work. All other authors have nothing to declare

**Patient consent for publication**: not required.

**Ethics approval:** This is a retrospective study where Research Ethics Committee approval is not required according to the local ethics guidelines.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

**Data availability statement:** all data relevant to the study are included in the article

**Figure Legends**

**Figure 2. Southend GCA Probability Score (*adapted from Laskou F et al. 2019*)**

**Figure 3. Categories according to the probability score**

**Figure 4. Probability-based diagnostic algorithm for suspected GCA**

**Supplementary data:**

**Figure S1. Probability-based diagnostic algorithm - *GCA unlikely* category**

**Figure S2. Probability-based diagnostic algorithm - *Treat as GCA* category**

**Figure S3. Probability-based diagnostic algorithm - *GCA uncertain* category**

**Figure S4. Probability-based diagnostic algorithm - *Treat as GCA with AT* category**

**Supplementary Table-1. Categories, ultrasound findings and statistics: *only patients who had Ultrasound scan***

**Figure 2: Southend giant cell arteritis (GCA) probability score (adapted from Laskou et al 2019).**

**Table I.** GCA probability score [GCAPS] proforma.

| Weightage | -3 | 0 | +1 | +2 | +3 |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age (years) | | ≤49 | 50-60 | 61-65 | ≥66 |
| Sex | | | M | F | |
| Duration | | | | | |
| Onset of symptoms | | >24 weeks | 12-24 weeks | 6-12 weeks | <6 weeks |
| Laboratory | | | | | |
| CRP | | 0-5 mg/L | 6-10 mg/L | 11-25 mg/L | ≥25 mg/L |
| Symptoms | | | | | |
| Headache | | N | Y | | |
| Polymyalgic | | N | | Y | |
| Constitutional | | N | Single | | Combination |
| Ischaemic | | N | | | Y |
| Signs | | | | | |
| Visual (AION, CRAO, Field loss, RAPD) | | N | | | Y |
| TA abnormality | | N | Tenderness | Thickening | Pulse loss |
| Extra-cranial artery abnormality | | N | Thickening | Bruit | Pulse loss |
| Cranial nerve paisy | | N | | | Y |
| Alternative | | | | | |
| Infection | Y | | | | |
| Cancer | Y | | | | |
| Systemic Rheumatic diseases | Y | | | | |
| Head and neck pathology | Y | | | | |
| Other | Y | | | | |
| Total score | | | | | |

**Figure 3: Categories according to the probability score**

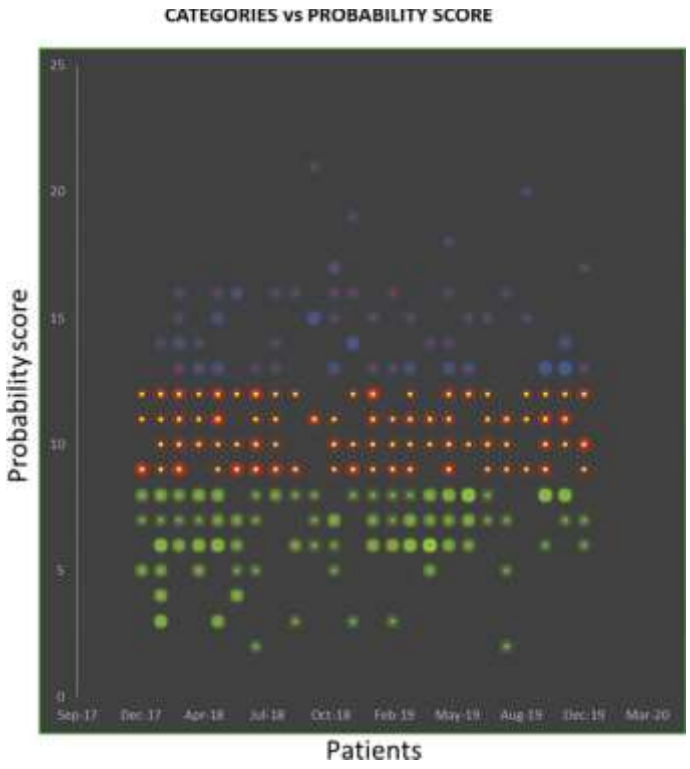


**Figure 4: Probability-based diagnostic algorithm for suspected giant cell arteritis (GCA).**

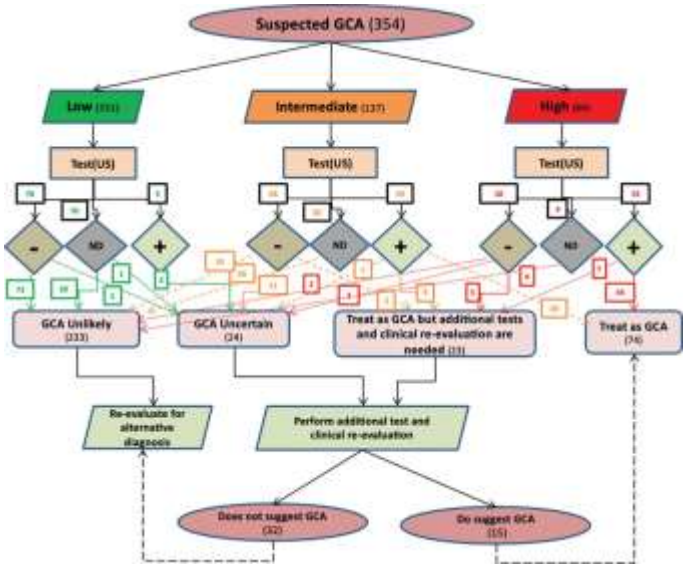



**Figure S1. Probability-based diagnostic algorithm - *GCA unlikely* category**

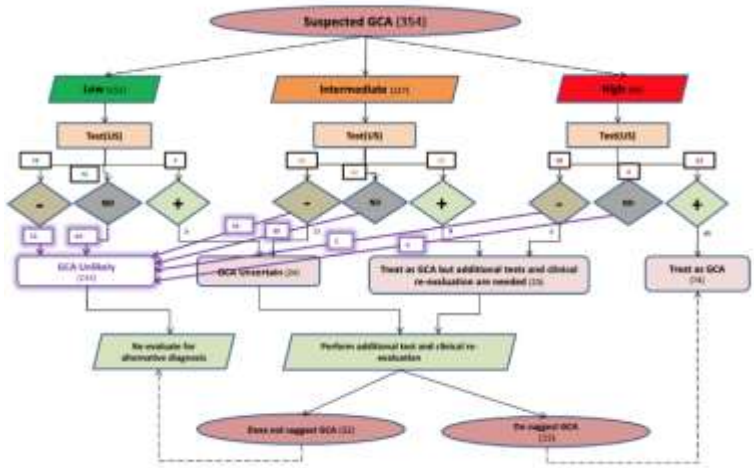


**Figure S2.** **Probability-based diagnostic algorithm - *Treat as GCA* category**

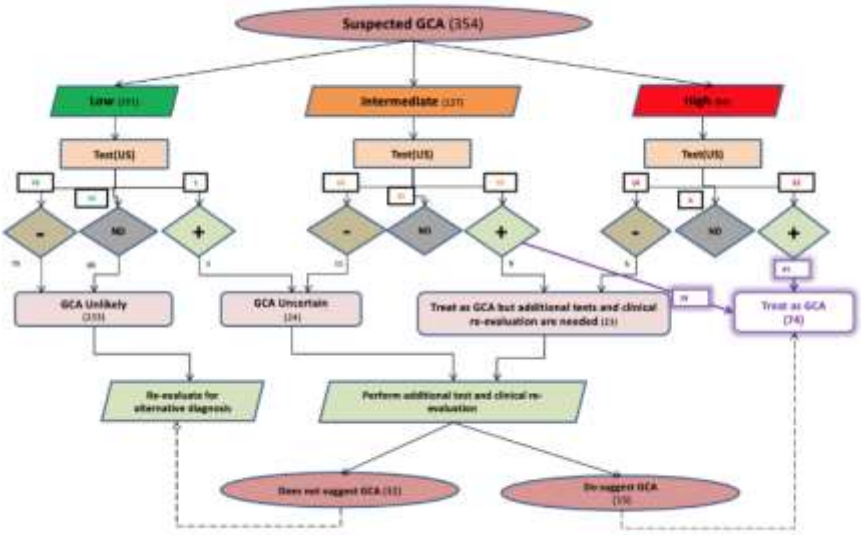



**Figure S3.** **Probability-based diagnostic algorithm - *GCA uncertain* category**

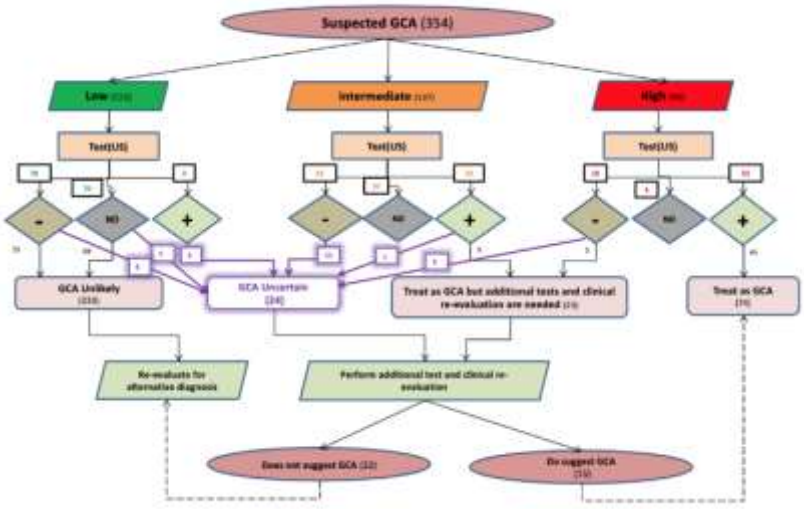
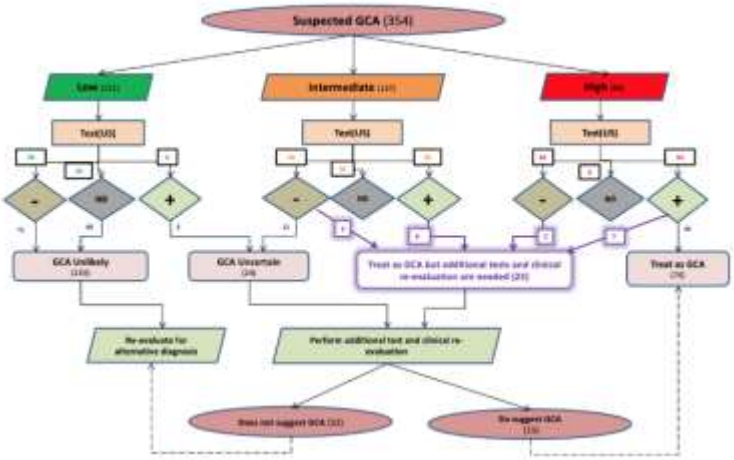


**Figure S4.** **Probability-based diagnostic algorithm - *Treat as GCA with AT* category**




**Supplementary Table-1.** **Categories, ultrasound findings and statistics:** ***only patients who had Ultrasound scan***

| GCA Risk category (n) | Vascular US | Final diagnosis | | Sensitivity % [95% CI] | Specificity % [95% CI] | PPV % [95% CI] | NPV % [95% CI] | Prevalence % [95% CI] | Accuracy % [95% CI] | LR+ [95% CI] | LR- [95% CI] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | GCA (n) | Non-GCA (n) | | | | | | | | |
| **High (62)** | Positive | 50 | 2 | 94 [84,99] | 78 [40,97] | 96 [88,99] | 70 [42,88] | 85 [74,93] | 92 [82,97] | 4.25 [1.25,14.44] | 0.07 [0.02,0.23] |
| | Negative | 3 | 7 | | | | | | | | |
| **Intermediate (107)** | Positive | 36 | 3 | 100 [90,100] | 96 [88,99] | 92 [80,97] | 100 | 34 [25,43] | 97 [92,99] | 23.67 [7.82,71.63] | 0.00 |
| | Negative | 0 | 68 | | | | | | | | |
| **Low (81)** | Positive | 0 | 3 | (*undefined*) | 96 [90,99] | 0 | 100 | 0 | 96 | - | - |
| | Negative | 0 | 78 | | | | | | | | |
| **Total (250)** | Positive | 86 | 8 | 97 [90,99] | 95 [90,98] | 91 [85,5] | 98 [94,99] | 36 [30,42] | 96 [9298] | 19.45 [9.89,38.26] | 0.04 [0.01,0.11] |
| | Negative | 3 | 153 | | | | | | | | |

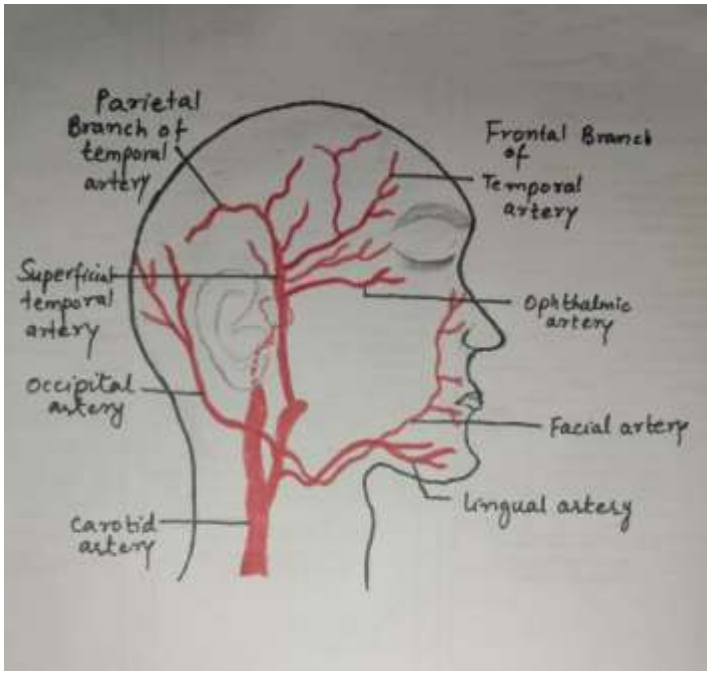
*GCA, Giant cell arteritis; LR+, Positive likelihood ratio; LR-, Negative likelihood ratio NPV, negative predictive value; PPV, positive predictive value; US, ultrasound*

### *2.2.3 Temporal artery biopsy*

1. Anatomy:

The temporal artery is a branch of the external carotid artery. The external carotid artery gives off the temporal artery when it reaches the level of the parotid salivary gland, just caudal to the neck of the mandible. The superficial temporal artery ascends vertically and crosses the zygomatic arch and periauricular point. Its pulse can be easily felt here, just in front of the auricle (347). It gives off two branches, anterior and posterior, 5cm above the level of the zygomata. These branches supply the areas of the temple and scalp, respectively. Moreover, two other arteries also arise from the superficial temporal artery, and these are the transverse facial artery and the middle temporal artery (that supply the temporalis muscle) (348) (Figure 5)

**Figure 5. Anatomy of Temporal Artery**



2. Histology

The wall of the temporal artery consists of three layers which are enlisted as follows:

a. Tunica Intima
    i. Endothelium
    ii. Sub endothelium
    iii. Internal elastic membrane
b. Tunica Media
c. Tunica Adventitia

The *tunica intima* of the temporal artery has a thick internal elastic lamina, therefore, stained dark. *Tunica media* is made up of several layers of smooth muscle fibres. These fibres are arranged in a circular pattern. Outside the muscular layer, there is an external elastic lamina. A connective tissue layer surrounds this middle layer, known as *tunica adventitia*. This layer has collagen fibres and elastic fibres. The collagen fibres are stained lighter, while elastic fibres are stained dark (349) (Figure 6)

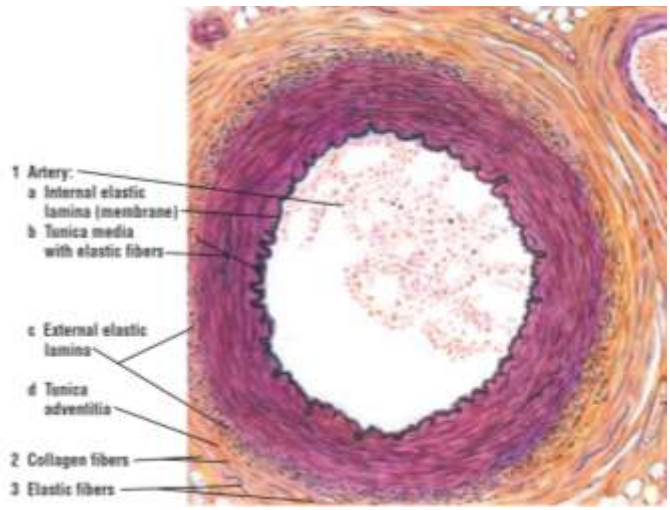



**Figure. 6. Temporal Artery (Transverse section, Elastic Stain)**

3. Role of Temporal artery biopsy (TAB)

TAB has been considered the gold standard test to yield the definitive pathologic diagnosis, and up to a decade ago, it was performed in all suspected cases for a definitive diagnosis. TAB is a low-risk invasive procedure, and a positive result rules in the diagnosis (317)(319)(350).

Research studies state that giant cell arteritis starts with the activation and infiltration of the inflammatory cells from the layers that are present away from the lumen of the artery. Principally the major sites of the inflammation in the walls of arteries are present in the tunica media and tunica adventitia (350)(351).

Positive TAB results of a clinically diagnosed case reveal chronic granulomatous inflammation, represented by the accumulation of multinucleated giant cells, macrophages, epithelioid histiocytes, and T lymphocytes. These cells are mainly seen to be accumulated in the internal elastic membrane (350).

The microscopy from the normal and confirmed cases' biopsy samples are illustrated in the following histology samples (350) (figure 7).

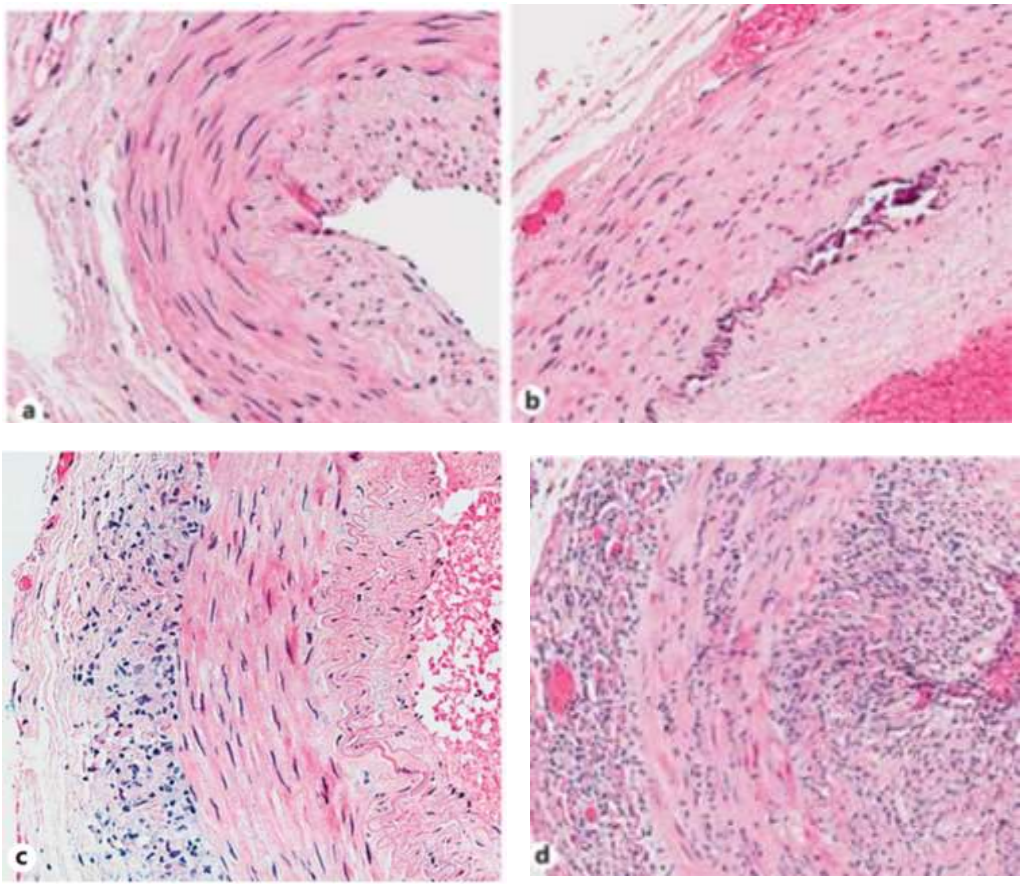



**Figure 7**: **Normal and pathological specimens**
*a; Negative sample of temporal artery biopsy tissue samples, stained with hematoxylin and eosin stain, b; Negative and normal sample of TAB tissue samples with H & E staining, showing a few calcific changes, c; Positive TAB specimen stained with H & E stain. This micrograph clearly shows the granulomatous inflammation at the levels of tunica media and tunica adventitia, d; Positive TAB specimen stained with H & E stain. This micrograph demonstrates the granulomatous inflammation with a full thickness of tunica media and tunica adventitia*

Initially, there is infiltration of the lymphocytes, which are one of the most common cell types at the inflammation site in the case of GCA. The giant cells are also present at the inflammation site. Other cell types present at the site include plasma cells, neutrophils, and eosinophils. As the condition prolongs and inflammation becomes chronic, lymphocytes remain the predominant cell types at the inflammation site. Plasma cells decrease in number and remain only half of the initial number. Eosinophils are rarely seen in chronic cases as the inflammation period prolongs, and the giant cell population increases in the tunica media and tunica adventitia(352).

There are several pieces of research and school of thought regarding the sensitivity of the TAB for the diagnosis of GCA over the other diagnostic tools. Some researchers believe that TAB is still the best diagnostic tool for GCA. In contrast, others have reported that further imaging is more robust to be used for diagnosing and confirming the GCA.

According to a study on 57 patients of GCA, Both US and TAB were used to diagnose of GCA, and follow-up of about 6 months in all patients. This study revealed that the sensitivity and specificity of the TAB were 73.7% and 100%, respectively, while the sensitivity and specificity of ultrasonography were 42.6% and 65.7%, respectively. According to this study's results, the US's usefulness and efficacy in diagnosing GCA are questionable. Moreover, the relatively higher sensitivity and specificity of TAB in this study supported the credibility of GCA (353). In another study with 430 suspected GCA patients, 381 had US and TAB. The results of this study revealed that the sensitivity of ultrasound (54%) was higher than that of TAB (39%).

In comparison, the specificity of the TAB (100%) was higher than of the ultrasound (81%). These figures indicate poor specificity but a better sensitivity of US compared to the specificity and sensitivity of TAB (342). A study conducted on 264 patients of GCA showed that the TAB was positive in only 8% of the total GCA patients. In some patients, US evaluation was done before TAB; in another group of patients, a biopsy was done before the US evaluation. The results showed that only a biopsy is not sufficient to get the ultimate diagnosis of GCA, and performing US before TAB may reduce the chances of doing unnecessary TABs in patients (354). Another study with on 114 suspected cases of GCA who underwent TAB between 2008-2017. Only 14.9% of cases had positive TAB, thus again questioning the role of TAB in diagnosing GCA (355). A systematic literature review and meta-analysis were published recently, in which 32 publications were analysed, including 3092 patients. These states the 77% sensitivity of TAB (356).

There may be a propensity of the clinicians to accept the GCA diagnosis without going for TAB over time, which has reduced the TAB-proved positive cases of GCA. However, in the majority of the cases, a negative TAB has no value in actual clinical practice in making a diagnosis of GCA. Current evidence suggests incorporating Doppler US in the clinical practice for the suspected GCA increases the positivity of TAB from 8.5 to 24%, with an associated 38% reduction in the TAB performed overall and with substantial cost-saving (357,358).

### *2.2.4 Role of Diagnostic imaging*

The current guideline recommends using an imaging modality to diagnose GCA. Since the EULAR stressed the importance of using US or a cross-section image such as CTA, MRI, MRA or PET CT as a first-line investigation in suspected GCA, recent ACR/EULAR classification criteria include the imaging to classify GCA (4) US remains the cheapest, non-radiating, bedside imaging model; its usefulness is limited primarily to diagnosing c-GCA. The newer technology allows the US to assess the extracranial vessels such as axillary and vertebral arteries to some extend to diagnose LV-GCA; the role of CTA, MRI, MRA or PET CT is vital for an accurate assessment of the presence of inflammatory vasculitic changes in the aorta and extracranial vessels (359).

#### *Role of Magnetic Resonance imaging for GCA diagnosis*

High-resolution MRI is useful in diagnosing and long-term monitoring GCA (360) (361). In a post-contrast image, inflammation of the vessel wall appears as an increased vessel wall thickening associated with mural swelling and enhancement. MRA provides detailed

information on the arterial lumen wall and any stenosis or occlusion of the lumen. MRI is primarily used to assess extracranial LV-GCA. However, recent data has shown its value in c-GCA (362–365). EULAR recommended a high-resolution 3-T MRI of cranial arteries as an alternative test for GCA diagnosis if the US is unavailable or inconclusive (4). However, in real practice, most studies have been conducted with 1T-1.5T MRI Machines.

Nevertheless, these studies have shown a high sensitivity and specificity of MRI for detecting cranial vessel wall inflammation(361–365). A recent meta-analysis showed a pooled sensitivity of 73% and a specificity of 88% for MRI compared to clinical diagnosis of GCA and a sensitivity of 93% and a specificity of 81% when TAB was used as the reference standard(361). A study with 35 patients compared MRI with US on a new or already diagnosed GCA revealed no statistically significant difference in vasculitic changes in temporal arteries, except for the frontal artery where MRI was superior to US(366). Another study with 27 patients looked at the role of three-dimensional high-resolution contrast-enhanced black blood MRI in detecting the arteritic origin of anterior ischemic optic neuropathy (AION). They found that the MRI detects the posterior ciliary artery involvement before the fundoscopy. The authors concluded that MRI would be useful over normal fundoscopy examination in GCA with visual impairment to rule out arteritic AION(367).

The major advantage of MRI in c-GCA is the potential evaluation of multiple cranial arteries simultaneously. It also shows an excellent resolution in assessing the cranial nerves in these patients(368). EULAR recommends using MRI to evaluate extracranial vessel involvement to diagnose LV-GCA and detect stenosis, occlusion, and aneurysms(4). However, most evidence-based practice with MRI in LV-GCA comes from Takayasu’s arteritis, and no specific dedicated studies thus far have been performed in LV-GCA(361,369).

MRI use is limited by the high cost and local availability of 3T MRI machines. Also, in conditions such as renal failure, pregnancy, implanted devices or claustrophobic patients, MRI is contraindicated.

In GCA diagnosis, it is apparent that US remains the choice of imaging modality over MRI in c-GCA.

***Role of Computed Tomography Angiography for GCA diagnosis***

CTA is an alternative option to MRI for diagnosing extracranial LV-GCA. Iodine-based contrast is injected through the vein, and vessel wall inflammation appears with mural thickening and double-ring enhancement. Several studies directly compared the use of CTA with PET-CT in LV-GCA. A study reported 95% sensitivity and 100% specificity of CTA, comparing PET CT as a reference(370). A retrospective study of 59 patients with clinical suspicion of LV-GCA had CTA and PET-CT. A sensitivity of 95.6% with PET-CT compared to 60.9% with CTA was observed(371). Similar results were found in another study with 36 patients comparing PET-CT and CTA. The area under the curve (AUC) for Maximum Standardised Uptake Value (SUVmax) on PET-CT was 0.95, and for mural thickening on CTA was 0.83(372). These results suggest PET-CT is better in detecting LV-GCA

***Role of 18F-FDG (Fluorodeoxyglucose)-Position Emission Tomography (PET) – Computed Tomography (CT) for GCA diagnosis***

18F-FDG PET combined with low-dose CT is a valuable tool in diagnosing LV-GCA(4,373). The scan can detect glucose uptake in the highly metabolically active immune and stromal cells. PET-CT is extremely useful in detecting the extension of LV involvement, such as the

aorta and branches to which the US has limited access. In addition, it is valuable in the inflammatory process and in recognising diseases such as malignancy and infections(360,361,373,374).

The interpretation and acquisition of FDG-PET-CT images in LV-GCA differ between the interpreters and observers; thus, it is pretty challenging. Therefore, the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the European Association of Nuclear Medicine (EANM), and the PET interests Group endorsed by the American Society of Nuclear Cardiology (ASNC)provided a joint procedural recommendation on FDG-PET-CT imaging for LV-GCA in 2018(373).

One of the pitfalls for accurate interpretation was GCs. As glucose is used as a transporter for FDG uptake, GCs may interfere and potentially reduce the vascular wall uptake of FDG, which will increase the liver FDG uptake. This results in a false reading of vascular FDG uptake. Therefore, stopping or delaying GCs treatment when feasible before the scan is recommended. To obtain the correct acquisition of FDG-PET-CT images, the evidence-based recommendation includes; fasting for at least 6 hours before FDG administration, blood glucose levels preferably <7mmol/L or acceptable level of < 10mmol/L, withdrawal or delay of GCs if possible, and at least 60 minutes between FDG administration and obtaining the images to ensure adequate biodistribution. In order to have a better delineation of the aortic wall uptake, some experts recommend 180 minutes after FDG injection(375,376). However, another study suggested a gap of 120 minutes(377).

To standardise the interpretation and to report the PET-CT results, it is recommended to use the Total Vascular Score (TVS), summing up the grades of uptake in different vascular areas. Individual visual grades between 0-3 are as follows: 0=no uptake (≤mediastinum); 1= low-

grade uptake (<liver);2=intermediate-grade uptake (=liver); 3=high-grade uptake (>liver), with grade 2 possibly indicative of and grade 3 considered positive for active LV-GCA(373).

Based on several meta-analyses that confirmed its diagnostic accuracy(378–380), EULAR includes PET-CT as an imaging choice for LV-GCA diagnosis. However, the most recent meta-analysis shows FDG-PET-CT has moderate diagnostic accuracy for detecting active disease with a pooled sensitivity of 77% and specificity of 71%(381).

In clinical practice, PET-CT is largely used to diagnose extracranial LV-GCA early. This is particularly useful for refractory PMR patients who present with atypical features such as pelvic girdle pain, inflammatory back pain, and limb claudication(382).

Currently, PET-CT is not routinely indicated for predominant presentation with cranial features of GCA. However, recent studies have shown the usefulness of PET-CT in c-GCA(383,384). A prospective study with 64 suspected new GCA patients had both PET-CT and TAB within 72 hours of starting GCs. It showed PET-CT had a sensitivity of 92% and specificity of 85% when using TAB as a reference and a sensitivity of 71% and specificity of 91% compared with clinical diagnosis(384).

The drawbacks of this technique are high cost and high-level radiation exposure. It also decreases the accuracy of the diagnosis when the patient is exposed to high-dose GCs. It has been suggested to perform PET-CT within ten days of high-dose GCs treatment for a reliable result(385). Differentiating atherosclerosis and vessel wall inflammation could be challenging. However, wh careful interpretation, it is possible to identify the focal or patchy uptake as likely atherosclerosis, and a diffuse pattern of vascular FDG uptake is likely vessel inflammation(386,387). The most significant advantages of using PET-CT scan. It is whole-body imaging, so it allows for an extensive assessment of all the large arteries in one scan.

Even with the newer improved high-resolution scans, it is possible to assess the cranial arteries (384,388).

***Role of Doppler Ultrasound for GCA diagnosis***

Doppler US use in diagnosing GCA is becoming a popular, first-line imaging modality. This is discussed in detail in the following section 2.3

## 2.3 **Vascular Ultrasound**

### *2.3.1 General aspects*

US is an emerging and alternative imaging tool to TAB for diagnosing c-GCA. Due to its improving diagnostic accuracy in c-GCA, the US has increasingly been used in c-GCA diagnosis. In 2014, only 1% of its use among rheumatologists in GCA and 74-94% preferred TAB as a confirmatory test over the US(389–391). The US is non-invasive, non-ionising radiations and provides the length of the temporal arteries and branches. The US, in many centres, has become a vital imaging modality of the GCA FTC that favours the early diagnosis of GCA(309,323,392). In the FTC rapid specialist assessment (majority of places within one working day) for a suspected GCA and with the clinical and US findings, GCA can be confirmed or excluded. If the results is equivocal or in doubt of the GCA diagnosis, additional tests such as TAB or other imaging techniques should be requested. In LV-GCA role of the US is still limited and often requires an additional imaging tool to confirm LV-GCA. The fundamental abnormality of the US finding in GCA is the ‘Halo Sign’(393).

### *2.3.2 Definitions of vascular ultrasound lesions*

The Outcome Measures in Rheumatology (OMERACT)group on the US for GCA, which included experts from Europe and USA, was created to reach consensus-based definitions of normal US appearance and 4 key US lesions in suspected GCA: Halo sign, Compression sign, Stenosis and Occlusion(394). They also recognised the atherosclerotic changes in the vessel wall.

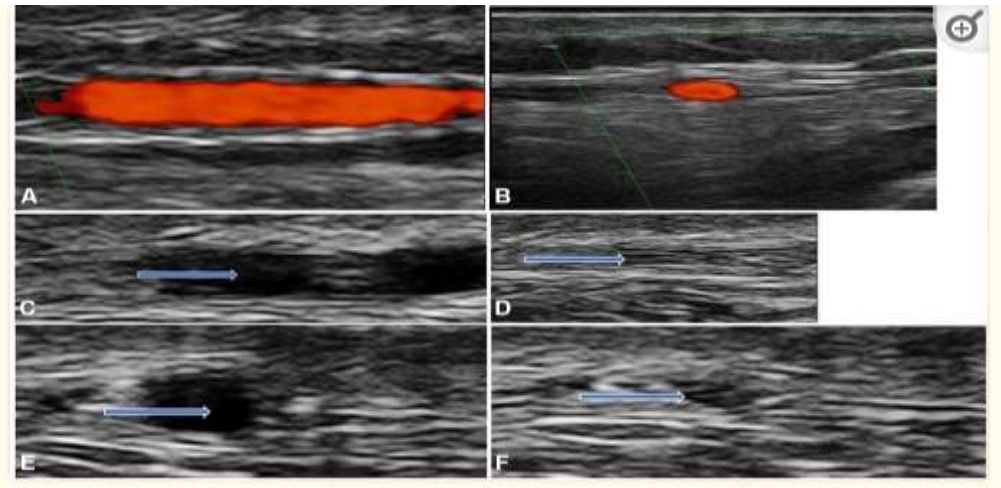
***Table 8: OMERACT definition of US appearance in temporal arteries***

| | |
|---|---|
| Normal temporal arteries | Pulsating, compressible artery with anechoic lumen surrounded by mid-echoic to hyperechoic tissue. Using US equipment with high resolution, the intima-media complex presenting as a homogenous, hypoechoic or anechoic echostructure delineated by two parallel hyperechoic margins (‘double line pattern’) may be visible. |
| ‘Halo’ sign of temporal arteries | Homogenous, hypoechoic wall thickening, well delineated towards the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans. |
| ‘Compression’ sign of temporal arteries | The thickened arterial wall remains visible upon compression; the hypoechogenic vasculitic vessel wall thickening contrasts with the mid-echogenic to hyperechogenic surrounding tissue. |
| Stenosis in temporal arteries | Stenosis is characterised by aliasing and persistent diastolic flow by colour Doppler US. The maximum systolic flow velocity determined within the stenosis by pulsed wave-Doppler US is ≥2 times higher than the flow velocity proximal or distal to the stenosis. |
| Occlusion in temporal arteries | Absence of colour Doppler signals in a visible artery filled with hypoechoic material, even with low pulse repetition frequency and high colour gain. |
| Arteriosclerotic arteries | Heterogeneous and in part hyperechoic, irregularly delineated and eccentric vessel wall alteration. |

***Table 9: OMERACT definition of US appearance in extracranial large arteries***

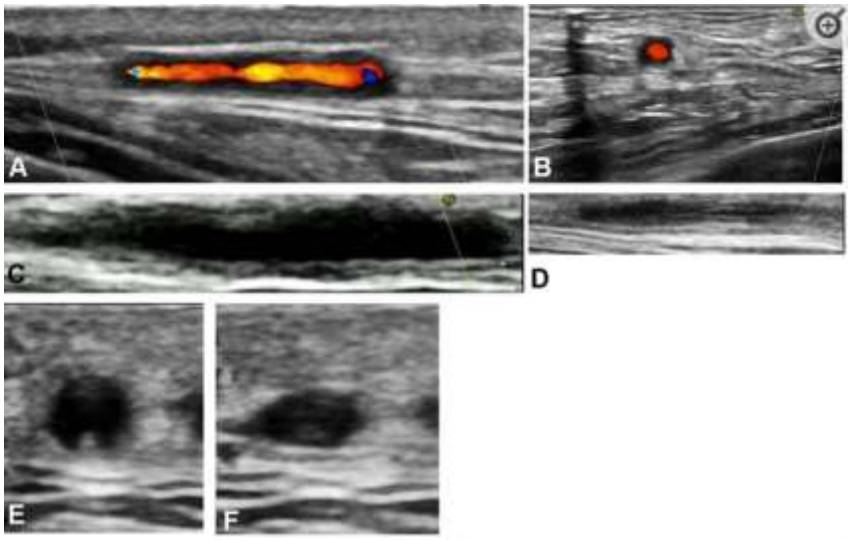
| | |
|---|---|
| Normal extracranial large arteries | Pulsating, hardly compressible artery with anechoic lumen; the intima-media complex presents as a homogenous, hypoechoic or anechoic echostructure delineated by two parallel hyperechoic margins (‘double line pattern’), which is surrounded by mid-echoic to hyperechoic tissue. |
| ‘Halo’ sign of extracranial large arteries | Homogenous, hypoechoic wall thickening, well delineated towards the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans. |
| Stenosis in extracranial large arteries | Typical vasculitic vessel wall thickening with characteristic Doppler curves showing turbulence and increased systolic and diastolic blood flow velocities. |
| Occlusion in extracranial large arteries | Absence of colour Doppler signals in a visible artery filled with hypoechoic material, even with low pulse repetition frequency and high colour gain. |
| Arteriosclerotic arteries | Heterogeneous and in part hyperechoic, irregularly delineated and eccentric vessel wall alteration. |

***Figure 8:*** **Normal temporal artery branch:**



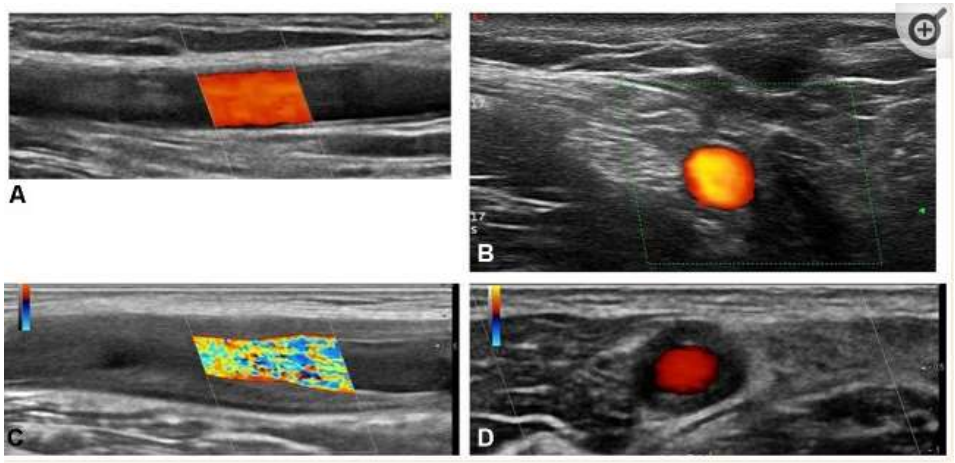

*(A) longitudinal view; (B) transverse view; (C) longitudinal view before compression; (D) longitudinal view with compression; (E) transverse view before compression and (F) transverse view with compression. The arrows are indicating the artery.*

***Figure 9:*** **Abnormal temporal artery branch**




*(A) longitudinal view with 'halo' sign; (B) transverse view with 'halo' sign; (C) longitudinal view before compression; (D) longitudinal view with compression ('compression' sign positive); (E) transverse view without compression and (F) transverse view with compression ('compression' sign positive).*

***Figure 10:*** **Axillary artery**




*(A) longitudinal view of normal artery; (B) transverse view of normal artery; (C) longitudinal view with 'halo' sign and (D) transverse view with 'halo' sign.*

### *2.3.3 Role of vascular ultrasound in GCA and reliability*

The current recommendation from EULAR to use the US as the first imaging model in suspected GCA when the expertise is available(4). Since 1995 Schmidt et al.(393) first reported the halo sign, the cardinal feature of sonographic vasculitis, the use of US in GCA has been increasingly accepted as a non-invasive and reliable tool in diagnosing GCA(25,322,342,392,394–399) . in a prospective study of 30 patients had a clinical diagnosis of GCA, confirmed by 2 rheumatologists agreed 22/30 had halo sign in the temporal arteries had a 100% agreement within them (400). The first meta-analysis included 23 studies published until 2004 and showed modest results for the use of US in GCA diagnosis (395). Later in 2010, Arida et al. published a meta-analysis including only the prospective studies that focused on the value of the halo sign in GCA. This study found a sensitivity of 68% and specificity of 91% for the halo sign, and when the presence of a bilateral 'halo sign' the specificity increases to 100% (398). In 2012, the "compression sign" was reported with a prospective cohort of 43/80 clinically diagnosed GCA patients who had bilateral temporal artery US by three physicians. They observed that 34/43 had both halo sign and compression sign were negative in non-GCA patients showing a 79% sensitivity and 100% specificity for both signs in diagnosing GCA (338,339). Most recent studies report the temporal artery US with a sensitivity of 91.6% and specificity of 95.8% using clinical diagnosis as a reference(399). De Miguel et al. reported excellent inter-reader reliability with kappa value >0.80(396). in 2018, the OMERACT LV US working group, a strong advocate of halo sign and compression sign in GCA diagnosis, found inter-rater agreement of 91-99% and a mean kappa value of 0.83-0.98 for both inter-rater and intra-rater reliabilities(394). a most recent meta-analysis published by our group included the high-quality studies, focused on the role of halo sign in GCA. This study found the halo sign had a pooled sensitivity of 67% and

specificity of 95% when the clinical diagnosis was standard and a sensitivity of 63% and specificity of 90% when using the TAB as standard(401).

It is recommended to scan the suspected c-GCA patients, including temporal (TA) and axillary arteries (AA). Performing axillary artery US (AAUS) increases the diagnostic yield for LV-GCA with a detection rate of 98% vs 62% for TAUS alone(402–404). TA assessment should include common TA and frontal and parietal branches, assessed bilaterally in both longitudinally and transverse planes. Other arteries, such as facial, maxillary, occipital, vertebral, subclavian and femoral arteries, are not routinely required to be scanned. However, it can be examined when there is a high clinical suspicion of GCA, and the routine scan does not yield the diagnosis(405–409). Some authors mentioned the usefulness of assessing the abdominal aorta, but the practical application is limited in clinical practice. Asymptomatic abdominal aortic aneurism may be detected in 33% of biopsy-proven GCA cases in the US despite no clinical evidence of the same(410).

With the increasing technology and availability of the different US machines and probes, detecting vascular wall pathology is becoming more straightforward. High-resolution linear probes with colour doppler mode is required for the TA assessment, and B-mode or colour doppler mode is needed for the AA assessment. It is recommended to use at least ≥ 12-18 MHz frequency probe for the TA and at least ≥ 12-15 MHz frequency probe for AA assessment(4). The resolution improvement with the technology of US probes can even auto-recognise the halo sign by measuring the intima-media thickness (IMT) in temporal and axillary arteries. Very-high resolution ultrasound (VHRU, MHz) was introduced recently, defining the thickness of the arterial intima layer. In 37 patients who had negative TAB, intimal thickening (>0.06mm on histology) could be identified as a “four-line pattern” in VHRU with a 96.3% sensitivity and 100% specificity with an excellent agreement between histology and VHRU intimal thickness measurement(411). A study that used contrast-

enhanced US of large vessels in 24 GCA patients had a sensitivity and specificity of 91.7 and 100% for detecting active LV-GCA(412). It captures lumen images of the vessel wall border, and pathology correlates well with FDG-PET-CT findings(413,414). Roncato et al. have described an automated image analysis tool for diagnosing GCA using an artificial intelligence algorithm. They used VIA software to record a retrospective cohort of 137 patients who had US. They got a 60% sensitivity and 95% specificity from this test. It also had a high inter-rater agreement but relied on the sonographers' experience(415).

In current practice, most sonographers use the published cut-off values by Schafer et al. for abnormal IMT to diagnose GCA, although there are no validated cut-off values yet. Cut-off values are as follows: Common TA- 0.42mm, frontal branch-0.34mm, parietal branch-0.29mm and AA-1.0mm(340). Also, IMT cut-off value values have been proposed for the TA compression sign(416). Czhihal et al. recently validated a cut-off value of ≥ 0.7mm in patients presenting with acute arterial ocular ischemia. However, the limitation of this study revealed the decreased specificity and positive predictive value in >70 years old male patients(417). Diagnostic accuracy of TA US seems to be influenced by age, gender and cardiovascular (CV) risk factors. A study observed that atherosclerosis in carotid arteries correlated with an increase in TA IMT looks like a false-positive halo. As atherosclerosis is prevalent in the age group of GCA patients, this group suggested a cut-off value of TA IMT to >0.34mm in at least two branches to minimise false positives in GCA diagnosis(418). A recent study looked at the IMT in patients with various degrees of CV risk. TA and AA US were performed in all 101 patients over 50 years of age without a diagnosis of GCA or PMR. They found in high/very high CV risk, mean IMT was greater than normal typical cut-off values in all TA and AA (419).

There is no reliable data available yet regarding the role of the US in monitoring GCA disease activity. In the past, authors agreed that halo regression happens within 3-4 weeks of

commencing GC treatment(400,420–423). However, some authors now report that with modern US technology, a halo can be visible up to 6 months after starting the immunosuppressive treatment(424–426). It is also observed that halo regression happens quicker in TA than in AA(427–429). However, it has been reported that there is no difference in relapse rate or GC dose between the wall-thickness regression(430). In 2021, a prospective study with 49 patients evaluated the role of the US in monitoring GCA activity by measuring the IMT over weeks 1,3,6, 12 and 24. It showed a significant difference at each follow-up measurement in TA and after six weeks in AA halo. In addition, relapsed cases 16/17 had increased IMT compared to the last measurement (431). However, no reliable conclusion can be made regarding the US use in monitoring GCA activity based on the available data.

Vascular US has been widely implemented in fast-track clinics. The finding of a segmental or continuous, homogeneous, hypoechogenic, incompressible wall thickening (halo) is consistent with GCA. However, simple binary assessment of the presence or absence of halos (Halo Sign) is not suitable to assess sensitivity to change since time to halo disappearance varies considerably. Also, US-proven wall oedema during a relapse is less pronounced than by the time of diagnosis and accordingly, binary assessment does not allow discrimination of remission and relapse.

Though still lacking evaluation of their discriminative properties, different, more comprehensive quantitative US scores based on halo features, including counting the number of halos (Halo Count), measuring wall thickness or composite scores (Halo score, OGUS) based on both, have been suggested and some have demonstrated potential to show sensitivity to change in patients with mainly cranial GCA. Including visually normal arteries in such scores could ensure potential changes on follow-up are captured and minimize the risk of assessment bias. Recently, a provisional OMERACT GCA US score (OGUS), for disease

monitoring in clinical trials has been suggested by the OMERACT Large Vessel Vasculitis Ultrasound Working Group. The OGUS is recommended using in clinical trials and only published this year and not considered part of our study.

As the halo sign remains dichotomous, to overcome this issue recently, a US composite scoring system, the “Halo Score”, was developed. This quantifies the extent of vessel wall inflammation in patients with GCA. The halo score measures the extent of inflammation in common TA, frontal branch, parietal branch and AA. The high scores support the diagnosis of GCA and correlate with the potential risk of patients with ocular ischemia (318,341). Quantified halo score minimises the operator dependent bias of measuring IMT.

## 2.4 **Ultrasound halo sign and ultrasound reliability exercise**

### 2.4.1 **Systematic review and metanalysis of halo sign**

**Published article:**

The following material in this chapter was published in August 2021 during the PhD. This published article is a systematic review and meta-analysis assessing the halo sign's role in GCA. 23 studies were included and had a pooled sensitivity of 67% and specificity of 95% compared with clinical ACR criteria as standard and a sensitivity of 63% and specificity of 90% when TAB was the standard. In the following material, the content is unchanged. The references, table and figure numbers in this article below are amended from the original publication to reflect the continuity of the PhD thesis references, Tables and figures.

**Role of the halo sign in the assessment of giant cell arteritis: a systematic review and meta-analysis**

Alwin Sebastian ✉, Fiona Coath, Sue Innes, Jo Jackson, Kornelis S M van der Geest, Bhaskar Dasgupta

*Rheumatology Advances in Practice*, Volume 5, Issue 3, 2021, rkab059, https://doi.org/10.1093/rap/rkab059

**Published:** 19 August 2021 **Article history**

pooled **sensitivity of 67%** (95% CI 51– 80) and a **specificity of 95%** (95% CI 89– 98%). This gave a positive and negative likelihood ratio for the diagnosis of GCA of 14.2 (95% CI: 5.7–35.5) and 0.375 (95% CI 0.22–0.54), respectively. Using TAB as the standard (15 studies) yielded a pooled **sensitivity of 63%** (95% CI : 50–75) and a **specificity of 90%** (95% CI: 81–95).

## Role of the 'halo sign' in the assessment of Giant Cell Arteritis (GCA): A systematic review and Meta-analysis

**Registration:** PROSPERO 2020 CRD42020202179

**Authors:**

1. Alwin Sebastian, Department of Rheumatology, Mid and South Essex University Hospital Groups Southend University Hospital, Westcliff-On-Sea, Essex, UK, School of Sport, Rehabilitation and exercise sciences, Colchester campus University of Essex, UK. alwinuk@yahoo.co.uk
2. Fiona Coath, Department of Rheumatology, Norfolk and Norwich University Hospitals NHS Foundation Trust, Colney Ln, Norwich, UK. Fiona.coath@nhs.net
3. Sue Innes, School of Sport, Rehabilitation and exercise sciences, Colchester campus, University of Essex, UK. inness@essex.ac.uk
4. Jo Jackson, School of Sport, Rehabilitation and exercise sciences, Colchester campus, University of Essex, UK. jo.jackson@essex.ac.uk
5. Kornelis S. M. van der Geest, Department of Rheumatology and Clinical Immunology, University medical centre Groningen, University of Groningen, Groningen, The Netherlands. k.s.m.van.der.geest@umcg.nl
6. Bhaskar Dasgupta, Department of Rheumatology, Mid and South Essex University Hospital Groups Southend University Hospital, Westcliff-On-Sea, Essex, UK**.** School of Sport, Rehabilitation and exercise sciences, Colchester campus University of Essex, UK, Bhaskar.dasgupta@southend.nhs.uk

**Contributions:**

Study concept and design: AS, FC, KSMvdG, SI and BD; data collection: AS and FC; statistical analysis and data interpretation: AS, FC, JJ and KSMvdG; all authors reviewed the manuscript content and gave the final approval of the version

**Corresponding Author:**

Name: Alwin Sebastian

Postal Address: Southend University Hospital, Prittlewell Chase, Southend-on-Sea, Westcliff-on-sea, SS0 0RY, United Kingdom

Email: alwinuk@yahoo.co.uk

**Funding:**

AS received an international educational (Bresnihan-Molloy) fellowship grant from the Royal College of Physicians of Ireland

**Acknowledgement:** All authors would like to thank the Southend University hospital librarian Mrs Karen Morgan for her extensive support with the literature search.

**Competing interest:** BD reports grants and personal fees from Roche, personal fees from GSK, BMS, Sanofi and Abbie, outside the submitted work. KSMvdG reports grants from the Mandema Stipend and the Dutch Society for Rheumatology, and personal fees from Roche, outside the submitted work. All other authors (AS, FC, SI, JJ) have nothing to declare

**Patient consent for publication**: not required.

**Ethics approval:** This is a Systematic review and meta-analysis where Research Ethics Committee approval is not required according to the local ethics guidelines.

**Data availability:** All data relevant to the study are included in the article. All authors agree to make materials, data and associated protocols promptly available to readers if requested.

## Abstract:

### Objectives

This systematic review and meta-analysis aimed to evaluate the diagnostic value of the 'Halo Sign' in the assessment of Giant Cell Arteritis (GCA)

### Methods

A systematic literature review was performed using MEDLINE, EMBASE and Cochrane central register databases up to August 2020. Studies informing on the sensitivity and specificity of the ultrasonographic halo sign for GCA (index test) were selected. Studies with a minimum of 5 participants were included. Study articles using clinical criteria, imaging

such as Positron emission tomography (PET-CT) and/or temporal artery biopsy (TAB) as the reference standards were selected. Meta-analysis was conducted with a bivariate model.

**Results**

The initial search yielded 4023 studies. 23 studies (patients n=2711) met the inclusion criteria. Prospective (11 studies) and retrospective (12 studies) studies in academic and non-academic centres were included. Using clinical diagnosis as the standard (18 studies) yielded a pooled sensitivity of 67% (95% CI 51- 80) and a specificity of 95% (95% CI 89- 98%). This gave a positive and negative likelihood ratio for the diagnosis of GCA of 14.2 (95% CI: 5.7-35.5) and 0.375 (95% CI 0.22-0.54), respectively. Using TAB as the standard (15 studies) yielded a pooled sensitivity of 63% (95% CI:50-75) and a specificity of 90% (95% CI: 81-95).

**Conclusion**

US halo sign is a sensitive and specific approach for GCA assessment and plays a pivotal role in diagnosing GCA in routine clinical practice.

**Key Words:**
Giant cell arteritis, Ultrasound, Halo sign, Glucocorticoids, Systematic review

**Key Messages**

1. Compared with previous meta-analysis, the halo sign had similar sensitivity (67%) but higher specificity (95%)
2. Higher specificity may potentially reflect improved technique and equipment.
3. Studies showed design heterogenicity, we recommend future researchers employ multi-centre prospective standardised study protocols.

**Introduction**

Giant cell arteritis (GCA) is a form of large vessel vasculitis, which can cause critical ischemia. Associated retinal ischemia can lead to permanent blindness in about 15-25% of patients, making it a medical emergency (432). However, making a diagnosis of GCA can be challenging, since none of the symptoms or laboratory findings have perfect sensitivity or specificity for the disease (433). The American College of Rheumatology (ACR) 1990 classification criteria for GCA have been developed for research purposes, but have limited specificity for GCA in daily clinical practice (341).

Since the publication of the ACR Classification criteria, ultrasonography has been shown to play a pivotal role in the diagnosis of GCA, with the most specific finding being the 'halo sign', a circumferential hypoechoic vessel wall thickening around the lumen, most likely due to vessel wall oedema (393) and intimal hyperplasia (318). GCA predominantly involves the external carotid artery and its branches, such as the temporal arteries (cranial GCA), the aorta, subclavian and axillary arteries (434). Traditionally, glucocorticoids (GC) have been the mainstay of treatment for GCA (166), although cohort studies and the GiACTA trial showed only 15-20% sustained remission with GC alone (435). Current guidelines suggest starting GC immediately in patients where GCA is strongly suspected, pending investigation, to prevent serious ischaemic complications (436). Long-term use of high dose GC can lead to severe adverse effects such as hypertension, hyperglycaemia, osteoporosis, Cushingoid changes, mood disturbance, electrolyte imbalance, cataracts and glaucoma, but this is not an exhaustive list (436)(437). Therefore a prompt and accurate diagnosis is vital to ensure that vision is preserved whilst avoiding unnecessary exposure to a potentially toxic treatment (438). GCA ‘fast track’ clinics have been shown to reduce permanent visual loss by

facilitating a rapid specialist clinical assessment with ultrasound (US) of the temporal and/or axillary arteries (311)(309).

A positive temporal artery biopsy (TAB) has historically been the gold standard test for a histological diagnosis of GCA (439)(440). However, TAB is invasive and lacks sensitivity (342). This deficiency is particularly true with extra-cranial involvement, where access to histological samples has obvious practical constraints and is usually identified incidentally following cardiovascular surgery (342). Non-invasive imaging techniques, including US, Magnetic resonance imaging (MRI) and positron emission tomography CT (PET-CT), are readily able to identify these patients (441)(402)(433). The European League Against Rheumatism (EULAR) recommends US of temporal and/or axillary arteries as the first imaging modality for suspected predominantly cranial GCA, where adequate expertise and equipment is available (4). US is safe, non-invasive and has high sensitivity. It is a relatively quick procedure, often used as a point of care test, well-tolerated by patients, with a growing body of evidence for its use in follow-up (398). At present, a non-compressible 'Halo sign' is the main finding on US of active GCA patients (393)(439)(326). Accuracy and criterion validity of US in the diagnosis of GCA was investigated in several studies (398)(395)(442)(361). A meta-analysis of prospective studies compared the final diagnosis of GCA to temporal artery US, showing a pooled sensitivity of 77% and a pooled specificity of 96% (338).

US also allows for assessment of the intimal media complex (IMC) and measurement of intimal medial thickness (IMT). Although no definite consensus has been reached, studies suggest that at the age of 70 years, a normal temporal artery has an IMT of about 0.2 mm, whilst abnormal or inflamed temporal arteries have an IMT range between 0.5-0.9 mm

(4)(443). Axillary arteries of patients aged about 70 have a normal IMT of around 0.6 mm, whilst patients with extra-cranial (large vessel) GCA have a mean IMT of 1.6-1.7 mm (443)(444). An axillary artery IMT of 1.0 mm was determined as a cut off value to discriminate between a normal and abnormal artery by Schäfer VS et al. (443). Currently, US assessment of suspected GCA patients is reported in a dichotomous manner (positive or negative). However, a range of extent and severity of these findings can be observed in the temporal and axillary arteries (337). A recent post hoc prospective study of a quantitative ultrasonographic 'halo 'score', which combines the grade and extent of halos seen in temporal arteries, their branches and axillary arteries in GCA, has shown value as a marker of disease activity and ocular ischemia (341). Whether the halo score may be of help with diagnosis, prognosis, and GCA monitoring is being tested in an ongoing prospective multi-centre study of patients presenting with new GCA (HAS-GCA study, NIHR IRAS# 264294) (439).

This systematic review and meta-analysis focused on evaluating the clinical role of the halo sign in managing a clinically suspected GCA population and ascertaining the areas that warrant further exploration. This study also updates estimates of diagnostic accuracy since newer studies have been published using modern US equipment.

## METHODS

For this literature review and meta-analysis, we followed the format of (PICO) Population, Intervention, Comparator, Outcome (445) (Supplementary Table 1) and guidelines of (PRISMA-DTA) Preferred Reporting Items for Systematic Reviews and Meta-Analyses (446)(447). This study protocol was registered with the international prospective register of systematic reviews (PROSPERO 2020 CRD42020202179). No ethical approval or informed consent was required.

### Literature search

The literature was searched systematically by two investigators (AS and FC) using a broad search of different databases; MEDLINE, EMBASE and Cochrane central registry (Supplementary Table 2). These databases were searched for original primary studies that examined the halo sign's sensitivity and specificity, demonstrated by temporal artery and/or axillary artery ultrasonography for GCA diagnosis, published in English, from their inception dates until August 2020. The search terms included *giant cell arteritis, temporal arteritis, diagnostic imaging, imaging, ultrasound, ultrasonography, halo sign and temporal artery biopsy*. An experienced medical librarian carried out the complete search.

### Study Selection and Eligibility Criteria

The titles and abstracts were screened by two independent reviewers (AS and FC). Full texts were independently assessed by two reviewers (AS and FC). Any disagreement between reviewers was resolved by consensus, or if consensus could not be obtained, by consulting a third reviewer (KSMvdG) who made the final decision.

We included prospective and retrospective cross-sectional or longitudinal studies, and randomised controlled trials of GCA, conducted in single or multi-centre settings, provided the patients had temporal and/or axillary artery ultrasound performed for diagnosis. We included studies 1) containing patients with suspected GCA; 2) using clinical diagnosis, an imaging test (US/PET CT) and/or TAB as the reference standard for GCA; 3) in which US was performed at any time from the clinical suspicion of GCA, 4) in which at least five patients had GCA, and at least five did not have GCA. Case reports, case series, conference abstracts and case-control studies were excluded as specificity could not be evaluated. Adult human subjects (age 50 years and above), clinically classified as suspected GCA, were included. The reference standard *clinical diagnosis* of GCA was considered when the treating clinician suspected GCA based on clinical criteria such as age ≥ 50 years, abnormal blood markers (CRP>5 mg/L, ESR >30mm/hr), unequivocal cranial symptoms of GCA and/or PMR symptoms and evidence of GCA by imaging (US, PET CT) or Positive TAB. All the participants must have had a temporal artery and/or axillary artery US to look for the halo sign and/or compression sign, occlusion, stenosis. Moreover, *TAB* was also used as a reference standard separately.

**Data Collection**

Study characteristics and data from 2 x 2 tables (true positive, false negative, false positive, true negative) were extracted by 1 reviewer (AS) and checked by a second reviewer (FC). If no consensus could be obtained, a third reviewer (KSMvdG) made the final decision. A standard data sheet was used to collect information on study characteristics. Authors of studies were not contacted. In case of potential overlap of patients between studies from the same hospital, data was obtained from the most extensive study for the meta-analysis. When multiple reference standards were used in the same study, the clinical diagnosis was used as

the primary reference standard for the data analysis. The other was used for sub-group analysis. Any disagreement between reviewers was either resolved by consensus or by consulting a third reviewer (KSMvdG).

**Quality assessment**

The risk of bias was evaluated by 2 reviewers (AS and FC) with the quality assessment of diagnostic accuracy studies (QUADAS-2) tool (448). Any disagreement between reviewers was resolved through discussion with other review authors (SI, JJ, BD). The QUADAS-2 tool focuses on the bias and applicability of study results regarding patient selection, the index test, the reference standard, and study flow and timing (448).

**Statistical analysis**

The halo sign's sensitivity and specificity, along with their 95% confidence intervals, were calculated for each study, and the total sample size of reviews was plotted.

Study heterogeneity was visually examined by plotting sensitivity and specificity in forest plots and receiver operating characteristics (ROC) space (449). We used hierarchical logistic regression modelling (bivariate model) (Supplementary figure 1) to determine pooled estimates of diagnostic accuracy parameters, i.e. sensitivity, specificity, diagnostic odds ratio and likelihood ratios. Stata V.15 software was used for the statistical analysis and creating HSROC plots. Forest plots were created in Review Manager 5.3.

**RESULTS:**

**Study Characteristics**

The initial search yielded 4023 unique studies. Based on title/abstract screening, 106 articles were selected for full-text screening. 23 articles were selected for the systematic review and meta-analysis (338,339,342,353,384,403,404,422,426,450–463). The flow of information through the review is illustrated in the PRISMA flow diagram (464)(465) (Figure 1).

A total of 2711 subjects were collected from twenty-three studies, and their characteristics are summarised in the study characteristics table (Table 10). There were 12 retrospective and 11 prospective studies performed at academic and non-academic centres. Clinical diagnosis was the most commonly used reference standard, while some reports presented TAB as the reference standard. A variable proportion of patients underwent unilateral or bilateral temporal artery (TA) US assessment (Table 13). The clinical diagnosis was mainly based on clinical and laboratory findings, imaging and/or TAB results. In the studies using clinical diagnosis as a reference standard (18 studies), all patients were reviewed to ensure the clinical diagnosis was not later revised. The majority of studies assessed the cranial arteries alone (15 studies), while others evaluated both cranial and extracranial arteries (8 studies). Most of the GCA studies tested the 'halo sign' as a main lesion to define vasculitis. Other US signs addressed (mostly in combination with the 'halo' sign) were stenosis and occlusion (353,450,455,458) and the 'compression sign' (338)(339). Two studies reported compression sign (338)(466), and four studies reported stenosis and occlusion along with halo sign (450)(353)(455)(458). Fifteen studies used TAB (342,353,426,450–455,458–463), and two studies used compression sign (338)(466) as reference. More than half of the publications

examined colour duplex US with frequencies of 5 to 15 MHz. The ultrasound specifications are summarised in table 11.

**Evaluation of Bias**

Patient selection and flow of timing were the primary sources of bias (Figure 12). Studies using TAB as the reference standard might have contributed to the selection bias, as there would be a strong initial clinical suspicion to request this invasive test. Studies using ACR 1990 clinical criteria as diagnosis standard were at high risk of bias, as the index test could have altered the initial clinical decision. The flow of timing had a considerable amount of risk of bias, as the index test was performed at various time periods from the initial clinical suspicion of GCA. Additional data and details on the risk of bias (RoB) assessment are summarised in figure 2 and supplementary figure 2. QUADAS-2 scale for diagnostic accuracy studies, the quality is reported in Supplementary Table 3.

**Meta-analysis**

Results of the pooled estimates for US signs of GCA compared to the clinical diagnosis or TAB as reference standard are summarised in Table 12. All 23 studies (patients n=2711) investigated the value of the 'halo' sign in comparison with the clinical diagnosis ± TAB, yielding a pooled sensitivity of 67% (95% CI 51 to 80) and a specificity of 95% (95% CI 89% to 98%). This gave a positive and negative likelihood ratio for the diagnosis of GCA of 14.2 (95% CI: 5.7-35.5) and 0.35 (95% CI 0.22-0.54), respectively (Figure 13A). When analysed, the halo sign with TAB as standard yielded a pooled sensitivity of 63% (95% CI:50-75) and a specificity of 90% (95% CI: 81-95). The halo sign against TAB as standard revealed a positive LR of 6.06 (95% CI: 3.34-11.0) and a negative LR of 0.41 (95% CI: 0.30-0.56) (Figure 13B). The analysis of the combining US signs (halo sign, stenosis or occlusion)

in comparison with clinical diagnosis or TAB (four studies, n=270) resulted in a sensitivity of 52 % (95% CI 18-84) and specificity of 81% (95% CI 64-91) (Supplementary figure 3A). The combination of halo sign and stenosis (four studies, n=230) resulted in a sensitivity of 43% (95% CI 12-80) and specificity of 85% (95% CI 66-94) (Supplementary figure 3B). Authors of two studies (n=140, both with low RoB), from the same research group, investigated the 'compression sign' (338)(466) and described the sensitivities between 77%–79% and a specificity of 100% of this compression sign when compared with the clinical diagnosis of cranial GCA. When comparing the studies done before 2010 (7 studies) and after 2010 (11 studies), later studies showed higher sensitivity of 71% (earlier studies- 63 %) and similar specificity 96% (earlier studies- 95%) (Supplementary table S4)

Forest plots and HSROC curves indicated that clinical diagnosis or TAB as a standard had limited heterogeneity, whereas halo sign with stenosis and occlusion or halo with stenosis showed high between-study heterogeneity (Supplementary Figure 1).

**DISCUSSION**

This systematic review and meta-analysis evaluated the role of halo sign in the assessment of GCA. When compared with previous meta-analysis, the diagnostic performance of the halo sign for the diagnosis of cranial GCA was of similar sensitivity (67% vs 68%-77%) (398)(442)(361)(467), but higher specificity (95% vs 81%-96%) (398)(442)(361)(467). When combining halo sign with occlusion or stenosis, the current study showed lower sensitivity (52% vs 78%)(467) and higher specificity (81% vs 79%)(467). This discrepancy could be due to the inclusion of high-quality studies and excluding overlapping studies, and might also be related to better equipment, with 5-15 MHz probes used in the earlier studies. Another reason could be that occlusion and stenosis is not as routinely assessed, as mentioned in OMERACT,

and certainly more work is needed to standardise the definition of these findings. A recent study showed when combining the GCA Pre-test probability score with the halo sign, the sensitivity increases to between 94%-100% (313).

The present study also showed a comparable diagnostic accuracy of the halo sign compared with TAB. US may be a more thorough GCA assessment than TAB, as it allows for detailed analysis of the temporal arteries along their entire length, minimising the effect of skip lesions (408). TAB is also an invasive procedure, which can have procedural complications, and is not readily available for re-assessment of the artery if relapse occurs. In line with these findings, a review by WA Schmidt et al. reported that biopsy has a relatively low yield compared to US in GCA diagnosis (392). The present study's statistical findings indicate the halo sign is a useful tool that could be incorporated in everyday clinical practice, as US is cost-effective and provides more accurate and specific results for the assessment of GCA. The TABUL study's findings provided significant results for the specificity and sensitivity of halo sign in GCA assessment, with the value of 69% and 82%, respectively (342). It asserts that the use of US in GCA assessment is highly dependent on the halo sign, as it determines the presence of an area of inflammation in the arteries. A recent publication of the novel halo score, graded with the halo thickness, confirms the halo sign and halo count are significantly correlated with inflammatory markers, ocular ischaemia and intimal hyperplasia on TAB(341).

Limitations of this systematic review and meta-analysis are the inclusion of both prospective and retrospective observational studies. The retrospective studies might have contributed to bias in analysing the final data. It has not been possible to evaluate the specific issues related to US operator and image interpretation variability (468). The reviews did not present inter-

rater/intra-rater reliability data. Different sonographic skill levels of the rheumatologists or sonographers may have had an impact on the final results. When the colour intensity is more robust, such as in smaller vessels, it is easier to distinguish the dark, hypoechoic halo sign (467). Other malignant conditions, ANCA vasculitis, infections or poor US technique, can give rise to a false positive halo (453). A further issue was the methodologies used between the studies. Studies concluding US is superior to TAB in diagnosing GCA vary in their design (422)(463). We included studies if they had US performed more than two weeks from the initial clinical suspicion of GCA, even though they would have been exposed to a high dose of corticosteroids, which may reduce the halo thickness and accuracy of US. When the ACR classification criteria for GCA were applied as the reference standard (442)(334), the meta-analyses reported a lower sensitivity and a higher specificity of the halo sign for GCA diagnosis. However, these criteria were designed for classification and research purposes, and are inadequate for diagnosing GCA in clinical practice (395). Therefore, ACR criteria as the reference standard could be a limiting factor in this study.

## CONCLUSION AND RECOMMENDATION

This meta-analysis shows that the US halo sign has a significant role in the assessment and diagnosis of GCA. US is a sensitive and specific approach for GCA assessment, which seems to be improving with better equipment and user familiarity with US techniques. However, the studies analysed showed heterogeneity in their design and outcomes. Therefore, it is recommended that future researchers conduct multicentre prospective studies for analysing the effectiveness of the halo sign in the assessment of GCA, with a standardised study protocol.

**Figure Legends**

**Figure 11.** PRISMA flow diagram

**Figure 12.** Overall Summary of QUADAS-2 items

**Figure 13.** Forest plot of the sensitivity and specificity of the temporal artery ultrasonography derived halo sign compared to the final diagnosis of GCA in patients with suspected clinical diagnosis (A) and Temporal artery biopsy as standard (B)

**Supplementary information**

**Supplementary figure S1**. A: Summary receiver operating characteristic (sROC) curves of the temporal artery ultrasonography derived halo sign compared to the final diagnosis of GCA in patients with suspected disease; B: Summary receiver operating characteristic (sROC) curves of the temporal artery ultrasonography derived halo sign compared to the final diagnosis of GCA in patients with the suspected disease (Temporal artery biopsy as reference); C: Summary receiver operating characteristic (sROC) curves of the temporal artery ultrasonography derived halo sign with stenosis and occlusion; D: Summary receiver operating characteristic (sROC) curves of the temporal artery ultrasonography derived halo sign with stenosis

**Supplementary figure S2-** Detailed summary of QUADAS-2 Items

**Supplementary figure S3-** A: analysis of Halo sign with stenosis and occlusion, B: analysis of halo sign with stenosis

**Supplementary Table S1-** Search strategy- PICO

**Supplementary Table S2-** Search strategy- Keywords

**Supplementary Table S3-** QUADAS 2 tool guidance for authors

**Supplementary Table S4** - Results of sensitivity/Specificity analysis of studies, Early (before 2010) vs later (after 2010)

**Table 10. Study characteristics and general information**

| Author/Year (No of patients) | Journal | Period of patients' inclusion | Study design | Hospital setting | Speciality identifying patients | Speciality referring patients | Included patients (patients undergoing ) | Consecutive patients | Avoiding case-control | Lab results reported before treatment | Type of reference standard | Test performed in every patient with clinical diagnosis | Focus diagnostic testing (arteries) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Schmidt et al. 1997(336) (n=112) | Rheumatology | January 1994 to October 1996 | Retrospective | Academic | Ophthalmology department | Primary care and hospital departments | TAB | Yes | Yes | Unclear | Clinical diagnosis (+TAB) | TAB, US | Cranial |
| Nesher et al. 2002(453) (n=69) | The Journal of Rheumatology | Unclear (2-year time span) | Prospective | Academic | Central imaging registry | Unclear | US | Yes | Yes | Yes | Clinical diagnosis (+TAB) | TAB, US | Cranial |
| Salvarani et al. 2002(451) (n=86) | Annals of Internal Medicine | January 1998 to October 1999 | Prospective | Academic | Central pathology/Surgery registry | Unclear | TAB | Yes | Yes | Unclear | Clinical diagnosis (+TAB) | TAB, PET-CT, CTA | Cranial and extra-cranial |
| Lesar et al. 2002(463) (n=32) | Journal of Vascular surgery | November 1997 to April 2001 | Prospective | Academic | Central imaging registry | Unclear | US | Yes | Yes | NA | TAB | TAB, US | Cranial |
| Reinhard et al. 2004(469) (n= 83) | Clinical and Experimental Rheumatology | July 1999 to July 2002 | Prospective | Academic | Multiple hospital departments | Unclear | clinical evaluation | Yes | Yes | NA | Clinical diagnosis (+TAB) | TAB, US | Cranial |
| Romera-Villegas et al. 2004(460) (n= 68) | Clinical Rheumatology | May 1998 to November 2002 | Retrospective | Academic | Central pathology/ Surgery registry | Unclear | TAB | Yes | Yes | Unclear | TAB | TAB, US | Cranial |
| Karahaliou et al. 2006(422) (n=55) | Arthritis Research & Therapy | 2000 to 2004 | Prospective | Academic | Multiple hospital departments | Unclear | clinical evaluation | Yes | Yes | Unclear | Clinical diagnosis | US | Cranial |
| Lopez et al. 2009(426) (n= 47) | Clinical and Experimental Rheumatology | March 2003 to July 2006 | Retrospective | Academic | Central pathology/Surgery registry | Unclear | TAB | Yes | Yes | NA | Clinical diagnosis (+TAB) | TAB | Cranial |
| Maldini et al. 2010(455) (n=31) | Journal of Nuclear Medicine | January 2002 to September 2008 | Retrospective | Academic | Central imaging registry | Unclear | PET | Yes | Yes | Unclear | Clinical diagnosis (+TAB) | TAB | Cranial and extra-cranial |
| Pfenninger et al. 2012(461) (n=57) | Journal of Rheumatology | January 1999 to February 2011 | Retrospective | Non-Academic | Central pathology/Surgery registry | Unclear | TAB | Yes | Yes | Unclear | TAB | TAB | Cranial |
| Aschwanden et al. 2012(338) (n=80) | Ultraschall in der Medizin | March 2009 to September 2011 | Prospective | Academic | Multiple hospital departments | Unclear | US | Yes | Yes | NA | Clinical diagnosis | US | Cranial |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Black et al. 2013(457) (n=50) | International Journal of Rheumatic diseases | September 2003 to September 2011 | Retrospective | Academic | Central imaging registry | Primary care and hospital department | US | Yes | Yes | NA | Clinical diagnosis | US | Cranial |
| Muratore et al. 2013(462) (n=160) | British Journal of Rheumatology | 2002 to 2010 | Retrospective | Academic | Central pathology/Surgery registry | Primary care | TAB | Yes | Yes | Unclear | TAB | TAB | Cranial |
| ASchwanden et al. 2015(466) (n= 60) | Clinical and Experimental Rheumatology | October 2011 to December 2012 | Prospective | Academic | Multiple hospital departments | Unclear | clinical; evaluation | Yes | Yes | NA | Clinical diagnosis | US | Cranial |
| Croft et al. 2015(456) (n=87) | Journal of the Royal College of Physicians of Edinburgh | January 2005 to January 2014 | Retrospective | Academic | Central imaging registry | Unclear | US | Yes | Yes | NA | Clinical diagnosis | US | Cranial and extra-cranial |
| Luqmani et al. 2016(342) (n=381) | Health Technology Assessment | June 2010 to July 2016 | Prospective | Non-academic and Academic | Multiple hospital departments | Unclear | TAB | Yes | Yes | Yes | Clinical diagnosis (+TAB) | TAB, US | Cranial and extra-cranial |
| Bilyk et al. 2017(458) (n=71) | American Ophthalmological society | 2017 (14 months) | Retrospective | Academic | Central imaging registry | Unclear | US | YES | Yes | NA | Clinical diagnosis (+TAB) | TAB, US | Cranial and extra-cranial |
| Porto et al. 2018(353) (n=56) | Rheumatology clinica | February 2015-July 2016 | Prospective | Academic | Central pathology/Surgery registry | Unclear | TAB | Yes | Yes | Unclear | Clinical diagnosis (+TAB) | TAB, US | Cranial |
| Nielsen et al. 2019(404) (n=90) | Rheumatology | October 2014 to June 2018 | Prospective | Academic | Rheumatology department | Unclear | clinical evaluation | Yes | Yes | NA | Clinical diagnosis | PET-CT, US | Cranial and extra-cranial |
| Sammel et al. 2019(384) (n=6) | Rheumatology | May 2016 to July 2018 | Prospective | Academic | Rheumatology department | Unclear | clinical evaluation | Yes | Yes | NA | Clinical diagnosis | US | Cranial |
| Sommer et al. 2019(459) (n=68) | Clinical and Experimental Ophthalmology | 2015 to 2017 | Retrospective | Academic | Ophthalmology department | Hospital department | TAB | Yes | Yes | Unclear | TAB | TAB | Cranial |
| Mukhtyar et al. 2019(454) (n=25) | Clinical Rheumatology | March 2013 | Retrospective | Academic | Multiple hospital departments | Unclear | TAB and US | Yes | Yes | Yes | Clinical diagnosis (+TAB) | TAB, US | Cranial and extra-cranial arteries |
| Hop et al. 2020(403) (n=113) | Rheumatology | January 2013 to November 2017 | Retrospective | Academic | Central imaging registry | Unclear | US | Yes | Yes | Unclear | Clinical diagnosis | US | Cranial and extra-cranial arteries |

**Table 11. Ultrasound specifications**

| Author/Year | Manufacturer | Equipment model | Type of probe | Probe frequency | Unilateral/bilateral TA assessment | Axillary artery assessment | Index test | Halo thickness | Time from clinical assessment to US |
|---|---|---|---|---|---|---|---|---|---|
| Schmidt et al. 1997 | ATL Bothell | Ultramark 9HDI | Linear | 5-10 MHz | Bilateral | Yes | Halo, Stenosis/occlusion | Yes | 10 days |
| Nesher et al. 2002 | Acuson | Sequoia 512 | Linear | 15 – 8 MHz | Uni/Bilateral | No | Halo | Yes | 3 days |
| Salvarani et al. 2002 | Àcuson Corp | Aspen | Linear | 5-10 MHz | Bilateral | No | Halo | Yes | NA |
| Lesar et al. 2002 | ATL Ultrasound Inc | ATL 5000 | Linear | 7 – 5 MHz | Uni/Bilateral | No | Halo, Stenosis | NA | NA |
| Reinhard et al. 2004 | ATL, Bothell | HDI 5000 | Linear | 5 – 10 MHz | Unilateral | No | Halo | NA | 6 days |
| Romera-Villegas et al. 2004 | Philip Bothell | HDI 5000 | Linear | 5 – 10 MHz | Unilateral | Yes | Halo | NA | NA |
| Karahaliou et al. 2006 | General Electric | LA39 | Linear array | 7 – 10 MHz | Uni/Bilateral | Yes | Halo, Stenosis | Yes | 3 months |
| Lopez et al. 2009 | Toshiba | Aplio-80 | Linear | 5 – 10 MHz | Uni/Bilateral | No | Halo, stenosis | Yes | 1-10 days |
| Maldini et al. 2010 | ATLToshiba | Apogee 800/Aplio 80 | Pencil probe | 5/7.5 MHz | Uni/Bilateral | No | Halo, Stenosis/Occlusion | BA | 30 days |
| Pfenninger et al. 2012 | Toshiba | Aplio 80 (SSA-770) | Linear | 5 – 10 MHz | Uni/Bilateral | Yes | Halo | Yes | 6 months |
| Aschwanden et al. 2012 | Philips, Best, Netherland | iU22 Duplex | Linear | 5 – 17 MHz | Uni/Bilateral | No | Halo/compression | NA | NA |
| Black et al. 2013 | Philips HDI, 5000 Philips IU22 | iU22 Duplex | Linear | 17 MHz | Uni/Bilateral | No | Halo | NA | NA |
| Muratore et al. 2013 | ATL Ultrasound Inc | ATL HDI 5000 | Linear | 7 – 5 MHz | Uni/Bilateral | No | Halo, Stenosis | Yes | NA |
| ASchwanden et al. 2015 | Philips Best, Netherlands | Iu22 Duplex | Linear | 5 – 17 MHz | Uni/Bilateral | No | Halo/Compression | Yes | NA |
| Croft et al. 2015 | Hitachi Medical systems | Hitachi HA700 | Multi-D linear | 13 – 5 MHz | Uni/Bilateral | No | Halo | Yes | 3 months |
| Luqmani et al. 2016 | NA | NA | Multi-D linear | 10/6 MHz | Uni/Bilateral | Yes | Halo | Yes | 10 days |
| Bilyk et al. 2017 | Mylab Twice | LA435 | Multi-D linear | 22 – 12.5 MHz | Uni/Bilateral | Yes | Halo, Stenosis/Occlusion | Yes | NA |
| Porto et al. 2018 | Mindray Z6 | Mindray Z6 | A7L4P linear | 5 – 10 MHz | Uni/Bilateral | No | Halo, stenosis/occlusion | NA | 3 months |
| Nielsen et al. 2019 | Hitachi | HI VISION Avius | EUP-L75 | 5 – 18 MHz | Uni/Bilateral | Yes | Halo | Yes | 3 months |
| Sammel et al. 2019 | NA | NA | NA | NA | Uni/Bilateral | No | NA | NA | NA |
| Sommer et al. 2019 | Philips | Affiniti | Linear | 5 -10 MHz | Bilateral | No | NA | NA | NA |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Mukhtyar et al. 2019 | Toshiba | Viamo | Linear | 4 – 14 MHz | Uni/Bilateral | No | Halo | Yes | 7 days |
| Hop et al. 2020 | Siemens Healthineers | ACUSON S2000 | 18L6 high density | 9 – 16 MHz | Uni/Bilateral | Yes | Halo | Yes | 6 months |

**Table 12. Meta-analysis of diagnostic accuracy of ultrasound signs for a diagnosis of Giant cell arteritis (GCA). A temporal artery biopsy was also performed in part of** studies with the clinical diagnosis as the reference standard for GCA.

| Index test | Reference standard | Number of patients | Number of studies | LR+ (95% CI) | LR- (95% CI) | Sensitivity % (95% CI) | Specificity % (95% CI) | DOR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Halo Sign | Clinical diagnosis ±TAB | 1502 | 18 | 14.21 (5.7 – 35.5) | 0.35 (0.22 – 0.54) | 67 (51-80) | 95 (89 – 98) | 40.9 (12.1-137.5) |
| Halo Sign | TAB | 1209 | 15 | 6.06 (3.34 – 11.0) | 0.41 (0.30 – 0.56) | 63 (50 – 75) | 90 (81 – 95) | 14.7 (7.3 – 29.6) |
| Halo sign ± Stenosis ± Occlusion | Clinical diagnosis/TAB | 270 | 4 | 2.70 (0.71 – 10.26) | 0.60 (0.24 – 1.51) | 52 (18 – 84) | 81 (64 – 91) | 4.5 (0.48 – 42.6) |
| Halo sign ± Stenosis | Clinical diagnosis/TAB | 230 | 4 | 2.92 (0.90 – 9.46) | 0.67 (0.73 – 3.04) | 43 (12 – 80) | 85 (66 – 94) | 4.4 (0.71 – 26.6) |

CI, confidence interval; clinical diagnosis, final diagnosis made according to the ACR criteria or physician diagnosis; DOR, Diagnostic odds ratio; LR, likelihood ratio; TAB, temporal artery biopsy.

**Figure 11: PRISMA Flow Diagram**

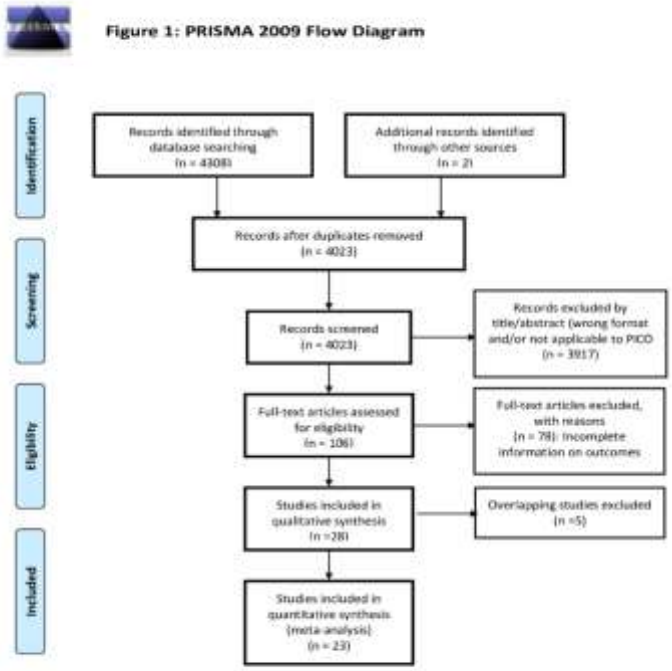
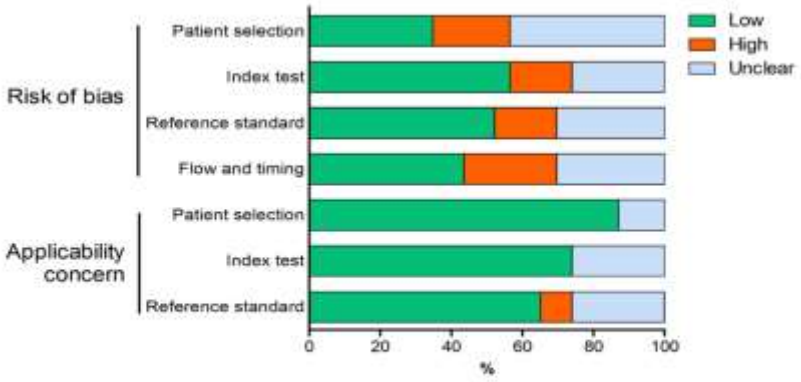


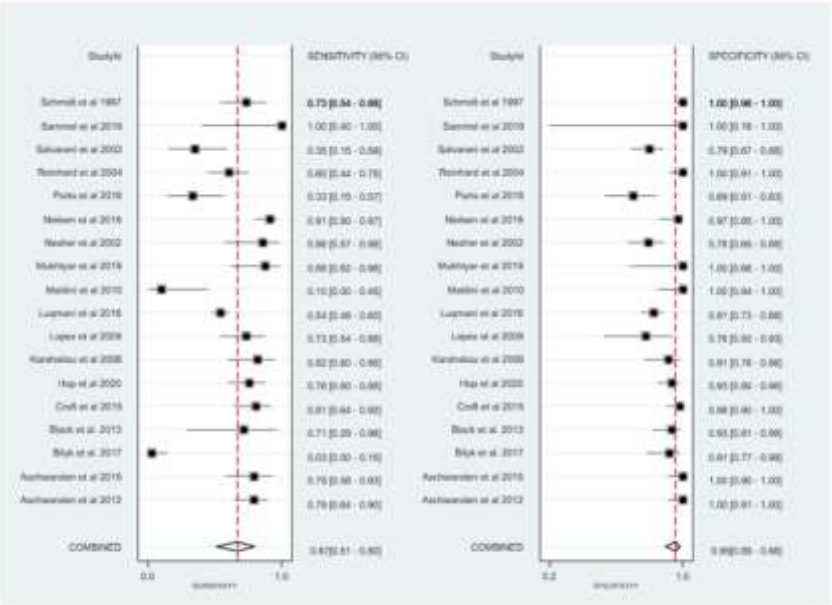

**Figure 12: Overall Summary of QUADAS-2 items**



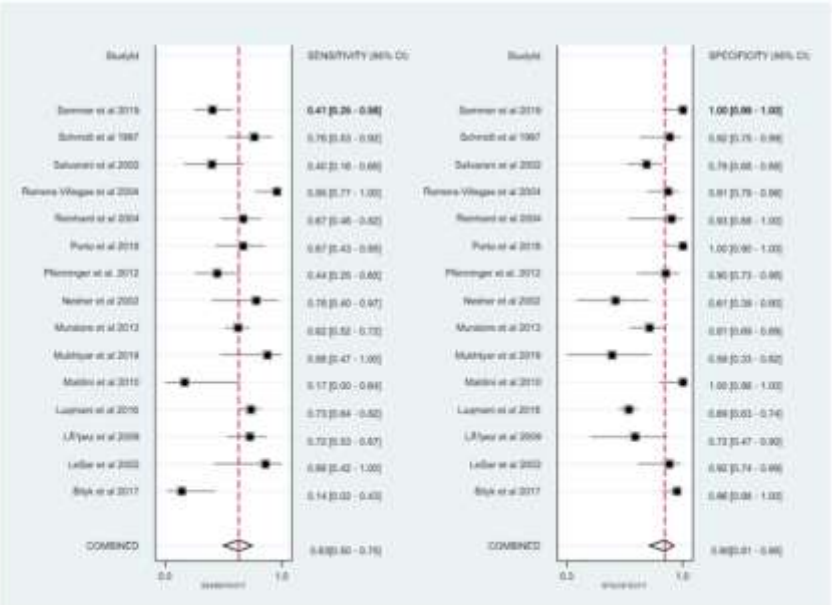

Risk of bias and concern of applicability was evaluated for the 23 studies included in the systematic review and meta-analysis

**Figure 13**: Forest plot of the sensitivity and specificity of the temporal artery ultrasonography derived halo sign for GCA. (A) Studies with the clinical diagnosis as the reference standard for GCA. Temporal artery biopsy was performed in part of these studies. (B) Studies with the temporal artery biopsy as the reference standard for GCA.

A: Halo Sign (Clinical diagnosis as standard)



B: Halo Sign (Temporal artery biopsy as standard)



### *2.4.2 US reliability- real-life reliability exercise*

## INTRODUCTION:

Ultrasound is an evolving first investigation of choice and recommended by EULAR in any suspected Giant cell arteritis. Halo sign is a recognised US sign to diagnose GCA. However, it is used in a dichotomous way. Recent meta-analysis shows halo sign has a sensitivity of 67% and specificity of 95% in diagnosing GCA compared with clinical and/or temporal artery biopsy as standard. Therefore, our group is in developing a halo score to qualify the inflamed segments of the cranial and axillary arteries (HAS GCA study) to diagnose GCA. Although, US is non-invasive and well tolerated by the patients, it is operator dependent. Therefore, it is imperative to have a standard validity of the assessment through a reliability exercise among vascular sonographers. We have initiated this exercise among our HAS GCA sonographers to check the validity of our study.

**Study Aim:**

validate the test-retest and inter-tester reliability of the IMT and HS of the study

**Raters' selection:**

At the end of the two days 8$^{th}$ GCA ultrasound international workshop and symposium in September 2021, 5 sonographers who were part of the HAS GCA were invited to participate in this exercise. All the sonographers' profile was collected through a structured proforma prior to the assessment. All of them were actively practising vascular US and they had the opportunity to refresh their skills during the 2 days' workshop under experienced mentors.

**Patients' selection:**

5 patients were randomly selected from the pool of patients attended the GCA clinics at the Southend University Hospital. Volunteered patients were invited to participate in this exercise. Patients were selected with pathology in cranial and large vessel and a control with

no previous history of GCA. Patients were selected by an independent assessor (BD) who was not a rater for this exercise. Patients' clinical information is blinded to the sonographers.

**Study design:**

definition of the halo sign and halo score was re-defined during the workshop. Halo sign cut-off values of Intimal medial thickness (IMT) for each branch were as per the published data. Halo score (HS) was calculated as per halo score grading table; HAS GCA study. There were 2 rounds of assessment. Each round had 5 raters and 5 patients (figure). Each rater was allowed to spend maximum of 20 minutes with each patient. Independent person (BD) acted as a timekeeper. 8 images from each patient were required (bilateral common, parietal, frontal temporal arteries and axillary arteries). This gave a total of 400 images after completion of both rounds.

**Statistical analysis:**

In this exercise only descriptive statistics were used. Test-retest and inter-tester reliability were calculated using the Intra class coefficient (ICC) correlation. ICC describes how strongly units in the same group resemble each other. It also used to assess the consistency, or conformity of measurements made by multiple observers measuring the same quality, assuming a normal distribution, continuous and independent variables. ICC were interpreted with a value between 0 and 1, where values below 0.5 indicate poor reliability, between 0.5 and 0.75 moderate reliability, between 0.75 and 0.9 good reliability, and any value above 0.9 indicates excellent reliability (Koo et al. J Chiropr Med. 2016). The statistical analysis was performed using SPSS V27.

# RESULTS

1. **Test-retest reliability: (TIME)**

   A. **Test-retest reliability of IMT measurements**

The total overall score based on 200 pairs of measurements (5 raters and 5 patients across 8 sites) absolute value of IMT on both occasions was excellent reliability with ICC of 0.99 (95% CI, 0.97—0.99).

When considering the individual arteries, Axillary arteries showed excellent reliability (RA; 0.98, LA; 0.96) compared to cranial arteries (ICC= 0.09 – 0.74). Similar results were seen with HS (Table 10). However, collectively temporal (ICC=0.90) and Axillary (ICC=0.99) arteries showed excellent reliability (Table 13)

   B. **Test-retest reliability of HALO SCORE**

The overall score based on 200 pairs of repeated measurements of HS was good reliability with an ICC of 0.88 (95% CI, 0.85-0.91).

When considering the individual arteries, Axillary arteries showed excellent reliability (RA; 0.96, LA; 0.98) compared to cranial arteries (ICC= -0.17 – 0.84). However, collectively temporal (ICC=0.74) arteries showed moderate reliability and Axillary (ICC=0.97) arteries showed excellent reliability (Table 13)

2. **Inter-tester reliability: (AGREEMENT)**

This showed the reliability within the same rater between rounds 1&2. RELIABILITY ACROSS ALL 5 TESTERS – each tester took 80 measurements (sets of 5)

   A. **Inter-tester reliability of IMT measurements**

The absolute value of IMT on both occasions was excellent reliability with ICC of 0.97 (95% CI, 0.96—0.98).

When considering the individual arteries, Axillary arteries showed excellent reliability (RA; 0.96, LA; 0.94) compared to cranial arteries (ICC= 0.10 – 0.77). Similar results were seen with HS (Table 2). However, collectively temporal (ICC=0.63) arteries showed moderate, and Axillary (ICC=0.95) arteries showed excellent reliability (Table 14)

**B. Inter-tester reliability of HALO SCORE**

The overall score based on 80 pairs of repeated measurements of HS was good reliability with an ICC of 0.88 (95% CI, 0.83-0.91).

When considering the individual arteries, Axillary arteries showed excellent reliability (RA; 0.96, LA; 0.96) compared to cranial arteries (ICC= 0.18 – 0.76). However, collectively temporal (ICC=0.74) arteries showed moderate reliability, and Axillary (ICC=0.96) arteries showed excellent reliability (Table 14)

**Table 13: Test-retest reliability of measures of GCA shown as a total score, temporal, axillary and individual as /IMT/HS Total, temporal, axillary and Individual arteries Intra class coefficient (ICC) correlation**

| | | | IMT | | | HS | | |
|---|---|---|---|---|---|---|---|---|
| | **No of Pairs** | **Artery** | **Value** | **95% CI** | **Reliability** | **Value** | **95% CI** | **Reliability** |
| **Total (200 pairs)** | **200** | | **0.988** | **0.974 – 0.995** | **Excellent** | **0.884** | **0.849 – 0.911** | **Good** |
| **Temporal arteries (150 pairs)** | **150** | **Temporal** | 0.898 | 0.782 – 0.954 | Excellent | 0.744 | 0.664-0.808 | Moderate |
| | **25** | **RC** | 0.682 | 0.404-0.846 | Moderate | 0.789 | 0.582 -0.901 | Good |
| | **25** | **RP** | 0.089 | -0.322 -0.465 | Poor | -0.116 | -0.503 – 0.295 | Poor |
| | **25** | **RF** | 0.743 | 0.504 – 0.877 | Moderate | 0.646 | 0.349 – 0.826 | Moderate |
| | **25** | **LC** | 0.736 | 0.472 – 0.877 | Moderate | 0.429 | 0.041 – 0.702 | Poor |
| | **25** | **LP** | 0.713 | 0.454 – 0.862 | Moderate | 0.513 | 0.155 – 0.752 | Moderate |
| | **25** | **LF** | 0.732 | 0.484 -0.872 | Moderate | 0.844 | 0.677 – 0.928 | Good |
| **Axillary arteries (50 pairs)** | **50** | **Axillary** | 0.991 | 0.981 – 0.996 | Excellent | 0.973 | 0.952-0.984 | Excellent |
| | **25** | **RA** | 0.985 | 0.968 – 0.994 | Excellent | 0.964 | 0.921 – 0.984 | Excellent |
| | **25** | **LA** | 0.962 | 0.917 – 0.983 | Excellent | 0.98 | 0.970 – 0.994 | Excellent |

**Table 14: Inter-tester reliability of measures of GCA shown as a total score, temporal, axillary and individual as /IMT/HS Total, temporal, axillary and Individual arteries Intra class coefficient (ICC) correlation**

| | | | IMT | | | HS | | |
|---|---|---|---|---|---|---|---|---|
| | **No of measurement** | **Artery** | **Value** | **95% CI** | **Reliability** | **Value** | **95% CI** | **Reliability** |
| **Total** | **80** | | **0.970** | **0.958 – 0.979** | **Excellent** | **0.876** | **0.834 – 0.912** | **Good** |
| **Temporal arteries** | **60** | **Temporal** | 0.628 | 0.519 – 0.731 | Moderate | 0.739 | 0.652 – 0.817 | Moderate |
| | **10** | **RC** | 0.562 | 0.279 – 0.833 | Moderate | 0.646 | 0.387 – 0.873 | Moderate |
| | **10** | **RP** | 0.101 | -0.084 – 0.478 | Poor | 0.182 | -0.040 – 0.569 | Poor |
| | **10** | **RF** | 0.769 | 0.551 – 0.924 | Good | 0.656 | 0.396 – 0.878 | Moderate |
| | **10** | **LC** | 0.754 | 0.505 – 0.920 | Good | 0.455 | 0.187 – 0.772 | Poor |
| | **10** | **LP** | 0.639 | 0.378 – 0.870 | Moderate | 0.532 | 0.259 – 0.818 | Moderate |
| | **10** | **LF** | 0.608 | 0.342 – 0.855 | Moderate | 0.767 | 0.550 – 0.923 | Good |
| **Axillary arteries** | **20** | **Axillary** | 0.950 | 0.906 – 0.977 | Excellent | 0.960 | 0.926 – 0.982 | Excellent |
| | **10** | **RA** | 0.956 | 0.895 – 0.987 | Excellent | 0.962 | 0.910 – 0.989 | Excellent |
| | **10** | **LA** | 0.939 | 0.846 - 0.983 | Excellent | 0.962 | 0.906 – 0.989 | Excellent |

## DISCUSSION:

The reliability exercise of this study revealed overall excellent reliability with IMT measurements and good reliability with Halo Score. There is a variation between the temporal arteries and axillary artery reliability. Temporal arteries showed a more mixture of reliability values, except RP showed poor relativity. RP was poor, possibly because of ICC bias towards measures of large value which artificially affect the ICC. Perhaps it also depends on the size of the artery.

IMT is measured in millimetres, and HS is a score defined within a range of the IMT. IMT is more prone to errors, and HS is more robust and clinically relevant.

Among the raters, rater-5 had the best, and rater-1 had the worst reliability. However, all five raters had high ICC values and agreed well. All the sonographers are actively involved in daily scanning in their respective departments with participating in the fast track GCA clinics with 3-10 years of experience. The experience of the sonographers reflect on the results of this exercise.

## CHAPTER THREE: AIMS AND OBJECTIVES

**Published article:**

The following material in this chapter was published in August 2020 during the PhD. This published article is the study protocol of the Halo score (temporal artery, its branches and axillary artery) as a diagnostic, prognostic, and disease-monitoring tool for Giant cell arteritis. The references, table and figure numbers in this article below are amended from the original publication to reflect the continuity of the PhD thesis references, Tables and figures.

***AIMS:***

*To determine whether the severity of vessel wall oedema (halo/IMT) in the common temporal artery, its branches and the axillary arteries, as measured by a composite ultrasound score, is of prognostic value in predicting severity and outcomes in GCA.*

*To determine the prognostic and monitoring value of the halo score (HS) and Total Halo Score (THS) in GCA, regarding predicting outcomes (remission, refractory or relapsing disease) in GCA. We will also determine the diagnostic value of the HS and THS for discriminating GCA from non-GCA*

Sebastian et al. BMC Rheumatology (2020) 4:35
https://doi.org/10.1186/s41927-020-00136-5

BMC Rheumatology

STUDY PROTOCOL Open Access

Halo score (temporal artery, its branches and axillary artery) as a diagnostic, prognostic and disease monitoring tool for Giant Cell Arteritis (GCA)

Alwin Sebastian[1,2], Kornelis S. M. van der Geest[3], Fiona Coath[4], Prisca Gondo[5], Abdul Kayani[1], Craig Mackerness[5], Bernard Hadebe[5], Sue Innes[6], Jo Jackson[6] and Bhaskar Dasgupta[1,2*]

.**Authors:**

1. Alwin Sebastian, Rheumatology, Mid and South Essex University Hospital Groups, Southend University Hospital, Westcliff-On-Sea, Essex, UK, University of Essex, UK
2. Kornelis S M van der Geest, Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
3. Fiona Coath, Norfolk and Norwich University hospitals NHS Foundation Trust, Colney Ln, Norwich, UK
4. Abdul Kayani, Rheumatology, Mid and South Essex University Hospital Groups, Southend University Hospital, Westcliff-On-Sea, Essex, UK
5. Craig Mackerness, R&D, Mid and South Essex University Hospital Groups, Southend University Hospital, Westcliff-On-Sea, Essex, UK
6. Prisca Gondo, R&D, Mid and South Essex University Hospital Groups, Southend University Hospital, Westcliff-On-Sea, Essex, UK
7. Bernard Hadebe, R&D, Mid and South Essex University Hospital Groups, Southend University Hospital, Westcliff-On-Sea, Essex, UK
8. Sue Innes, School of Sport, Rehabilitation and exercise sciences, Colchester campus, University of Essex, UK
9. Jo Jackson, School of Sport, Rehabilitation and exercise sciences, Colchester campus, University of Essex, UK
10. Bhaskar Dasgupta, Rheumatology, Mid and South Essex University Hospital Groups, Southend University Hospital, Westcliff-On-Sea, Essex, UK, University of Essex, UK

## Corresponding author:

Name: Prof Bhaskar Dasgupta, Email: Bhaskar.dasgupta@southend.nhs.uk

## Abstract:

**Background:**

Giant cell arteritis (GCA) is a common large vessel vasculitis of the elderly, often associated with sight loss. Glucocorticoids (GC remain the mainstay of treatment, although biologic treatments have been approved. Biomarkers predicting disease severity, relapse rates and damage are lacking in GCA.

EULAR recommends ultrasound (US) as the first investigation for suspected GCA. The cardinal US finding, a non-compressible halo, is currently categorised as either negative or positive. However, the extent and severity of this finding may vary.

In this study, we hypothesise whether the extent and severity of the halo sign [calculated as a single composite Halo score (HS)] of temporal and axillary arteries may be of diagnostic, prognostic and monitoring importance; whether baseline HS is linked to disease outcomes, relapses and damage; whether HS can stratify GCA patients for individual treatment needs; whether HS can function as an objective monitoring tool during follow up.

**Methods:**

This is a prospective, observational study. Suspected GCA Participants will be selected from the GCA FTC at the participating centres in the UK. Informed consent will be obtained, and patients managed as part of standard care. Patients with GCA will have HS (temporal and axillary arteries) measured at baseline and months 1,3,6 and 12 long with routine clinical assessments, blood sampling and patient-reported outcomes (EQ5D). Non-GCA patients will be discharged back to the referral team and will have a telephone interview in 6 months

We aim to recruit 272 suspected GCA referrals which should yield 68 patients (25% of referrals) with confirmed GCA. The recruitment will be completed in one year with an estimated total study period of 24 months.

**Discussion:**

The identification of prognostic factors in GCA is both timely and needed. A prognostic marker, such as the HS, could help to stratify GCA patients for an appropriate treatment regimen. Tocilizumab, an IL-6R blocking agent, switches off the acute phase response (C-Reactive Protein), making it difficult to measure the disease activity. Therefore, an independent HS, and changes in that score during treatment and follow-up, maybe a more objective measure of response compare to patient-reported symptoms and clinical assessment alone.

**Trial registration:**

Research ethics committee (REC- London- Stanmore) # 10/LO/1375, 22/08/2019

National Health Services Health Research Authority (HRA) # 264294, 11/09/2019

University of Essex # ETH1920-0145, 17/10/2019

**Keywords:**

Outcomes in GCA

Risk stratification

Prognostic factors

Halo score

GCA probability score

Clinical severity index

Glucocorticoid toxicity

## Background

Giant cell arteritis (GCA) is a common form of systemic vasculitis characterised by granulomatous inflammation of large and medium-sized arteries (470). GCA predominantly affects Caucasian, older people (>50 years), with a peak incidence among those 70-80 years old (469,470). The incidence of GCA rises with increasing age, ranging from 2.6 per 100,000 in patients aged 50-59 to 44.6 per 100,000 in patients over the age of 80 (471). GCA predominantly involves branches of the external carotid arteries such as the temporal arteries and the aorta and its large branches, including the subclavian and axillary arteries. Common presenting symptoms include new headache, scalp tenderness, jaw claudication, diplopia and amaurosis fugax (362,469,470). GCA can cause significant morbidity and ischaemic complications, including irreversible sight loss. Other complications include aortitis, myocardial infarction and stroke. The 1990 American College of Rheumatology (ACR) classification criteria were not intended for diagnosis (472) and may not be accurate, particularly for cases with ophthalmic involvement (333). The criteria have low specificity and predictive values (334,469,473). Screening tests are vital as the GCA symptoms can be often non-specific and missing the diagnosis can be devastating (463).

Glucocorticoids (GC) have remained the cornerstone of treatment for GCA (166), although cohort studies show only 15-20% sustained remission with glucocorticoids alone Glucocorticoid-sparing treatments in GCA are also needed due to the harmful effects of long-term glucocorticoid use. This includes hypertension, hyperglycaemia, osteoporosis, cushingoid changes, mood disturbance and electrolyte imbalance, but this is not an exhaustive list (180,437). It is recommended to start GC immediately in strongly suspected GCA pending investigations(436). Targeted treatments have recently been introduced, but heterogeneity in

disease outcomes has still been observed. In GiACTA, the landmark trial of Tocilizumab in GCA that provides the evidence base for its current use, 42% of participants randomised to weekly Tocilizumab still did not achieve sustained remission (168). Currently, validated biomarkers predicting disease severity, relapse rates and damage are lacking in GCA.

A positive temporal artery biopsy (TAB) has been the gold standard for histological diagnosis of GCA (440,474,475). However, a biopsy is invasive, and it lacks sensitivity. This is particularly true in extra-cranial involvement, termed large-vessel GCA (LV-GCA), where access to sample material has obvious practical constraints and is usually identified incidentally following cardiovascular surgery (342). Non-invasive imaging techniques, including ultrasound (US), Magnetic resonant image (MRI) and position emission tomography (PET-CT) are increasingly being used to identify these patients (402,404,441).

Ample evidence now indicates that US of temporal arteries can promptly diagnose cranial forms of GCA, as well as screening for LV-GCA at the axillary arteries (476). US is a safe, non-invasive and higher sensitivity, particularly in extra-cranial disease. It is a relatively quick procedure (477), often delivered as a point of care test, well tolerated by patients and is suitable for follow-up examinations. Timely diagnosis of GCA by ultrasound in GCA fast track clinics has resulted in a significant reduction in permanent visual loss (7,309,311).

The EULAR recommendations for imaging in Large Vessel Vasculitis recommend US of temporal and/or axillary arteries as the first imaging modality, where there is adequate expertise and equipment, particularly in patients with suspected predominantly cranial GCA (4). Estimation of GCA probability has become important given recent EULAR recommendations suggesting different diagnostic strategies in patients with low, intermediate or high GCA

probability. In patients where there is a high clinical suspicion of GCA and an initial positive imaging test e.g. US, the diagnosis of GCA may be made without additional investigations (e.g. biopsy or further imaging). In patients with a low clinical probability and a negative imaging result, the diagnosis of GCA can be considered unlikely, and the patient reassured (342). There is also a report from Southend suggesting that the 'pre-test GCA Probability Score' may be a useful tool for rating the pre-test probability of GCA, stratifying patients into 'low' or 'not-low' probability groups (312). This score may also reflect clinical severity and extent of disease.

The main finding on US in GCA patients is the halo sign: non-compressible hypoechoic wall swelling (326,393). Several studies have been conducted to investigate the accuracy, construct and criterion validity of US in the diagnosis of GCA (361,395,442,478). The latest meta-analysis of prospective studies has shown a pooled sensitivity of 77% and a pooled specificity of 96% for temporal artery US when compared to the final clinical diagnosis of GCA (338). US allows measurement of the arterial intimal media complex (IMC). Studies show that at the age of 70 years the temporal artery has a normal IMC diameter of about 0.2 mm, whilst inflamed temporal arteries have a diameter of 0.5-0.9 mm (4,443). Axillary arteries of patients aged about 70 have a normal IMC diameter of 0.6 mm, whilst patients with extra-cranial GCA have an average diameter of 1.6-1.7 mm (340,443). A cut off value was determined at 1.0 mm (443). Currently, the temporal artery US of GCA patients are categorised as either negative or positive. However, variation in extent and severity of these findings on temporal and axillary artery US in GCA is observed (337). We have recently developed an ultrasonographic halo score that correlates with arterial inflammation in GCA (341). In the current study, will further investigate the novel halo score as a diagnostic, prognostic and disease monitoring tool for GCA.

We will systematically measure the extent and severity of the halo sign. Bilateral US assessment of the common temporal artery, the parietal branch, the frontal branch and axillary arteries will be performed (Figures 14 and 15). The halo sign at each branch of the common temporal, parietal and frontal arteries will be scored 0-4 points, giving a maximum possible halo score (HS) score of 24 (Table 15). At the axillary arteries, the IMT will be scored 0-4 points on each side, allowing a maximum total score 8, which will be multiplied by 3 (Figure 15). A total halo score (THS) will be constructed by adding the scores of the temporal artery branches with the axillary artery score.

**Table 15: Halo Score Grading**

Table 1. Halo Score Grading

| Halo Grading | Common superficial TA halo thickness (mm) | Parietal TA halo thickness (mm) | Frontal TA halo thickness (mm) | Axillary artery halo thickness (mm) |
|---|---|---|---|---|
| Grade 0 | 0.3 or less | 0.2 or less | 0.1 or less | 0.5 or less |
| Grade 1 | 0.4 | 0.3 | 0.2 | 0.6 |
| Grade 2 | 0.5 | 0.4 | 0.3 | 0.7-0.8 |
| Grade 3 | 0.6-0.7 | 0.5* | 0.4 | 0.9-1.5 |
| Grade 4 | 0.8 or more | 0.6 or more | 0.5 or more | 1.6 or more |

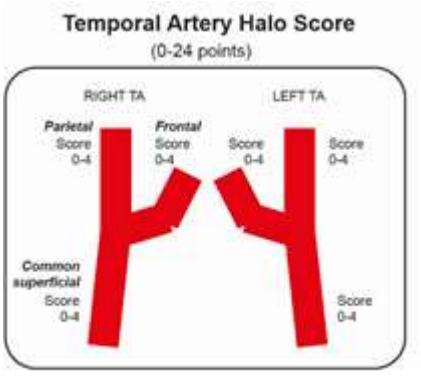



Figure 1

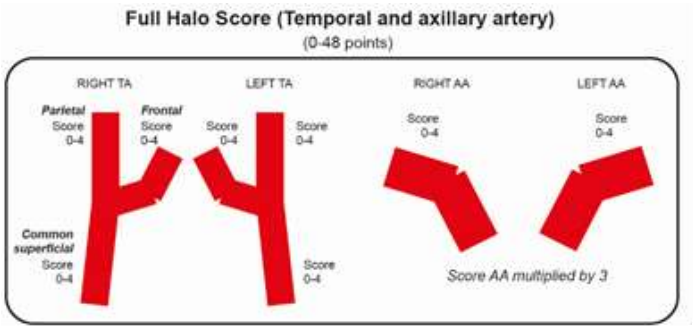



Figure 2

**Figure 14: Temporal artery halo score** **Figure 15: Total Halo score**

Subsequently, the HS and THS will be assessed for any correlation to disease outcomes in GCA, as characterised by responsiveness to therapy - remitting, relapsing or refractory disease.

Other outcome measures that may be reviewed include the development of large vessel disease and vascular damage (as assessed by cross-sectional scanning such as PET-CT), accumulation of glucocorticoid related adverse events and need for additional conventional (e.g. leflunomide, methotrexate) or biologic (Tocilizumab) DMARDs. Remitting disease in GCA is defined as a disease under sustained satisfactory control with minimum one flare during standard GC taper. The relapsing disease is where the condition initially comes under control but then flares on GC tapering. Refractory GCA patients are those who do not respond to GC at all.

The identification of prognostic factors in GCA is both timely and needed. The GiACTA trial has shown that IL-6R blocking therapy may help to sustain glucocorticoid free remission (168). In addition, the GiACTA trial has shown that a subset of GCA patients can be quickly withdrawn from glucocorticoid therapy without the development of relapses. A prognostic marker, as outlined above, could help to stratify GCA patients to an appropriate treatment regime. IL-6R blockade switches off the inflammatory marker response, making it difficult to use traditional biomarkers such as CRP to measure disease activity. Therefore, an independent HS, and changes in that score during treatment and follow-up, maybe a more objective measure of response, rather than relying only on patient-reported symptoms and clinical assessment.

# CHAPTER FOUR: METHODS

**Published article:**

The material below is the continuation of the published article from chapter three. This chapter highlights the methodology of the study. The following material in this chapter was published in August 2020 during the PhD. This published article is the study protocol of the Halo score (temporal artery, its branches and axillary artery) as a diagnostic, prognostic, and disease monitoring tool for Giant cell arteritis. The references, table and figure numbers in this article below are amended from the original publication to reflect the continuity of the PhD thesis references, Tables and figures.

## Study design

This is a pragmatic, prospective, observational study.

This study will involve two specific phases- (Figure 16: Study flow chart)

1) Initial presentation and diagnosis of GCA or non-GCA.
2) Follow-up over 12 months for GCA patients and 6 months for non-GCA patients.

### 1) Initial presentation and diagnosis:

This phase will involve recruiting patients from the GCA FTP at participating sites. Patients recruited will be subject to inclusion/exclusion criteria detailed below. Their General Practitioner, Emergency Department or other specialities refer patients to the FTP. Patients will be invited to participate in this study by the Rheumatology Research team, who will provide them with information about the study. Patients will be informed of the phases of participation, the voluntary nature of the study, and their right to withdraw at any stage. Written consent to

participate will be obtained by the researcher prior to the commencement of the screening assessments.

In this phase following will be assessed:

- Clinical history
- Clinical examination
- Routine bloods including biomarkers
- Patient-reported outcome (EQ5D)
- Starting dose of GC
- US scan of the temporal artery including its branches (frontal and parietal) and the axillary artery bilaterally
- Probability score (appendix 3) GCA Probability score will be calculated on all the patients referred to the FTP to clinically stratify their risk of having GCA and as a measure of severity of the disease

A diagnosis of GCA will be based on revised classification criteria as proposed recently (Dejaco et al. Rheumatology 2016) in the modified GiACTA criteria detailed below. The accuracy of the diagnosis will be evaluated after 6 months.

**Patients were classified as having GCA if all of the following criteria were met:**

- Age ≥50 years with ESR > 30 mm/hr or CRP > 10 mg/L
- Unequivocal cranial symptoms of GCA (i.e. new-onset localised headache, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth

or jaw pain upon mastication) or symptoms of polymyalgia rheumatica (PMR), defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

   a. *Cranial symptoms defined as new localised head pain, generalised scalp tenderness, tender temporal artery, AION or PION, jaw claudication or tongue claudication in the current study*
   b. *PMR symptoms defined as morning stiffness > 1 hour with bilateral shoulder pain and/or bilateral hip pain or stiffness in the current study*

- Temporal artery biopsy revealing features of GCA or evidence of GCA by imaging (i.e. ultrasound or cross-sectional imaging such as CTA or PET-CT)

2) Follow-up period:

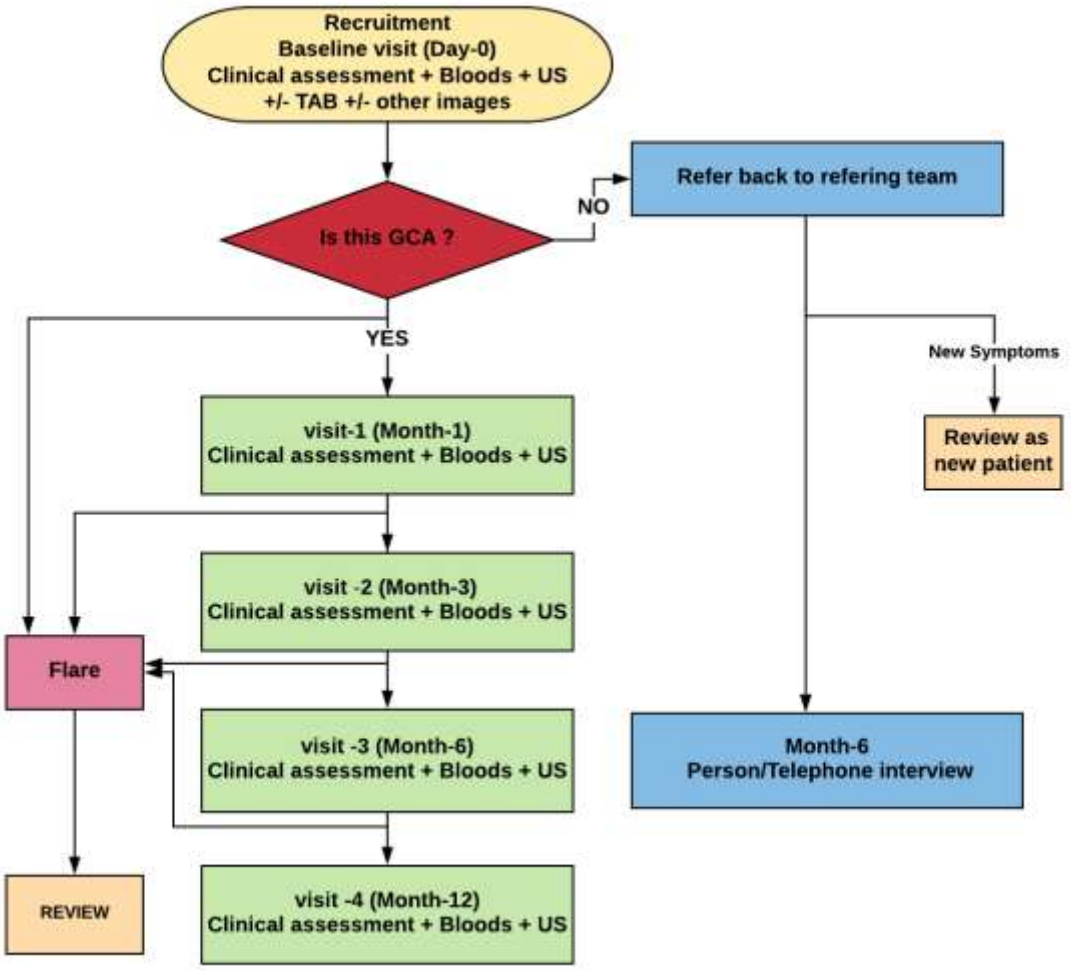
Participants who are diagnosed with GCA will be seen for follow-up visits at 1, 3, 6 and 12 months. Participants with a non-GCA diagnosis will be seen or through a telephone interview one further time at 6 months to confirm the non-GCA diagnosis. At any time, point throughout the follow-up period patients may require unscheduled visits if they have symptoms of relapse. Patients will be educated at baseline as to the symptoms that might be expected with relapse and guided to contact their clinician or Rheumatology Research team (if different) immediately.

For study purposes, relapse means those patients whose GCA symptoms flare or return in response to current standard treatment, that is a tapering regimen of glucocorticoids. Refractory GCA patients are those who do not respond from the outset.

In this phase, following will be assessed:

- Clinical history
- Clinical examination
- Routine bloods including biomarkers
- US scan of the temporal artery including its branches (frontal and parietal) and the axillary artery bilaterally
- Patient-reported outcomes (EQ5D)
- Cumulative GC requirement

**Figure 16: Study Flow chart:**




*Abbreviation: GCA, Giant cell arteritis; TAB, Temporal artery biopsy; US, Ultrasound*

**DEFINITION OF RELAPSE AND REMISSION**

1. Remission is defined as absence of clinical signs and symptoms of GCA and normalization of ESR [<30mm/hr] and CRP [< 10 mg/L]

2. Relapse is defined as recurrence of symptoms attributable to active GCA, with or without ESR >30mm/hr and CRP > 10 mg/L

Eligibility Criteria

Patients with clinical suspicion of GCA referred to the FTC would be eligible for the study subjects to the inclusion and exclusion criteria below.

**Inclusion criteria**

The clinician responsible for the patient's care will make the diagnosis of GCA as part of the standard of care using the modified GiACTA criteria.

•Age ≥50 years with ESR > 30 mm/hr or CRP > 10 mg/L

•Unequivocal cranial symptoms of GCA (i.e. new-onset localised headache, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication) or symptoms of polymyalgia rheumatica (PMR), defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness

a. Cranial symptoms defined as new localised head pain, generalised scalp tenderness, tender temporal artery, AION or PION, jaw claudication or tongue claudication in current study

b.PMR symptoms defined as morning stiffness > 1 hour with bilateral shoulder pain and/or bilateral hip pain or stiffness in the current study

•Temporal artery biopsy revealing features of GCA or evidence of GCA by imaging (i.e. ultrasound or cross-sectional imaging such as CTA or PET-CT)

•Participants must have the capacity and willingness to give informed written consent

**Exclusion criteria**

- Participants must not have a previous diagnosis of GCA
- Participants must not have had a previous temporal artery biopsy i.e. as part of diagnostics for previously suspected GCA
- Participants must not be under 18 years
- Participants must not be on treatment with a high dose of steroids (>7.5 mg) more than 2 weeks prior to the first review in the FTP
- Inability to give informed consent

**Sampling**

The nature of this disease is rare; thus, the number of participants will be collected up to 12 months and will be followed up to 12 months as per the study protocol. Patients will be recruited after referral to the participating site FTP.

**Participants**

The cohort of patients for this study will be recruited from the fast track GCA clinics (FTC), which is currently the standard of care for patients with clinical suspicion of GCA. The FTC has been demonstrated a reduced incidence of vision loss and cost-effectiveness (334). Patients can be referred to the FTC from General Practitioners (GP), Emergency Department (ED), Ophthalmology or from any other specialities. Initial assessment includes clinical assessment (patient history and physical examination), blood tests (ESR, CRP, full blood count, renal profile, liver function tests), and US of the Temporal and axillary arteries. Those who are diagnosed with GCA will be monitored in the GCA follow-up clinics. Those patients with low probability and a non-GCA diagnosis would be referred back to the primary referral team.

<u>Intervention</u>

Potential study participants will be identified from patients referred by their GP, ED, Ophthalmology or other specialities to the FTP. For study purposes, referred patients will be informed about the study and provided with a study invitation letter and patient information sheet (PIS) during the first contact with the research team. All participants will need to

provide written, informed consent to take part in the study. Due to the nature of the study, researchers will provide as much as information as possible at the time of the first assessment. The research team will answer any questions from the patients. Patients are reassured that their decision will not impact on their standard of care. Those who understand and agreed to participate will be consented and given a unique identification number.

The US of the temporal artery branches and axillary artery on both sides is a key element of the study, which will measure the IMT of each artery and a total halo score (THS) calculated. This score will be used to assess the severity of the disease. It will also be calculated on each follow-up visit to determine how the THS changes with treatment

Operator's experience

- All sonographers participating in this study have experience of scanning more than 30 people with temporal artery and axillary scans and at least 5 cases with GCA.
- All sonographers have completed either face to face or web-based training on the temporal artery and axillary artery scanning requirements for this study.
- All sonographers have completed the online BSR e-learning module on Ultrasound scanning for LVV
- We have documented the experience of sonographers and equipment characteristics with completion of a standardised form (Appendix 4)

Outcome measures

**Primary outcome:**

1. Analysis of data to see how many patients sustained remission had (achieving a daily prednisolone dose of ≤5mg of glucocorticoid dose equivalent) at 12 months from baseline (one flare is acceptable in this study period). All patients follow the same tapering scheme as outlined in the British Society for Rheumatology (BSR) guidelines. To then determine if the initial baseline HS correlates with this clinical outcome at 12 months.

**Secondary outcomes:**

1. To determine if a change in HS over the 12-month disease monitoring period correlates to prognosis
2. To determine if there is any correlation of HS to quality-of-life measures, as assessed by EQ5D
3. To determine any correlation between the HS and biomarkers of GCA patients
4. Evaluate if the Probability Score (Appendix 3) prospectively correlates with GCA outcomes at 12 months
5. To determine the diagnostic accuracy of the HS for discriminating GCA from non-GCA Reference standard for the diagnosis of GCA will be the clinical diagnosis after 6 months follow-up.
6. To determine the diagnostic accuracy of the GCA probability score for discriminating GCA from non-GCA patients. The reference standard for the diagnosis of GCA will be the clinical diagnosis after 6 months follow-up.

Data analysis and monitoring

Descriptive statistics such as mean (with standard deviation), median (with range) and percentages will be used for reporting HS, relative change in HS, number of patients in remission with prednisolone dose ≤ 5 mg daily after 12 months, cumulative prednisolone dose at 12 months follow-up, time to first relapse, number of relapses, levels of inflammatory markers, quality of life questionnaire outcomes and GCA probability scores. Temporal artery, axillary artery halo scores and the total halo score (temporal score plus axillary score) will be calculated.

Primary outcome analysis and power calculation

Percentages of GCA patients in remission with a prednisolone dose of ≤ 5 mg per day will be determined at 12 months follow-up. A ROC analysis of baseline HS will be performed to identify the optimal HS cut-off point that discriminates between patients reaching remission and those that do not. Subsequently, the Chi-square test will be used to compare remission rates at 12 months follow-up between patients with a HS above the optimal cut-off point versus those with a HS below the optimal cut-off points.

A power calculation was performed to determine the number of patients needed for investigating this primary outcome. Based on two previous studies, it is expected that 45% of GCA patients will be in remission at 12 months with a prednisolone dose of ≤ 5 mg per day (479,480). For the current study, we propose that a 40% difference in patients reaching sustained remission at 12 months follow-up is clinically relevant.

As the optimal prognostic HS cut-off point is not yet known, we propose that a 25% versus 75% distribution is still clinically relevant. If the smallest group becomes smaller (and the

biggest group bigger), we believe risk stratification by HS would have limited overall value for clinical practice. With an alpha of 0.05 and power of 0.80, we calculate that 61 GCA patients are needed for the study.

Taken into consideration a 10% loss of patients during 12 months follow-up, we expect that 68 GCA patients should be initially recruited into the study.

In our experience, 25% of patients entering a GCA FTP, will be ultimately diagnosed with GCA after 6 months follow-up. Thus, we anticipate that we would need to recruit a total of 272 patients suspected of having GCA in our study, of which 68 are eventually diagnosed as having GCA.

G.Power 3.1.9.4

**z tests** – Proportions: Difference between two independent proportions

| | | | |
|---|---|---|---|
| **Analysis:** | A priori: Compute required sample size | | |
| **Input:** | Tail(s) | = | Two |
| | Proportion p2 | = | 0.65 |
| | Proportion p1 | = | 0.25 |
| | α err prob | = | 0.05 |
| | Power (1−β err prob) | = | 0.80 |
| | Allocation ratio N2/N1 | = | 3 |
| **Output:** | Critical z | = | 1.9599640 |
| | Sample size group 1 | = | 15 |
| | Sample size group 2 | = | 46 |
| | Total sample size | = | 61 |
| | Actual power | = | 0.7979079 |

Secondary outcome analysis

- In patients with a clinical diagnosis of GCA: the prognostic value of the absolute and relative change in HS between baseline and 1 month's follow-up will be investigated in a similar analysis as mentioned under the primary outcome analysis
- In patients with a clinical diagnosis of GCA: we will perform a paired analysis of the HS measured at different time points by paired t-test or Wilcoxon signed-rank rest depending on normality of the data
- In patients with a clinical diagnosis of GCA: correlation between HS and measures of quality of life will be determined by Pearson or Spearman's rank correlation coefficient depending on normality of data
- In patients with a clinical diagnosis of GCA: correlation between HS and inflammatory markers in blood will be determined by Pearson or Spearman's rank correlation coefficient depending on normality of data
- In patients with a clinical diagnosis of GCA: the prognostic value of the GCA probability score will be assessed similar to the analysis of the prognostic value of the HS as mentioned under the primary outcome analysis
- In all patients suspected of having GCA: the diagnostic accuracy of the HS for discriminating GCA from non-GCA patients will be determined by ROC analysis and the Youden index. Sensitivity, specificity and likelihood ratios at the optimal diagnostic cut-off point will be evaluated. The reference standard for the diagnosis of GCA will be the clinical diagnosis after 6 months follow-up.
- In patients with a clinical diagnosis of GCA: the diagnostic accuracy of the HS for discriminating relapsing and non-relapsing GCA patients during follow-up measurements. Sensitivity, specificity and likelihood ratios at the optimal diagnostic cut-off point will be evaluated. Relapse definition is described elsewhere.

- In patients with a clinical diagnosis of GCA: the predictive effect of the baseline HS and GCA probability score on GCA patients achieving remission at 12 months with prednisolone dose of ≤ 5 mg will be evaluated by multivariate logistics regression analysis.
- In patients with a clinical diagnosis of GCA: the predictive effect of the HS and GCA probability score on cumulative prednisolone dose at 12 months follow-up will be evaluated by multivariate linear regression analysis.
- In addition to the total halo score in the axillary and temporal artery, changes in individual vessel halo grades will be analysed.

# CHAPTER FIVE: FINDINGS/RESULTS

## 5.1 Demographics

Two-hundred and twenty-nine patients were prospectively recruited to the HAS GCA study from 7 European centres in the United Kingdom, Italy, Spain and the Netherlands (Table 16). 65% of them were female participants. Inclusion criteria include Over 50 years of age, males and females, have suspected GCA referred to FTC and who can consent to participate in the study. Exclusion criteria include, Below 50 years of age, or over 50 years of age and those who cannot consent to the study or had a previous TAB. According to the inclusion criteria, 84 had a confirmed diagnosis of GCA and 145 did not have a diagnosis of GCA and they were recruited as non-GCA controls using US and additional tests (AT) such as PET-CT if required. 6 patients were not included ino this study from the referrals to the FTC according to the exclusion criteria ( had previous temporal artery biopsy). The median age in the GCA group was 75 (range 60-92), and 68 (range 44-96) years in the control group. 73 of the GCA cohort completed 12 months of follow-up, and 11 lost to follow-up (7 died due to severe pneumonia, COVID and metastatic malignancy, and 4 withdrew their consent due to the COVID pandemic). Of the 73 who completed 12-month follow-ups, 65 (89%) of them achieved remission/primary outcome by fulfilling remission criteria (daily dose of prednisolone $\leq$ 5mg at 12 months). 8 (11%) had a relapsing disease at 12 months. Clinical features and demographic data are summarised in table 17. Among the GCA patients, 60 (71%) had cranial GCA only, 5 (6%) had LV-GCA, and 19 (23%) had mixed phenotypes.

**Table 16: Recruitment by all the participating centres**

| Center | Total | GCA | Non-GCA | Completed 12 months | Lost to follow up | Remission | Relapse at 12 months | Median age | Male | Female |
|---|---|---|---|---|---|---|---|---|---|---|
| Southend, UK | 126 | 45 | 81 | 37 | 8 | 34 | 3 | 71.5 | 42 | 84 |
| Poole, UK | 13 | 6 | 7 | 5 | 1 | 4 | 1 | 76 | 2 | 11 |
| Reggio, Italy | 49 | 13 | 36 | 13 | 0 | 10 | 3 | 71 | 20 | 29 |
| Milan, Italy | 8 | 5 | 3 | 5 | 0 | 5 | 0 | 80 | 1 | 7 |
| Siena, Italy | 6 | 4 | 2 | 4 | 0 | 4 | 0 | 79.5 | 4 | 2 |
| Santander, Spain | 16 | 6 | 10 | 4 | 2 | 4 | 0 | 70.5 | 8 | 8 |
| Groningen, NL | 11 | 5 | 6 | 5 | 0 | 4 | 1 | 66 | 2 | 9 |
| **Total** | 229 | 84 | 145 | 73 | 11 | 65 | 8 | | 79 | 150 |

**Table 17: Patient characteristics at baseline**

| Patients' characteristics | All patients (n=229) | Patients with GCA (n=84) | Patients without GCA (n=145) | P-Value |
|---|---|---|---|---|
| Age, median (range) years | 72 (44-96) | 75 (60-92) | 68 (44-96) | 0.000 |
| Sex, Females, n (%) | 150 (65%) | 50 (60%) | 100 (69%) | 0.1525 |
| High dose steroids at baseline, n (%) | 93 (41%) | 39 (46%) | 54 (37%) | 0.209 |
| Steroid dose (mg) at baseline, median (range) | 40 (1-312.5) | 40 (20-60) | 40 (1-312.5) | |
| **GCAPS category, n (%)** | | | | |
| Low risk | 67 (29%) | 0 (0%) | 67 (46%) | 0.000 |
| Intermediate risk | 73 (32%) | 18 (21%) | 55 (38%) | 0.0121 |
| High risk | 89 (39%) | 66 (79%) | 23 (16%) | 0.000 |
| **Halo Score (HS) median (range)** | | | | |
| Temporal artery HS | 3 (0-24) | 13 (0-24) | 2 (0-17) | 0.000 |
| Axillary artery HS | 6 (0-21) | 12 (0-21) | 6 (0-18) | 0.000 |
| Total HS | 12 (0-41) | 21.5 (2-41) | 8 (0-29) | 0.000 |
| **Clinical features, n (%)** | | | | |
| Generalised headache | 63 (27%) | 16 (19%) | 47 (32%) | 0.032 |
| Temporal headache | 164 (72%) | 62 (74%) | 102 (70%) | 0.6491 |
| Scalp tenderness | 88 (38%) | 42 (50%) | 46 (32%) | 0.0074 |
| Jaw claudication | 55 (24%) | 45 (54%) | 10 (7%) | 0.000 |
| Tongue pain | 8 (3%) | 8 (10%) | 0 (0%) | 0.000 |
| Polymyalgic symptoms | 75 (33%) | 37 (44%) | 38 (26%) | 0.0082 |
| Constitutional symptoms | 74 (32%) | 44 (52%) | 30 (21%) | 0.000 |
| Any visual disturbance | 108 (47%) | 46 (55%) | 62 (43%) | 0.0992 |
| Blurred vision | 66 (29%) | 25 (30%) | 41 (28%) | 0.8799 |
| Double vision | 29 (13%) | 13 (15%) | 16 (11%) | 0.4098 |
| Amaurosis | 25 (11%) | 15 (18%) | 10 (7%) | 0.0147 |
| Partial or complete vision loss | 30 (13%) | 21 (25%) | 9 (6%) | 0.000 |
| **Examination findings, n (%)** | | | | |
| Temporal artery thickening | 25 (11%) | 23 (27%) | 2 (1%) | 0.000 |
| Temporal artery tenderness | 45 (20%) | 24 (29%) | 21 (14%) | 0.0150 |
| Temporal artery abnormal pulse | 21 (9%) | 14 (17%) | 7 (5%) | 0.0040 |
| Bruits | 2 (1%) | 2 (2%) | 0 (0%) | 0.1335 |
| AION | 18 (8%) | 15 (18%) | 3 (2%) | 0.000 |
| CRAO | 8 (3%) | 4 (5%) | 4 (3%) | 0.4691 |
| Ocular nerve palsy | 9 (4%) | 4 (5%) | 5 (4%) | 0.7278 |
| **Past medical history** | | | | |
| Stroke/TIA | 19 (8%) | 5 (6%) | 14 (10%) | 0.4571 |
| Hypertension | 99 (43%) | 47 (56%) | 52 (36%) | 0.0036 |
| Atrial fibrillation | 17 (8%) | 11 (13%) | 6 (4%) | 0.0177 |
| Diabetes mellitus | 39 (17%) | 12 (14%) | 27 (19%) | 0.4679 |
| Thyroid disease | 18 (8%) | 4 (5%) | 14 (10%) | 0.2131 |
| Osteoporosis | 18 (8%) | 3 (4%) | 15 (10%) | 0.0774 |
| Any malignancy | 21 (9%) | 7 (8%) | 14 (10%) | 0.8160 |
| Pre-existing eye disease | 25 (11%) | 10 (12%) | 15 (10%) | 0.8264 |
| PMR | 26 (11%) | 10 (12%) | 16 (11%) | 0.8321 |
| Other rheumatological diseases | 9 (4%) | 2 (2%) | 7 (5%) | 0.4917 |
| **Laboratory markers** | | | | |
| CRP mg/dL, median (range) | 19 (0.5-292) | 59.5 (6-292) | 11.4 (0.5-167) | 0.000 |
| ESR mm/hour, median (range) | 40 (2-131) | 59 (2-130) | 28 (2-131) | 0.000 |
| Haemoglobulin (g/L), median (range) | 127 (88-256) | 120.5 (88-167) | 131.5 (88-256) | 0.0002 |
| Platelets, $10^9$/L, median (range) | 310.5 (71-743) | 359.5 (110-743) | 266 (71-587) | 0.000 |

*Details of 229 patients recruited to HAS GCA study*

*AION, anterior ischemic optic neuritis; CRAO, central retinal artery occlusion; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, Giant cell arteritis; PMR, polymyalgia rheumatica; TIA, transient ischemic attack*

Categorical variables are presented as frequency and percentage (%). Quantitative variables were compared between groups using Mann–Whitney *U* test (eg- CRP levels). Categorical variables ( scalp tenderness) were compared between groups using the Two-tailed Fisher's exact test. $P < .05$ indicates statistical significance

### 5.2 Clinical features & examination

The baseline characteristics of the cohort revealed that, compared to controls, GCA patients had more clinical features (Table:17). They were significantly more likely to have scalp tenderness (50% vs 32%), Jaw claudication (54% vs 7%), Tongue pain (10% vs 0%), polymyalgic symptoms (44% vs 26%) and one or more constitutional symptoms such as fever, night sweat and weight loss (52% vs 21%). When considering the visual disturbance in general, there is a slight difference between GCA and controls (55% vs 43%). However, a notably high proportion of GCA patients had Amaurosis (18% vs 7%) and partial or complete visual loss (25% vs 6%) compared to controls. Blurred vision was seen in both groups almost equally (30% vs 28%). On the other hand, the temporal headache was observed without any significant difference in both groups (GCA-74%, controls-70%). Also, not surprisingly, the generalised headache was seen predominantly if controls than GCA group (32% vs 19%)

The examination findings were very prominent in GCA than in controls (Table: 17). Temporal artery thickness (27% vs 1%), temporal artery tenderness 29% vs 14%), reduced or absent temporal artery pulse (17% vs 5%) and AION (18% vs 2%) were shown a clear differentiating finding in clinical examination in GCA patients.

When compared, the GCA group completed the 12-month follow-up (n=73) with the loss to the follow-up group (n=11), lost to the follow-up group had a significant rise in visual disturbance (91% vs 49%) with a notable difference in Amaurosis (73% vs 10%) and Partial or complete visual loss (55% vs 21%). Also, it was noted that the lost to the follow-up group predominantly had males (73%) (Table: 18).

**Table 18: All GCA patients in the study: who completed and lost to follow-up**

| Patients' characteristics | GCA with completed follow-up (n=73) | GCA lost to follow-up (n=11) | P-Value |
|---|---|---|---|
| **Age, median (range) years** | 74 (60-89) | 80 (71-92) | 0.0187 |
| **Sex, Females, n (%)** | 47 (64%) | 3 (27%) | 0.0438 |
| **High dose steroids at baseline, n (%)** | 71 (97%) | 11(100%) | 1.000 |
| **Steroid dose (mg) at baseline, median (range)** | 50 (0-60) | 60 (40-60) | |
| **GCAPS category, n (%)** | | | |
| **Low risk** | 0 (0%) | 0 (0%) | 0.000 |
| **Intermediate risk** | 16 (22%) | 2 18%) | 1.000 |
| **High risk** | 57 (78%) | 9 (82%) | 1.000 |
| **Halo Score (HS) median (range)** | | | |
| **Temporal artery HS** | 12 (0-23) | 19 (5-24) | 0.1443 |
| **Axillary artery HS** | 12 (0-21) | 9 (3-18) | 0.4839 |
| **Total HS** | 21 (2-41) | 28 (8-38) | 0.5418 |
| **Clinical features, n (%)** | | | |
| **Generalised headache** | 15 (21%) | 1 (9%) | 0.6816 |
| **Temporal headache** | 55 (75%) | 7 (64%) | 0.4673 |
| **Scalp tenderness** | 36 (49%) | 6 (55%) | 1.000 |
| **Jaw claudication** | 39 (53%) | 6 (55%) | 1.000 |
| **Tongue pain** | 7 (10%) | 1 (1%) | 1.000 |
| **Polymyalgic symptoms** | 34 (47%) | 3 (27%) | 0.3323 |
| **Constitutional symptoms** | 39 (53%) | 5 (45%) | 0.7499 |
| **Any visual disturbance** | 36 (49%) | 10 (91%) | 0.0102 |
| **Blurred vision** | 20 (27%) | 5 (45%) | 0.2901 |
| **Double vision** | 12 (16%) | 1 (9%) | 1.000 |
| **Amaurosis** | 7 (10%) | 8 (73%) | 0.000 |
| **Partial or complete vision loss** | 15 (21%) | 6 (55%) | 0.0247 |
| **Examination findings, n (%)** | | | |
| **Temporal artery thickening** | 21 (29%) | 2 (18%) | 0.7192 |
| **Temporal artery tenderness** | 24 (33%) | 0 (0%) | 0.0290 |
| **Temporal artery abnormal pulse** | 10 (14%) | 4 (36%) | 0.0808 |
| **Bruits** | 2 (3%) | 0 (0%) | 1.000 |
| **AION** | 11 (15%) | 4 (36%) | 0.1020 |
| **CRAO** | 3 (4% | 1 (9%) | 0.4359 |
| **Ocular nerve palsy** | 4 (5%) | 0 (0%) | 1.000 |
| **Past medical history** | | | |
| **Stroke/TIA** | 4 (5%) | 1 (9%) | 0.5134 |
| **Hypertension** | 38 (52%) | 9 (82%) | 0.1019 |
| **Atrial fibrillation** | 10 (14%) | 1 (9%) | 1.000 |
| **Diabetes mellitus** | 10 (14%) | 2 (18%) | 0.6535 |
| **Thyroid disease** | 4 (5%) | 0 (0%) | 1.000 |
| **Osteoporosis** | 2 (3%) | 1 (9%) | 0.3472 |
| **Any malignancy** | 5 (7%) | 2 (18%) | 0.2268 |
| **Pre-existing eye disease** | 9 (12%) | 1 (9%) | 1.000 |
| **PMR** | 9 ((12%) | 1 (9%) | 1.000 |
| **Other rheumatological diseases** | 2 (3%) | 0 (0%) | 1.000 |
| **Laboratory markers at baseline** | | | |
| **CRP mg/dL, median (range)** | 68 (6-292) | 21 (11-244) | 0.061 |
| **ESR mm/hour, median (range)** | 62 (2-130) | 42 (13-114) | 0.317 |
| **Haemoglobulin (g/L), median (range)** | 120 (88-167) | 123.5 (98-147) | 0.3221 |
| **Platelets, $10^9$/L, median (range)** | 369 (110-743) | 312.5 (199-431) | 0.0672 |

*Details of 84 GCA patients recruited to HAS GCA study*

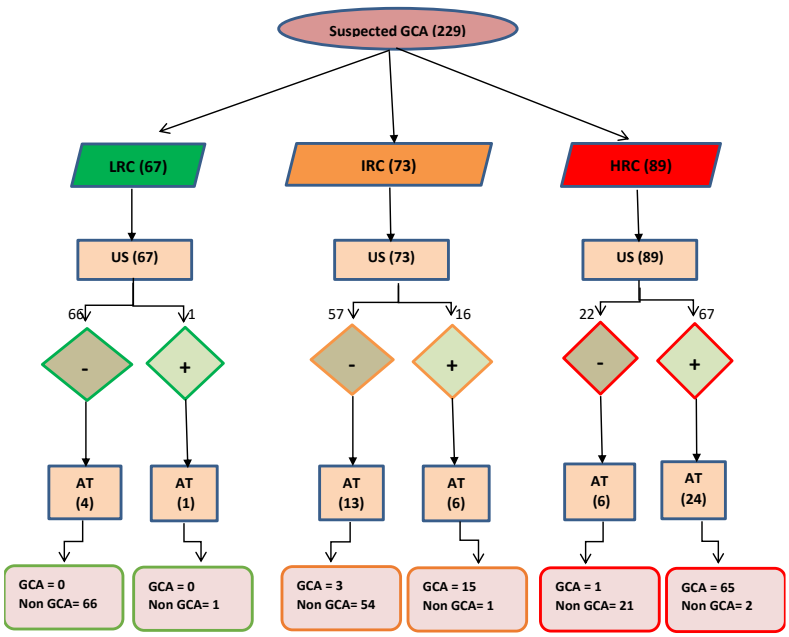
*AION, anterior ischemic optic neuritis; CRAO, central retinal artery occlusion; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, Giant cell arteritis; PMR, polymyalgia rheumatica; TIA, transient ischemic attack*

Categorical variables are presented as frequency and percentage (%). Quantitative variables were compared between groups using Mann–Whitney *U* test (eg- CRP levels). Categorical variables ( scalp tenderness) were compared between groups using the Two-tailed Fisher's exact test. $P < .05$ indicates statistical significance

## 5.3 GCA probability score (GCAPS) and algorithm

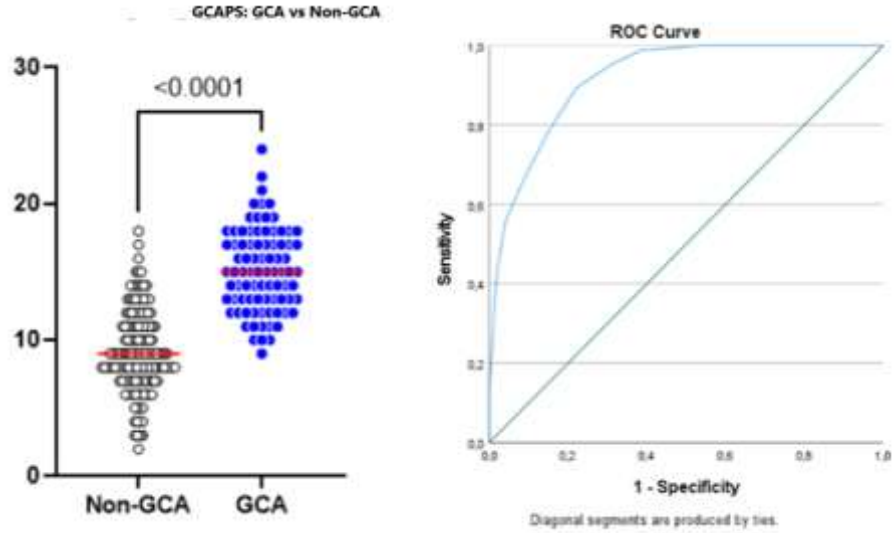
All the patients were stratified using GCAPS into Low risk (LRC), Intermediate risk (IRC) and High Risk (HRC). LRC was classified as GCAPS<9, IRC as GCAPS 9-12 and HRC as GCAPS >12 (Figure 17). After the application of the GCAPS, the LRC had 67 (29%), IRC had (73 (32%), and HRC had 89 (39%). The median GCAPS in GCA was 15 (range 9-24), and Controls were 9 (range 2-18). The overall median GCAPS score in LRC was 7 (range 2-8), IRC was 10 (range 9-14), and HRC was 15 (range 12-24). The GCAPS optimum cut-off value for GCA vs non-GCA was 12, with a sensitivity of 89% and specificity of 78% (Figure 18).

**Figure 17: Southend pre-test probability score (GCAPS) algorithm shows the categories, number of additional tests performed in each category and number of confirmed GCA**




*Abbreviations: AT, Additional Test; GCA, Giant cell arteritis; HRC High Risk Category; IRC, Intermediate Risk Category; LRC, Low Risk Category; US, Ultrasound*

**Figure 18:** Southend pre-test probability score (GCAPS) discriminating GCA and Non-GCA. Y-axis shows the score and 'The x-axis shows participants of GCA and non-GCA




### 5.4 Ultrasound results and additional tests (AT)

Ultrasound of the temporal artery (TA) and its branches parietal and frontal branches and axillary arteries on both sides (8 segmental images per patient) were performed in all GCA and non-GCA patients at baseline and GCA patients on their follow-ups as per the schedule in months 1,3,6 and 12. US was used to diagnose or exclude GCA in 215 (94%) total cohorts (PET-CT 9 (4%), TAB 5 (2%). 87% of GCA diagnosed only with the US (PET-CT 8%, TAB 5%). 98% of the non-GCA patients were excluded from the diagnosis of GCA by the US alone. The intimal medial thickness of the vessel wall was measured, and the halo score was calculated per the pre-defined cut-off scores. The results were positive in 1/67 LRC (1.4%), 16/73 IRC (22%) and 67/89 HRC (75%) patients. Overall, in the total cohort, the US sensitivity was 95%, specificity was 97%, and accuracy was 96.5% (Table 19).

**Table 19:** Risk categories, US findings and statistics of all the participants recruited to the study. Risk is categorised as Low, Intermediate and high based on the GCAPS.

| Risk Category (n) | US | GCA, n | Non-GCA, n | Sensitivity (%) [95% CI] | Specificity (%) [95% CI] | PPV (%) [95% CI] | NPV (%) [95% CI] | Prevalence (%) [95% CI] | Accuracy (%) [95% CI] |
|---|---|---|---|---|---|---|---|---|---|
| **High (89)** | Positive | 65 | 2 | 98.5 [92-100] | 91.3 [72-99] | 97.0 [90-99] | 95.5 [75-99] | 74.1 [64-83] | 96.6 [90-99] |
| | Negative | 1 | 21 | | | | | | |
| **Intermediate (73)** | Positive | 15 | 1 | 83.3 [59-96] | 98.2 [90-100] | 93.8 [68-99] | 94.7 [86-98] | 24.6 [15-36] | 94.5 [87-98] |
| | Negative | 3 | 54 | | | | | | |
| **Low (67)** | Positive | 0 | 1 | Undefined [-] | 98.5 [92-100] | 0.0 [-] | 100 [-] | 0.0 [0-5] | Undefined [-] |
| | Negative | 0 | 66 | | | | | | |
| **Total (229)** | Positive | 80 | 4 | 95.2 [88-99] | 97.2 [93-99] | 95.2 [88-98] | 97.2 [93-99] | 36.7 [30-43] | 96.5 [93-98] |
| | Negative | 4 | 141 | | | | | | |

*Abbreviations: GCA, Giant cell arteritis; NPV, Negative predictive value; PPV, Positive predictive value; US, Ultrasound*

### 5.4.1 High-risk category

Of the 67 US-positive HRC patients, 24 had AT while receiving treatment as GCA. of these, 65 were confirmed diagnosed as GCA. Only two patients were eventually diagnosed with non-GCA. One had a raised temporary artery halo score (TAHS) and a negative TAB. Another patient, with both high TAHS and axillary artery halo score (AAHS), underwent TAB and PET-CT, both negative for inflammation. Of the 22 US negative HRC patients, only one (5%) was subsequently diagnosed with GCA but only after AT. This patient had low TAHS, but very high inflammatory markers and a PET CT diagnosed vertebral arteritis. The total number of GCA and non-GCA in this category was 66 and 23, respectively. As a consequence, the sensitivity of the US in HRC was 98%, specificity was 91% and accuracy was 97% (Table 19 & Figure 17).

### 5.4.2 Intermediate risk category

The US was positive in 16 IRC patients, and of these, 15 were eventually diagnosed as GCA after AT. Six patients had AT in this category. One patient was diagnosed as non-GCA. This

patient had a raised TAHS; TAB was negative, and eventually, CT abdomen and pelvis were diagnosed with Renal cell carcinoma. Of the 57 negative US in this category, 13 underwent AT. Three patients were diagnosed with GCA after the AT. One patient had raised AAHS and was diagnosed with vertebral arteritis with PET-CT. Another one had low TAHS and normal AAHS and had a negative TAB, but PET CT diagnosed vertebral arteritis. The last patient had a low TAHS and high AAHS, with positive TAB diagnosed with C-GCA. The total number of GCA and non-GCA in this category was 18 and 55, respectively. Regarding the performance of the US in IRC, sensitivity was 83%, specificity was 98%, and accuracy was 95% (Table 19 & Figure 17).

### 5.4.3 Low-risk category

Only one LRC patient had a positive US (high AAHS). However, this patient was not treated as GCA but subsequently underwent PET-CT and excluded GCA. Sixty-six had negative US, and none of them was diagnosed as GCA. In total, GCA prevalence in this category was 0%. Therefore, in LRC, the US had high specificity (98%) and accuracy (Table 19 & Figure 17).

### 5.4.4 Halo score

Halo scores were calculated from pre-graded scores based on the vessel wall IMT. All eight vessels from TA and branches and axillary arteries were assessed and scored individually. Then calculated the TAHS and AAHS and summed both to give a THS. The HS is defined as ‘high/raised’ when above the optimum cut-off value (AHS-6, AAHS-11, THS-17) and ‘low’ when below the optimum cut-off value in their respective branches.

When comparing the GCA with controls, there is a significant difference in the median halo scores (Table 20). In GCA, median TAHS, AAHS, and THS were 13, 12 and 21.5, and in controls, 2, 6, and 8, respectively. These results were statistically significant: $P<0.0001$

(Figure 19). The optimum cut-off value of the halo score in diagnosing GCA vs non-GCA was TAHS 6 (Sensitivity-86%, Specificity-92%), AAHS 11(Sensitivity-52%, Specificity-75%), and THS was 17 (Sensitivity-76%, Specificity-91%). When assessing the phenotypes of the GCA separately, the C-GCA has higher TAHS than AAHS; in contrast, LV-GCA and Cranial and LV mixed GCA has higher AAHS than TAHS (Table 20).

When the halo score was followed in GCA patients over 12 months, the TAHS, AAHS and THS were reduced from 13 to 3, 12 to 9 and 21.5 to 15, respectively (Figure 20).

Halo score shows a correlation with intimal hyperplasia of the temporal artery biopsy. 32 TAB were carried out in the cohort and had 12 positive biopsies. Median TAHS was 12.5 (range1-22) biopsy-positive group compared to 3 (range1-10) in negative biopsy group. High halo scores were noted in the sight loss patients. Median TAHS was 15 (range 3-22). Also, there was a significant increase in the halo score in the sight loss patient who lost to follow-up (TAHS- 17)

**Table 20:** Temporal, Axillary and Total median halo scores at baseline on all the participants and in different GCA phenotypes.

| | All GCA | Controls | **P-Value** | C-GCA | LV-GCA | C+LV GCA |
|---|---|---|---|---|---|---|
| TAHS, median | 13 (0-24) | 2 (0-17) | 0.000 | 13 (1-24) | 2 (0-6) | 14 (4-23) |
| AAHS, median | 12 (0-21) | 6 (0-18) | 0.000 | 9 (0-18) | 6 (0-21) | 18 (6-21) |
| THS, median | 21.5 (2-41) | 8 (0-29) | 0.000 | 20.5 (5-37) | 6 (2-26) | 33 (17-41) |

*Abbreviation: AAHS, Axillary artery halo score; C-GCA, Cranial GCA; C+LV GCA, Cranial and large vessel GCA;GCA, Giant cell arteritis; LV-GCA, Large vessel GCA; TAHS, Temporal artery halo score; THS, Total halo score*. P value was calculated using Mann–Whitney *U* test to compare the categorical variables

**Figure 19:** Temporal (TAHS), axillary(AAHS), and total median halo (THS) with ROC analysis at baseline compares between GCA and non-GCA. The Y-axis shows the halo scores, and the X-axis shows all the GCA and non-GCA participants

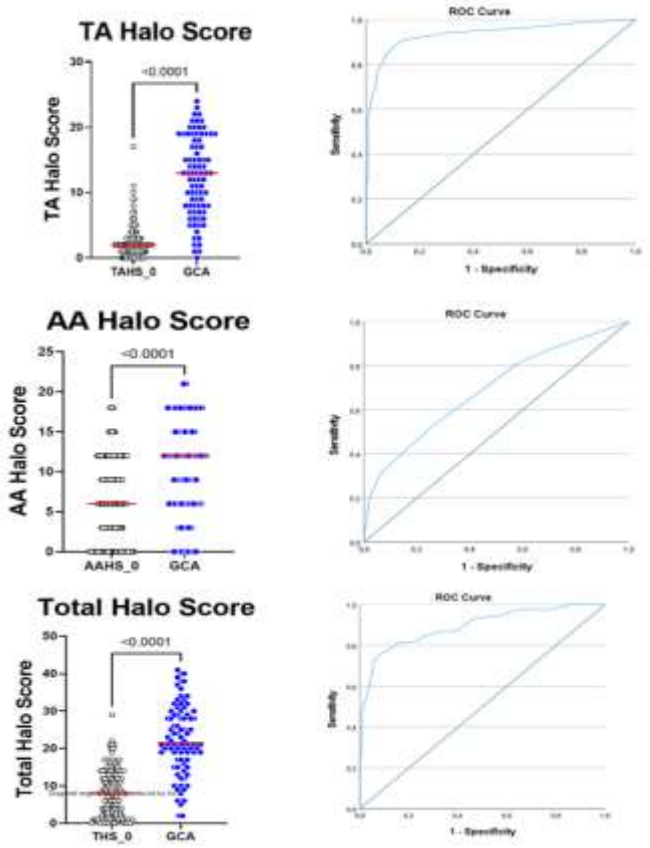
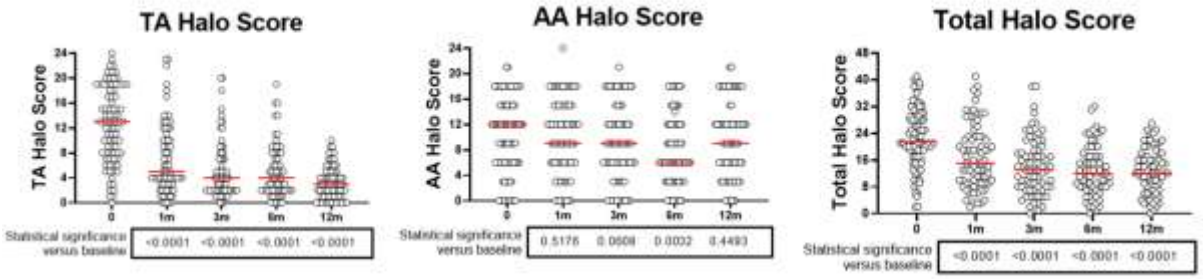



**Figure 20:** Temporal (TAHS), axillary(AAHS), and total median halo (THS) of GCA participants at baseline and 1,3,6,12 month follow-up. The Y-axis shows the halo scores, and the X- axis shows the follow-up months.



### 5.5 Treatment with Glucocorticoids and Disease-modifying anti-rheumatic drugs (DMARDs)

Per the study protocol, participants should be assessed at the FTC and perform a US within 14 days of starting glucocorticoids (GC). However, the majority of the patients in our cohort were seen within 1-5 calendar days. It was noted that with a high dose of GC treatment a significant reduction in median TAHS (from 13 to 5) within one month compared to median AAHS (from 12 to 9) (Figure 20). In the cohort of patients who completed 12 months of follow-up (73 patients), half of them were treated only with GC, and another half-received treatment combined with a DMARD and GC (30, 83%) or DMARD alone (6, 17%). No significant difference was noted in GCAPS at baseline or clinical symptoms, except the polymyalgic symptoms more in the DMARD group than in the GC-only group (58% vs 35%). Notably, 89% of the GC-only group had C-GCA, and 50% of the DMARD group had LV involvement. There was no difference in the remission rate (89%) at 12 months. However, it was observed that in the DMARD group, 75% of the patients had relapsing and refractory disease. DMARD group had high level of C-Reactive protein (CRP) at baseline compared to GC only group. There was no difference in the cumulative dose of GC at 12 months between both groups; however, we hypothesise that in the DMARD group, GC use could have been much higher if the DMARD was not introduced in this group to achieve remission (Table 21).

**Table 21. GCA patients completed 12 months of follow-up (GC only vs DMARD use)**

| Patients' characteristics | GCA with completed follow-up (n=73) | | P-Value |
|---|---|---|---|
| | GCA treated with DMARD=36 | GCA not treated with DMARD=37 (GC only) | |
| Age, median (range) years | 73.5 (60-89) | 76 (60-89) | 0.4271 |
| Sex, Females, n (%) | 23 (64%) | 24 (65%) | 1 |
| High dose steroids at baseline, n (%) | 35 (97%) | 36 (97%) | 1 |
| Steroid dose (mg) at baseline, median (range) | 45 (0-60) | 50 (0-60) | |
| **GCAPS category, n (%)** | | | |
| Low risk | 0 (0%) | 0 (0%) | 1 |
| Intermediate risk | 8 (22%) | 8 (22%) | 1 |
| High risk | 28 (78%) | 29 (78%) | 1 |
| **Halo Score (HS) median (range)** | | | |
| Temporal artery HS | 11 (0-23) | 13 (1-22) | 0.7039 |
| Axillary artery HS | 12 (0-21) | 12 (0-18) | 0.4777 |
| Total HS | 22.5 (2-41) | 21 (5-40) | 0.7718 |
| **Type of GCA** | | | |
| Cranial, no. of patients (%) | 18 (50%) | 33 (89%) | <0.001 |
| LV, no. of patients (%) | 5 (14%) | 0 (0%) | 0.0251 |
| Cranial + LV, no. of patients (%) | 13 (36%) | 4 (11%) | 0.0134 |
| **Clinical features, n (%)** | | | |
| Generalised headache | 6 (17%) | 9 (24%) | 0.5642 |
| Temporal headache | 25 69%) | 30 (81%) | 0.2871 |
| Scalp tenderness | 17 (47%) | 19 (51%) | 0.8163 |
| Jaw claudication | 18 (50%) | 21 (57%) | 0.6418 |
| Tongue pain | 4 (11%) | 3 (8%) | 0.7106 |
| Polymyalgic symptoms | 21 (58%) | 13 (35%) | 0.618 |
| Constitutional symptoms | 21 (58%) | 18 (49%) | 0.4844 |
| Any visual disturbance | 15 (42%) | 21 (57%) | 0.2447 |
| Blurred vision | 7 19%) | 13 (35%) | 0.190 |
| Double vision | 4 (11%) | 8 (22%) | 0.3447 |
| Amaurosis | 1 (30.1148%) | 6 (16%) | 0.107 |
| Partial or complete vision loss | 8 (22%) | 7 (19%) | 0.7784 |
| **Examination findings, n (%)** | | | |
| Temporal artery thickening | 10 (28%) | 10 (27%) | 1 |
| Temporal artery tenderness | 12 (33%) | 12 (32%) | 1 |
| Temporal artery abnormal pulse | 2 (6%) | 8 (22%) | 0.0854 |
| Bruits | 2 (6%) | 0 (0%) | 0.2397 |
| AION | 6 17%) | 5 (14%) | 0.7537 |
| CRAO | 2 (6%) | 1 (3%) | 0.6145 |
| Ocular nerve palsy | 1 (3%) | 3 (8%) | 0.6145 |
| **Past medical history** | | | |
| Stroke/TIA | 0 (0%) | 4 (11%) | 0.1148 |
| Hypertension | 17 (47%) | 21 (57%) | 0.4856 |
| Atrial fibrillation | 6 (17%) | 4 (11%) | 0.5151 |
| Diabetes mellitus | 6 (17%) | 4 (11%) | 0.5151 |
| Thyroid disease | 4 (11%) | 0 (0%) | 0.0541 |
| Osteoporosis | 0 (0%) | 2 (5%) | 0.4932 |
| Any malignancy | 4 (11%) | 1 (3%) | 0.1992 |
| Pre-existing eye disease | 5 (14%) | 4 (11%) | 0.7355 |
| PMR | 6 (17%) | 3 (8%) | 0.3081 |
| Other rheumatological diseases | 1 (3%) | 1 (3%) | 1 |
| **Laboratory markers at baseline** | | | |
| CRP mg/dL, median (range) | 72.2 (6.4-292) | 59 (6-206) | 0.4321 |
| ESR mm/hour, median (range) | 67 (9-130) | 57 (2-120) | 0.0762 |

| | | | |
|---|---|---|---|
| Haemoglobulin (g/L), median (range) | 120 (88-167) | 122 (103-150) | 0.9762 |
| Platelets, $10^9$/L, median (range) | 362 (234-567) | 375 (110-743) | 0.4238 |
| **Disease course during 12m** | | | |
| Stable remission after start of treatment, no. of patients (%) | 32 (89%) | 33 (89%) | 1 |
| Refractory disease, no. of patients (%) | 18 (50%) | 4 (11%) | <0.001 |
| Relapsing disease (at least one relapse), no. of patients (%) | 9 (25%) | 0 (0%) | 0.001 |
| Refractory and relapsing disease, no. of patients (%) | 0 (0%) | 0 (0%) | 1 |
| **DMARD treatment** | | | |
| No DMARD used, no. of patients (%) | 36 (100%) | 0 | ** |
| MTX used, no. of patients (%) | 8 (22%) | 0 | |
| LEF used, no. of patients (%) | 15 (42%) | 0 | |
| TCZ used, no. of patients (%) | 10 (28%) | 0 | |
| MTX+TCZ used, no. of patients (%) | 1 (3%) | 0 | |
| LEF+TCZ used, no. of patients (%) | 1 (3%) | 0 | |
| Other DMARD used, no. of patients (%) | 1 (3%) | 0 | |
| **Reasons for DMARD use** | | | |
| Refractory | 18 (50%) | | |
| Relapse | 9 (25%) | | |
| Ischemic | 4 (11%) | | |
| Steroid toxicity / contra-indication | 4 (11%) | | |
| **GC treatment** | | | |
| Prednisolone starting dose, median (baseline) | 45 (0-60) | 50 (0-60) | 0.6031 |
| Prednisolone dose at 1m, median (range) | 30 (15-60) | 37.5 (15-60) | 0.3220 |
| Prednisolone dose at 3m, median (range) | 15 (5-40) | 15 (1-30) | 0.0039 |
| Prednisolone dose at 6m, median (range) | 6.75 (0-15) | 7.5 (0-35) | 0.1221 |
| Prednisolone dose at 12m, median (range) | 5 (0-25) | 2.5 (0-10) | 0.000 |
| Cumulative prednisolone dose at 12m, median (range) | 4627.5 (2600-10260.5) | 4622.5 (944-10737.5) | 0.0277 |
| **Outcome** | | | |
| Remission with prednisolone dose ≤5 mg at 12m, no. of patients (%) | 32 (89%) | 33 (89%) | 1 |

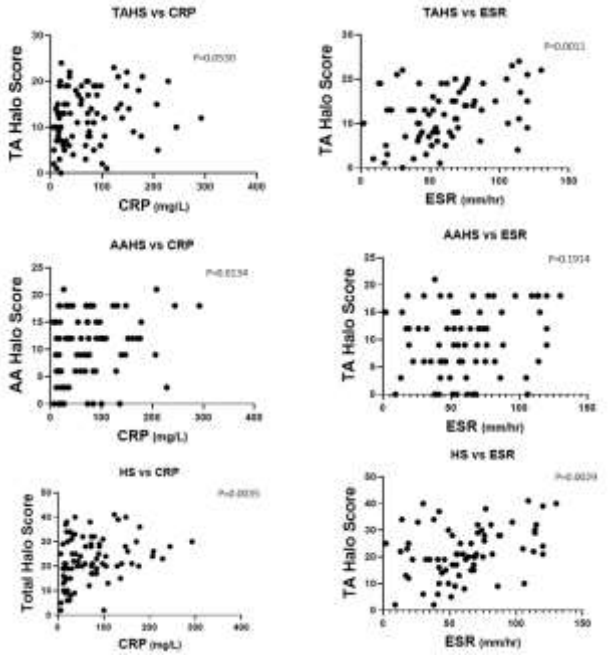
*Abbreviation: DMARD. Disease-modifying anti-rheumatic drug; GCA, Giant cell arteritis; GC, Glucocorticoids; LEF, Leflunomide; MTX, Methotrexate; TCZ, Tocilizumab; ** 2nd column not received DMARDs, thus no P-value*

Categorical variables are presented as frequency and percentage (%). Quantitative variables were compared between groups using Mann–Whitney *U* test (eg- CRP levels). Categorical variables ( scalp tenderness) were compared between groups using the Two-tailed Fisher's exact test. $P < .05$ indicates statistical significance

## 5.6 Vascular and systemic inflammation

We hypothesise that the ultrasound findings could be linked to systemic inflammation in patients with GCA. It was noted that the AAHS and THS had a good correlation with CRP. There was a lack of correlation between TAHS with CRP. However, it was noted TAHS had a good correlation with ESR (Figure 21). Pre-treatment median CRP was 59.5 mg/ and ESR 59 mm/hour dL in GCA patients.

**Figure 21: Correlation between Halos score (Y-axis) and inflammatory markers (CRP/ESR) (X-axis), scatter plot showing corresponding values of CRP and ESR and different measures of TA halo score, AA halo score and Total halo score.**




## 5.7 Remission/primary outcome

65 of 73 GCA patients completed the 12 months follow-up and achieved remission. No big difference was noted in the halo scores in both groups in remission and not in remission. Polymyalgic symptoms (49%) and visual disturbance (52%) were higher in the remission group. It was noted that the median CRP was elevated in the not remission group at baseline (118 mg/dL). In both groups, half of them used the DMARD. The median cumulative dose of GC was higher in not remission group than remission group (5573mg vs 4435mg) (Table 22)

**Table 22: Outcome: patients in remission vs not in remission**

| Patients' characteristics | All GCA =84 | | | P-Value (1st vs 2nd columns) |
|---|---|---|---|---|
| | GCA in remission=65 | GCA not in remission = 8 | GCA not in remission (8) + Lost to follow up (11) = 19 | |
| Age, median (range) years | 75 (60-89) | 72 (63-82) | 75 (63-92) | 0.242 |
| Sex, Females, n (%) | 41 (63%) | 6 (75%) | 9 (47%) | 0.7033 |
| High dose steroids at baseline, n (%) | 63 (97%) | 8 (100%) | 19 (100%) | 1.000 |
| Steroid dose (mg) at baseline, median (range) | 50 (0-60) | 50 (40-60) | 50 (40-60) | 0.7039 |
| GCAPS category, n (%) | | | | |
| Low risk | 0 (0%) | 0 (0%) | 0 (0%) | 1 |
| Intermediate risk | 14 (22%) | 2 (25%) | 4 (21%) | 1 |
| High risk | 51 (78%) | 6 (75%) | 15 (79%) | 1 |
| Halo Score (HS) median (range) | | | | |
| Temporal artery HS | 12 (0-23) | 13.5 (4-21) | 15 (4-24) | 0.7039 |
| Axillary artery HS | 12 (0-21) | 9 (0-18) | 9 (0-18) | 0.4777 |
| Total HS | 21 (2-41) | 21.5 (6-39) | 22 (6-39) | 0.7718 |
| Type of GCA | | | | |
| Cranial, no. of patients (%) | 45 (69%) | 6 (75%) | 15 (79%) | 1 |
| LV, no. of patients (%) | 5 (8%) | 0 (0%) | 0 (0%) | 1 |
| Cranial + LV, no. of patients (%) | 15 (23%) | 2 (25%) | 4 (21%) | 1 |
| Clinical features, n (%) | | | | |
| Generalised headache | 13 20%) | 2 (25%) | 3 (16%) | 0.6645 |
| Temporal headache | 47 (72%) | 8 (100%) | 15 79%) | 0.1871 |
| Scalp tenderness | 30 (46%) | 6 (75%) | 12 (63%) | 0.1522 |
| Jaw claudication | 33 (51%) | 6 (75%) | 12 (63%) | 0.2707 |
| Tongue pain | 5 (8%) | 2 (25%) | 3 (16%) | 0.1672 |
| Polymyalgic symptoms | 32 (49%) | 2 (25%) | 5 (26%) | 0.2707 |
| Constitutional symptoms | 35 (54%) | 4 (50%) | 9 (47%) | 1 |
| Any visual disturbance | 34 (52%) | 2 (25%) | 12 (63%) | 0.2611 |
| Blurred vision | 19 (29%) | 1 (13%) | 6 (32%) | 0.4321 |
| Double vision | 11 (17%) | 1 (13%) | 2 (11%) | 1 |
| Amaurosis | 6 (9%) | 1 (13%) | 9 (47%) | 0.5727 |
| Partial or complete vision loss | 15 (23%) | 0 (0%) | 6 (32%) | |
| Examination findings, n (%) | | | | |
| Temporal artery thickening | 18 (28%) | 3 (38%) | 5 (26%) | 0.6819 |
| Temporal artery tenderness | 21 (32%) | 3 (38%) | 3 (16%) | 0.7129 |
| Temporal artery abnormal pulse | 8 (12%) | 2 (25%) | 6 (32%) | 0.3003 |
| Bruits | 2 (3%) | 0 (0%) | 0 (0%) | 1 |
| AION | 11 (17%) | 0 (0%) | 4 (21%) | 0.346 |
| CRAO | 3 (5%) | 0 (0%) | 1 (5%) | 1 |
| Ocular nerve palsy | 4 (6%) | 0 (0%) | 0 (0%) | 1 |
| Past medical history | | | | |
| Stroke/TIA | 4 (6%) | 0 (0%) | 1 (5%) | 1 |
| Hypertension | 34 (52%) | 4 (50%) | 13 (68%) | 1 |
| Atrial fibrillation | 9 (14%) | 1 (25%) | 2 (11%) | 1 |
| Diabetes mellitus | 10 (15%) | 0 (0%) | 2 (11%) | 0.5884 |
| Thyroid disease | 3 (5%) | 1 (13%) | 1 (5%) | 0.3780 |
| Osteoporosis | 2 (3%) | 0 (0%) | 1 (5%) | 1 |
| Any malignancy | 4 (6%) | 1 (13%) | 3 (16%) | 0.4501 |
| Pre-existing eye disease | 8 (12%) | 1 (13%) | 2 (11%) | 1 |
| PMR | 7 (11%) | 2 (25%) | 3 (16%) | 0.2548 |
| Other rheumatological diseases | 2 (3%) | 0 (0%) | 0 (0%) | 1 |
| Laboratory markers at baseline | | | | |
| CRP mg/dL, median (range) | 68 (6-292) | 118.1 (25-228) | 34 (11-244) | 0.0989 |
| ESR mm/hour, median (range) | 57 (2-130) | 85.5 (41-120) | 61 (13-120) | 0.0587 |
| Haemoglobulin (g/L), median (range) | 120.5 (88-167) | 118 (100-135) | 121 (98-147) | 0.7188 |
| Platelets, $10^9$/L, median (range) | 361 (110-743) | 432.5 (338-552) | 345 (199-552) | 0.1052 |

| | | | | |
|---|---|---|---|---|
| **Disease course during 12m** | | | | |
| Stable remission after start of treatment, no. of patients (%) | 65 (100%) | 0 (0%) | 0 (0%) | ** |
| Refractory disease, no. of patients (%) | 17 (26%) | 1 (13%) | 4 (21%) | 0.670 |
| Relapsing disease (at least one relapse), no. of patients (%) | 6 (9%) | 3 (38%) | 3 (16%) | 0.054 |
| Refractory and relapsing disease, no. of patients (%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 |
| **DMARD treatment** | | | | |
| No DMARD used, no. of patients (%) | 32 (49%) | 4 (50%) | 8 (42%) | 1 |
| MTX used, no. of patients (%) | 7 (11%) | 1 (13%) | 1 (5%) | 1 |
| LEF used, no. of patients (%) | 13 (20%) | 2 (25%) | 6 (32%) | 0.6645 |
| TCZ used, no. of patients (%) | 9 (14%) | 1 (13%) | 1 (5%) | 1 |
| MTX+TCZ used, no. of patients (%) | 1 (2%) | 0 (0%) | 0 (0%) | 1 |
| LEF+TCZ used, no. of patients (%) | 1 (2%) | 0 (0%) | 0 (0%) | 1 |
| Other DMARD used, no. of patients (%) | 1 (2%) | 0 (0%) | 0 (0%) | 1 |
| Reasons for DMARD use | | | | |
| Refractory | 17 (26%) | 1 (13%) | 4 (21%) | 0.670 |
| Relapse | 6 (9%) | 3 (38%) | 3 (16%) | 0.054 |
| Ischemic | 4 (6%) | 0 (0%) | 1 (5%) | 1 |
| Steroid toxicity / contra-indication | 4 (6%) | 0 (0%) | 0 (0%) | 1 |
| **GC treatment** | | | | |
| Prednisolone starting dose, median (baseline) | 50 (0-60) | 50 (0-60) | 50 (40-60) | 0.7039 |
| Prednisolone dose at 1m, median (range) | 37.5 (15-60) | 38.75 (30-45) | 40 (10-60) | 0.3320 |
| Prednisolone dose at 3m, median (range) | 15 (1-40) | 19.38 (10-25) | 18.75 (10-25) | 0.0048 |
| Prednisolone dose at 6m, median (range) | 7.5 (0-15) | 9 (2.5-35) | 7.5 (2.5-35) | 0.1211 |
| Prednisolone dose at 12m, median (range) | 2.5 (0-5) | 7.5 (7-25) | 7.5 (7-25) | 0.000 |
| Cumulative prednisolone dose at 12m, median (range) | 4435 (944-10260.5) | 5573.75 (4595-10737.5) | 5573.75 (4595-10737.5) | 0.0257 |
| **Outcome** | | | | |
| Remission with prednisolone dose ≤5 mg at 12m, no. of patients (%) | 65 (100%) | 0 (0%) | 0 (0%) | ** |

*Abbreviation: DMARD. Disease-modifying anti-rheumatic drug; GCA, Giant cell arteritis; GC, Glucocorticoids; LEF, Leflunomide; MTX, Methotrexate; TCZ, Tocilizumab; **2nd column not reached remission, thus no P-value*

Categorical variables are presented as frequency and percentage (%). Quantitative variables were compared between groups using Mann–Whitney *U* test (eg- CRP levels). Categorical variables ( scalp tenderness) were compared between groups using the Two-tailed Fisher's exact test. $P < .05$ indicates statistical significance

# CHAPTER SIX: DISCUSSION

Ultrasound is a non-invasive procedure, safe and easily accessible and repeatable in the GCA FTC setting, without any radiation exposure to the patient or the sonographer. EULAR recommends ultrasound as a first-choice imaging investigation in suspected GCA(4), and the British Society of Rheumatology strongly recommends Ultrasound or TAB as a confirmatory test in suspected GCA(436). A recent study by Monti et al. suggests using ultrasound as a surrogate tool to replace TAB(345). Ultrasound has now become an essential part of the workup of GCA in many centres. However, current US practice in GCA is to declare the positive or negative test for the 'Halo sign' in a dichotomous manner. The extent and severity of the halo sign in assessing disease diagnosis (in the context of differing pre-test probabilities), severity and prognosis are yet to be studied. Halo is morphologically defined as a dark hypoechoic area around the vessel lumen representing vessel wall inflammation. In temporal arteries, the compression sign, with a video in the transverse plane, will be assessed to confirm all diagnoses of GCA. Non-compressible halo is the key lesion in GCA. Halo thickness will be measured in TA, its branches and axillary arteries.

We used the published cut-off values of the IMT of TA and axillary arteries as assessed by the high-frequency probe (22 MHz)(340). We used the 18 MHz probe in this study for TA assessment and at least a 15 MHz probe for axillary artery assessment, which complies with EULAR recommendations of using a probe of frequency >15 MHz. Importantly, US is an operator-dependent technique associated with remarkable sensitivity and specificity only when performed by a skilled clinician. In this study, experienced sonographers from all the participating centers measured the IMT from all the 8 vessels and transformed to pre-defined quantified graded halo scores. Although, in our study showed IMT measurement is reliable it

is not possible in different clinic setup which is run by the sonographers with different level of experience. Thus, a quantifying the halo is the way to overcome this issue. We have developed a halo score grading the halo thickness in temporal and axillary arteries(341). Ultrasound halo score correlates with vascular inflammation in GCA and is strongly associated with ocular ischemia in GCA(341).

Our current prospective, the multicentre study, supports that the extent of vascular inflammation on Ultrasound, as quantified by the halo score, can be reliably used for diagnosis and monitoring the disease activity in GCA by the change of the score from diagnosis to prognosis, assessing the treatment response and more importantly the link with the degree of intimal hyperplasia correlates with histology. The above is not possible only measuring the IMT. IMT measures in millimetres and the reliability is not guaranteed if this is not done by the experienced sonographers.The extent of inflammation was measured in the three TA branches and axillary arteries. Subclavian, facial or vertebral arteries were not evaluated in this assessment. However, axillary artery involvement identifies the vast majority of patients with inflammation of large systemic arteries (402), whereas TA involvement identifies nearly all patients with cranial artery involvement(407). EULAR recommendations accept temporal and axillary artery ultrasound assessment to start with suspected GCA (4). Evaluation of temporal and axillary arteries might therefore provide a reasonable estimation of the disease extent of GCA. Other arteries, such as facial, vertebral or occipital arteries, also diagnose GCA in selected subjects (407). It is not routinely used in clinical practice. This may be a future research interest to extend the vessel assessment in GCA.

A previous study has shown that a raised ultrasonographic halo score in GCA patients had a link with the temporary artery histological pattern observing the intimal hyperplasia (318).

intimal hyperplasia is caused by the proliferation of myofibroblasts in the intimal layer of the arterial wall. These cells are derived from activated vascular smooth muscle cells in the medial layer(481). Intimal hyperplasia is associated with GCA-related sight loss. Therefore, halo scores may identify a subset of GCA patients with intimal hyperplasia and a degree of ischemic sight loss. Patients with a positive TAB and intimal hyperplasia showed the most extensive arterial wall swelling on ultrasound, as indicated by high halo scores. This supports that ultrasonographic halos primarily reflect the thickening of the intima-media complex, particularly the intima (392,482). An earlier study indicated that halos are linked to the presence of transmural infiltrates in the TAB, but the impact of intimal hyperplasia was not evaluated(462). However, a later study suggested that halo scores are strongly associated with intimal hyperplasia in patients with GCA (318). Our study strongly supports the correlation between these patients' positive TAB and high halo scores. On the other hand, transmural inflammation in the absence of intimal hyperplasia was associated with low halo scores, as seen in our TAB-negative patients.

To the best of our knowledge, this is the first prospective, multicentre study to assess the diagnostic and prognostic value of the ultrasonographic halo score. Our study strongly supports the role of diagnostic accuracy of cranial GCA with high temporal artery halo scores. The optimum cut-off halo score in diagnosing GCA was a temporal artery halo score of 6 or above. This had high sensitivity and specificity (86% and 92%). When applying the same morphological principle of halo definition to axillary arteries, the dark hypoechoic halo patterns differ from the normal intima-media complex, which can be identified as a double line in the axillary artery(394). Part of the halos reported in the axillary arteries were smaller than a published diagnostic cut-off value of 1.0 mm on ultrasound(444). However, some reports have already suggested that axillary arteries may be inflamed despite a halo thickness <1.0 mm on

ultrasound(483,484). Since there is evidence that <1.0 mm might still relate to the disease activity and our study gives an optimum cut-off halo score of 11 in diagnosing GCA with low sensitivity (52%) and fair specificity (75%), we are not entirely convinced that axillary artery halo score has a role in diagnosing GCA. A more, deep study into this is required.

Although the US is a valuable tool for studying the haemodynamic and morphology of the blood vessels(485) it remains a challenge to interpret the morphological changes in the different sizes of the blood vessels. A follow-up study observed an 85% reduction of the vessel wall in the temporal artery with treatment contrasted to the large vessels showing a decrease of 45%(430). A possible explanation is an inclusion of popliteal and femoral arteries frequently involved in atherosclerosis. This is true in assessing the axillary arteries, where atherosclerosis can mimic a false halo which gives a false positive interpretation(418). There is a potential notion that the male sex was associated with higher halo scores in patients with GCA. A study reported that the male sex predicted a halo sign on ultrasound in patients with GCA (486). it might be possible that GCA is associated with more arterial thickening in men than women. However, it is understandable that the arterial calibre and arterial thickness are generally higher in men than in women(400). It is not part of our study to assess gender involvement in GCA, but it would be interesting to evaluate sex-specific analysis on arterial wall thickness.

The identification of prognostic factors in GCA is both timely and needed. Recent British Society of Rheumatology guidelines recommends initiating a high dose of glucocorticoids immediately in highly suspected patients with GCA(436). At presentation, extensive vascular involvement of both cranial and large vessels, evidenced by ultrasound, showed a poor response to GC treatment in GCA and often required steroid-sparing agents(487). This is particularly true in large vessel GCA. A case series showed a significant vessel wall reduction in the ultrasound and PET CT in response to Tocilizumab treatment in large vessel

GCA (488). The GiACTA trial has demonstrated that IL-6R blocking therapy may help to sustain glucocorticoid-free remission(168). In our study, half of the patients who completed the 12-month follow-up were on disease-modifying anti-rheumatic drug therapy such as Methotrexate, Leflunomide or Tocilizumab. Half of these on this treatment have large vessel vasculitis and are in sustained remission.

On the other hand, the patients only on glucocorticoid treatment majority (89%) had only cranial GCA. We did not observe that the halo score was a predictor and stratified the patients who should receive steroid-sparing agents at the initial visit. However, we propose that starting a steroid-sparing agent early in large vessel-involved GCA would achieve remission, reduce the glucocorticoid burden, and avoid adverse effects. A recent study showed that Anakinra, an IL-1 inhibitor, had a role in GCA(489) and several other studies are underway in GCA treatment.

There are reports of serial ultrasound examinations pre, and post-glucocorticoid treatment that have shown that it takes weeks to months before the majority of temporal artery halos disappear, while only a few axillary artery halos disappear(400,428,430). Previously, we have reported no clear association between short-term glucocorticoid treatment and the extent of vascular inflammation on ultrasound(341). Our current study observed a significant reduction in the temporal artery halo scores at four weeks of initiation of glucocorticoid treatment. Axillary artery halo scores didn’t show any dramatic reduction as temporal artery halo scores but showed a 50 % reduction by six months. It is interesting to see the halo reduction within the first month of initiation of glucocorticoids to check the reliability of the halo in diagnosing GCA. This has practical challenges and needs more extensive studies.

Inflammatory markers play a major role in systemic inflammation. The erythrocyte sedimentation rate (ESR) was included in the previous ACR 1990 classification criteria for

GCA(19). The newer ACR/EULAR 2022 criteria include CRP or ESR as acceptable inflammatory markers(27). However, it is evidenced that more recent biologic treatment, such as Tocilizumab, switches off the inflammatory marker response, making it challenging to use traditional biomarkers such as CRP to measure disease activity(490). therefore, we questioned the role of the halo score in predicting the inflammatory response. We have previously published our retrospective data showing a positive correlation between CRP and halo scores(491). Our current study observed that the axillary artery and total halo score positively correlated with CRP. However, the correlation with the temporal artery halo score is less clear. The ESR is traditionally used with the Westergren method, and currently, many laboratories use the Alifax method. The Westergren method measures the distance (in millimetres) at which red blood cells in anticoagulated whole blood fall to the bottom of a standardized, upright, elongated tube over one hour due to the influence of gravity(492). The Alifax method measures ESR, a capillary photometric kinetic technique(493). Previously we reported no correlation between ESR and halo count or halo scores(341). However, our current data showed a positive correlation between ESR and temporal artery halo scores. As this is a multicenter study, this remains questionable as we do not know which method was used across the centres to measure the ESR. A sub-group analysis and more studies may give light on this.

Southend GCA probability score (GCAPS) allows the GCA suspects to be stratified in to Low, Intermediate and high-risk categories based on the scoring system. This is very easy to use in clinical practice and has now been integrated in to the GCA fast-track clinics in many centres. The GCAPS was initially defined as a cut-off score of 9.5 to discriminate between GCA and non-GCA(312). Later, we developed the probability-based algorithm using the GCAPS and stratified it into three risk groups (<9: Low risk, 9-12: Intermediate risk and > 12 High risks). This also allows clinicians to identify the necessity for additional tests in selected

cases(313). Since this algorithm was developed, many centres have tried to validate the algorithm externally. A study has reported a GCAPS < 10 gives a sensitivity of 100% and specificity of 67.1%(315). Another study published they have few GCA cases in the low-risk category, and thus the low-risk category had a sensitivity of 90.5%(314). Another abstract presented at the ACR 2022 (abstract 1265) highlighted that GCAPS <8 can safely rule out GCA. In our current prospective multicenter HAS GCA study, the overall prevalence of GCA was increased to 37%. This prevalence rose satisfactorily through the various pre-test probability groups (Low, 0%, Intermediate, 24%, High, 74%). We, therefore, feel that this algorithm successfully stratifies suspected GCA referrals for ultrasound and additional tests and simplifies the diagnostic approach. It also validates our previous single-centre retrospective three-group categories(313). The test performance of ultrasound in GCA was considerably enhanced with this probability-based approach, as sensitivity, specificity, positive and negative predictive values in all categories were much higher than previously reported (sensitivity in the Low-risk group was undefined since there were no false negatives)(342). We feel such a pre-test approach markedly augments the diagnostic performance of a test such as ultrasound and forms the rational basis for planning additional tests based on progress through the algorithm. In the 67 cases in the low-risk category, the prevalence of GCA was 0%. Although one was interpreted as US-positive, they were not started on treatment, and further investigations failed to confirm the diagnosis. Based on this result, there is enough evidence that low-risk patients may not require a face-to-face review in a specialist clinic, providing a trained assessor accurately computes the GCAPS. This significantly reduces the in-person consultation time, where the health care services are already stretched to the maximum and struggling to meet the target to see patients post-COVID pandemic. A primary objective of the FTC is that it also speedily diagnoses severe non-GCA pathology. Hence, our probability score can allow the inclusion of other serious

mimics of GCA (as alternative diagnosis), which are rapidly confirmed with appropriate additional tests if ultrasound is negative, equivocal or discordant with clinical clues. Making a diagnosis in the high-risk group of GCA in 74% of patients with related ultrasound specificity of 91% reflects the fact that our keenness to make a correct diagnosis of GCA in this group is matched by an equal desire not to miss a non-GCA serious mimics such as malignancy, infection or systemic rheumatological disease. This probability bases approach is more cost-effective since it reduces the requests for invasive and expensive tests, such as TAB and PET-CT. The skill required to perform a TAB, the disincentive of an invasive test and the cost and waiting time of a PET-CT is ongoing challenges in most healthcare services. It makes the alternative pathology more rapid and should enable higher patient satisfaction, education, reassurance, and immediate treatment of GCA after speedy diagnostic confirmation.

The three currently existing ultrasonographic scores, originally described for assessment of disease extent and severity in temporal and axillary arteries of patients with GCA, performed equally well for diagnosis. This includes the Halo count, which is the simplest score, the Halo Score and the OGUS. We are in the process of updating the Halo Score to reflect changes to axillary artery reference values. In the current study we included the axillary IMT >1.0mm as published before and the halo score was graded accordingly. We learned now that this could potentially change to >0.9mm to consider as abnormal. We need more studies to validate this. As protocolised in our study we calculated the axillary artery halo score multiplied by three to equalise with temporal halo score, however in future studies we are proposing to leave the grades as a single grade similar to temporal artery scores. Since the collection of the original measurement underlying the latter score, the definitions of abnormal findings and machine performance have changed considerably, leading to updated EULAR imaging recommendations. Nevertheless, temporal artery grading still performed well, despite the

Halo Score being developed with data obtained over 10 years ago in the TABUL study. The OGUS, which is the most complex score, has been provisionally selected as the score for therapy monitoring based on its performance in an online reliability exercise. This is currently only recommended to use in clinical trials. Interestingly, our patient-based reliability exercise showed equally good reliability for all three scores.

Integration of clinical and ultrasound features currently remains a subjective process dependent on the expertise of individual physicians. To standardise the assessment of GCA probability, we aimed to develop a prediction model that 1) incorporates the full range of SGCAPS and ultrasonographic scores and 2) accurately identifies patients with or without GCA, as well as patients that would benefit from additional diagnostic testing. We are currently developing this prediction model from patients recruited in the HAS-GCA study, a multi-centre, prospective, longitudinal inception cohort study of newly diagnosed GCA and relevant controls recruited from suspected GCA referrals to fast-track clinics.

The strength of our study includes its prospective design and a protocol-driven multicentre approach with the patients undergoing a fixed scheduled clinical assessment and ultrasound scans. The clinical diagnosis was rigorously established after six months. More importantly, non-GCA patients also had a consultation after six months to ensure their diagnoses were not reversed. The ultrasound scans were done by vastly experienced sonographers, either rheumatologists with many years of scanning experience or vascular sonographers with expert skills. We acknowledge that not all the sonographers were participants in the inter-rater, intra-rater reliability exercise. Still, the impressive results from the real-life experience of five sonographers resemble the reliably converted to the entire group. Our study also has potential limitations. Despite our best effort to avoid this, not all the sonographers were not blinded to

the clinical data. However, a symptom likely to bias the ultrasonographer, an abnormal temporal artery on palpation, showed no effect on the halo score or probability score. As we already acknowledged, inter-rater and intra-rater reliabilities were not tested among all sonographers and should be a focus in future studies. Another issue to acknowledge is the treatment of GCA was not protocolised between the centres. In the UK, centres followed the British Society of Rheumatology treatment guidelines. However, all other centers followed their relevant guidelines depending on their country of origin. We need to be cautious that this is an observational study, and in the real-life clinical set up it is not practical to protocolise the treatment model, which can jeopardise the patients' management. Positively, from this multicentre approach we did not see any major drawbacks; in fact we learned the different modalities of treatment with initiation of the steroid-sparing agents and the prognostic effect. In the DMARD group 50% of them were LV-GCA, and in the GC group only 11% were LV-GCA. This shows the importance of DMARD use in LV-GCA. The COVID pandemic affected the study by the reduced number of control participants than expected, increased anxiety among the patients to attend scheduled appointments and pause of the study for a time period for the safety of all.

## CHAPTER SEVEN: CONCLUSION & FUTURE IMPLICATIONS

The Southend GCA probability score (GCAPS) is a promising, stratifying tool in the GCA fast-track clinic referrals and excludes mimics. The probability-based algorithm interprets ultrasound in context, clarifies a diagnostic approach and identifies an uncertain need for re-evaluation and alternative tests. This algorithm is validated in many centres around the world and become a part of the daily GCA FTC practice. The major objective of the FTC is that it allows to have a quicker diagnosis of GCA and exclude the non-GCA mimics. Hence our probability score can allow inclusion of other serious alternative diagnosis, which are confirmed with appropriate additional tests if US is negative, equivocal or discordant with clinical clues. Making a diagnosis in the high-risk group of GCA in 74%of patients with related US specificity of 91% reflects the fact that our keenness to make a correct diagnosis of GCA group is matched by an equal desire not to miss a non-GCA serious mimic such as head and neck cancer, infection or systemic rheumatological disease. On the other hand, in the low-risk GCA group having a 100% negative predictive value confirmed the value of the GCAPS in FTC and exclude one third of the referred patients from a diagnosis of GCA. This avoids unnecessary steroid exposure in this group.

Current hypothesis proposes that GCA and PMR are not monolithic diseases, and that they represent parts of a single disease spectrum more easily identified as GPSD and that differences at baseline and during disease course can be recognised employing a combination of clinical, laboratory and imaging parameters. Early disease stratification may help with assessment of severity and extent, identification of organ involvement, prevention of ocular and vascular damage, choice of appropriate non-steroid therapy, reduction of flare rates and steroid-related adverse events. Such a timely approach to disease assessment and effective therapy may yield major cost savings, while improving patient outcomes. Disease stratification may allow development of separate categories of assessment of response to

therapy, one related to systemic inflammation and the other related to disease activity and damage seen at anatomical sites of involvement. Prospective research is urgently required.

The value of using the US in the GCA FTC is becoming part of the clinical practice and recommended by EULAR and BSR to use as a first line investigation in suspected GCA when adequate expertise is available. US is cheap, and no radiation on the patients and tolerated by all the patients at the bedside. Our study proved the vastly experienced sonographer's involvement in their respective centres to recruit the study participants. Our real-life reliability exercise among the 5 experienced sonographers had high ICC values and agreed well. The experience of the sonographers reflects on the results of this exercise. Also, this exercise emphases the measurement of IMT in millimetres is more prone to errors and quantifying the halo score within the range of the IMT is more robust and clinically relevant.

Halo sign and compression sign has been used to measure the IMT in a dichotomous way to diagnose or eliminate GCA. Our systematic review and meta-analysis of the role of the halo sign in the assessment of GCA showed that at present halo sign plays a pivotal role in sonographic identification of vessel wall inflammation and it is comparable to temporal artery biopsy. However, temporal artery biopsy is an invasive procedure and can have skip lesions which can be easily missed. This given the biopsy has very low sensitivity compared to halo sign. In addition, US has the advantage of assessing the large vessels such as axillary arteries which is not possible to biopsy. This review included both the retrospective and prospective observational studies. The retrospective studies might have contributed to bias in analysing the final data. Selection bias may occur when imaging is only performed in certain patient groups (eg, dubious cases), rather than in all patients with suspected disease. Expectation bias may lead to an overestimation of diagnostic properties when the imaging assessor is also aware of the clinical symptoms of a patient (which is common in retrospective studies).

Lastly, the selection bias inherent in case–control studies can lead to an overestimation of the value of the imaging technique, as controls are usually not patients with suspected GCA, but rather healthy controls or patients with other diseases, leading to an unrealistically large contrast between cases and controls. In future studies by including prospective studies only will increase precision. We believe that further meta-analysis in the field should include only prospective studies, which is now possible, due to the large number of high-quality studies. Our current HAS-GCA study is a multicentre, prospective study has overcome some of these issues. By qualifying the halo and grading, the halo score minimises the operator dependency of the results of the scan. Also, the halo score, graded with halo thickness, confirms the halo sign and halo count are significantly correlated with inflammatory markers, ocular ischemia and intimal hyperplasia on temporal artery biopsy.

Test performance of ultrasound is significantly enhanced with GCAPS. The extent of arterial inflammation in GCA can be quantified by ultrasound halo scoring. Also, the halo score showed a positive correlation with the temporal artery intimal hyperplasia. Therefore, ultrasound's high volume of vascular inflammation might strongly support the diagnosis of GCA and identify patients at risk for ocular ischemia. This approach overcomes the bias of the traditional use of dichotomous halo sign. Ultrasound is the bedside, non-invasive tool that can be reliably used in GCA diagnosis and follow-up in most GCA suspects, reducing the waiting time and the unnecessary expensive other investigations. The clinical application of GCAPS and halo scores warrants further validation in other studies**.**

Future research in GCA should focus on using ultrasounds with high-frequency probes, which auto-generate the intimal medial thickness and identify the halos. This will reduce the inter-rater and intra-rater variable bias. Ultrasound halo scores should need validation in other centres and focus on developing a universal score, perhaps an age and sex-matched score. Another research interest would be to expand the examinations of the other arteries, such as

vertebral, facial, occipital and maxillary arteries to have a wider examination to see the sensitivity changes and to conclude when we need to assess the other arteries to evaluate GCA. There is an unmet need for a wider reliability exercise among the sonographers and perhaps to group them according to their level of experience, and this should be a future focus in the studies. Our group is currently developing a diagnostic prediction model using the SGCAPS and named HAS-GCA score. HAS-GCA score, we are integrating the halo count, OGUS and halo score with SGCAPS. An important advantage of the HAS-GCA score is that it effectively uses all clinical and ultrasonographic data obtained in patients suspected of GCA. Categorisation of SGCAPS (i.e. low, intermediate, high risk) and ultrasonography findings (halo present or absent) might lead to loss of predictive information and introduce subjectivity dependent on the clinician's expertise. Our findings standardise the prediction of GCA probability by incorporating the full range of SGCAPS and ultrasonographic scores to accurately identify patients with or without GCA, as well as patients that would benefit from additional diagnostic testing. Importantly, the HAS-GCA score is easy to use without the need for a computer/calculator.This needs validation in future prospective studies.

**Ethical approval and consent to participate.**

The study was performed in accordance with the declaration of Helsinki. The research protocol has been approved by the National health services health research authority (IRAS number 264294), the research ethics committee- London Stanmore (REC number 19/LO/1375), the University of Essex research committee (ETH1920-0145) and all the participating centres in Spain, Italy and Netherland in their local ethics committee according to their local research ethics approval process. On the day of the study, patients attending the GCA FTC were provided with information about the study and invited to volunteer. Written consent was obtained from each participant prior to commencing the initial screening interview. Participants were provided with study information again at this point and encouraged to ask any specific questions from researchers. Participants were advised to opt out of the study at any stage. Participants invited to attend follow-up appointments for the study were again required to provide informed verbal and written consent at the beginning of this research phase. Verbal consent was continually obtained at the beginning of each sub-phase, and participants were reminded of the voluntary nature of their participation.

**Availability of data and materials**

Research team members ensured that participants' anonymity was maintained. Participants were identified by a unique study number on all documents and electronic databases. All records were stored securely and accessible by research team members and authorised personnel. The data will be saved for a minimum of 5 years. The study complied with General Data Protection Regulation (GDPR), which requires data to be anonymised as soon as it is practical. The collected data was stored electronically in an encrypted file, and the consent forms were securely stored in a storage facility. The chief investigator was responsible for all the data stored securely.

**Funding**

Dr Alwin Sebastian is funded by the Royal College of Physicians of Ireland (RCPI) for a two years research/clinical fellowship (Bresnihan-Molloy international education fellowship), part of the higher specialist training in Rheumatology. RCPI does not have any impact on study design, data analysis, data interpretation, and the thesis's writing.

## References


1. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: Duration and adverse outcomes. Arthritis Rheum. 2003 Oct;49(5):703–8.
2. Sebastian A, Tomelleri A, Dasgupta B. Current and innovative therapeutic strategies for the treatment of giant cell arteritis. Expert Opin Orphan Drugs. 2021;9(5).
3. Ashton-Key MR, Gallagher PJ. False-negative temporal artery biopsy. Vol. 16, American Journal of Surgical Pathology. 1992.
4. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis. 2018;
5. Petri H, Nevitt A, Sarsour K, Napalkov P, Collinson N. Incidence of giant cell arteritis and characteristics of patients: Data-driven analysis of comorbidities. Arthritis Care Res (Hoboken). 2015;
6. Hayreh SS, Podhajsky PA, Zimmerman B. Occult giant cell arteritis: Ocular manifestations. Am J Ophthalmol. 1998;
7. van der Geest KSM, Sandovici M, van Sleen Y, Sanders JS, Bos NA, Abdulahad WH, et al. Review: What Is the Current Evidence for Disease Subsets in Giant Cell Arteritis? Arthritis and Rheumatology. 2018.
8. Vodopivec I, Rizzo JF. Ophthalmic manifestations of giant cell arteritis. Rheumatology (United Kingdom). 2018.
9. Prior JA, Ranjbar H, Belcher J, Mackie SL, Helliwell T, Liddle J, et al. Diagnostic delay for giant cell arteritis - a systematic review and meta-analysis. BMC Med. 2017;
10. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. The Lancet. 2008.
11. Horton BT, Magath TB, Brown GE. Arteritis of the temporal vessels: A previously undescribed form. Arch Intern Med. 1934;
12. WAGENER HP. Temporal arteritis and loss of vision. Am J Med Sci. 1946;
13. Jennings GH. ARTERITIS OF THE TEMPORAL VESSELS. The Lancet. 1938;
14. Sproul EE, Hawthorne JJ. Chronic Diffuse Mesaortitis: Report of Two Cases of Unusual Type. Am J Pathol. 1937;
15. SHICK RM, BAGGENSTOSS AH, FULLER BF, POLLEY HF. Effects of cortisone and ACTH on periarteritis nodosa and cranial arteritis. Proc Staff Meet Mayo Clin. 1950;
16. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill consensus conference nomenclature of vasculitides. In: Arthritis and Rheumatism. 2013.
17. Watts RA, Scott DGI, Mukhtyar C. Vasculitis in clinical practice, second edition. Vasculitis in Clinical Practice, Second Edition. 2015.

18. Kobayashi S, Yano T, Matsumoto Y, Numano F, Nakajima N, Yasuda K, et al. Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: The first government-supported nationwide survey. Arthritis Care and Research. 2003.

19. Hunder GG, Arend WP, Bloch DA, Calabrese LH, Fauci AS, Fries JF, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis: Introduction. Arthritis Rheum. 1990;

20. Prieto-Peña D, Remuzgo-Martínez S, Ocejo-Vinyals JG, Atienza-Mateo B, Genre F, Jiménez AM, et al. The presence of both HLA-DRB1*04:01 and HLA-B*15:01 increases the susceptibility to cranial and extracranial giant cell arteritis. Clin Exp Rheumatol. 2021;39(2).

21. Deng J, Ma-Krupa W, Gewirtz AT, Younge BR, Goronzy JJ, Weyand CM. Toll-like receptors 4 and 5 induce distinct types of vasculitis. Circ Res. 2009;104(4).

22. Koster MJ, Warrington KJ. Giant cell arteritis: Pathogenic mechanisms and new potential therapeutic targets. Vol. 1, BMC Rheumatology. 2017.

23. Samson M, Corbera-Bellalta M, Audia S, Planas-Rigol E, Martin L, Cid MC, et al. Recent advances in our understanding of giant cell arteritis pathogenesis. Vol. 16, Autoimmunity Reviews. 2017.

24. Ben-Shabat N, Tiosano S, Shovman O, Comaneshter D, Shoenfeld Y, Cohen AD, et al. Mortality among patients with giant cell arteritis: A large-scale population-based cohort study. Journal of Rheumatology. 2020;

25. Dejaco C, Duftner C, Buttgereit F, Matteson EL, Dasgupta B. The spectrum of giant cell arteritis and polymyalgia rheumatica: Revisiting the concept of the disease. Rheumatology (United Kingdom). 2017.

26. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;

27. Ponte C, Grayson PC, Robson JC, Suppiah R, Gribbons KB, Judge A, et al. 2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis. Arthritis & Rheumatology. 2022 Dec 8;74(12):1881–9.

28. Tomelleri A, van der Geest KSM, Sebastian A, van Sleen Y, Schmidt WA, Dejaco C, et al. Disease stratification in giant cell arteritis to reduce relapses and prevent long-term vascular damage. Lancet Rheumatol. 2021 Dec 1;3(12):e886–95.

29. Buttgereit F, Matteson EL, Dejaco C. Polymyalgia Rheumatica and Giant Cell Arteritis. JAMA. 2020 Sep 8;324(10):993–4.

30. Schmidt WA. Ultrasound in the diagnosis and management of giant cell arteritis. Rheumatology (United Kingdom). 2018;

31. Biousse V, Newman NJ. Ischemic Optic Neuropathies. Campion EW, editor. https://doi.org/101056/NEJMra1413352. 2015 Jun 17;372(25):2428–36.

32. Salvarani C, Cimino L, Macchioni P, Consonni D, Cantini F, Bajocchi G, et al. Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. Arthritis Care Res (Hoboken). 2005 Apr 15;53(2):293–7.

33. Cid MC, Font C, Oristrell J, De A, Sierra LA, Urbano-Marquez A, et al. ASSOCIATION BETWEEN STRONG INFLAMMATORY RESPONSE AND LOW RISK OF DEVELOPING VISUAL LOSS AND OTHER CRANIAL ISCHEMIC COMPLICATIONS IN GIANT CELL (TEMPORAL) ARTERITIS. Arthritis Rheum. 1998;41(I).

34. van der Geest KSM, Wolfe K, Borg F, Sebastian A, Kayani A, Tomelleri A, et al. Ultrasonographic Halo Score in giant cell arteritis: association with intimal hyperplasia and ischaemic sight loss. Rheumatology. 2020;

35. Makkuni D, Bharadwaj A, Wolfe K, Payne S, Hutchings A, Dasgupta B. Is intimal hyperplasia a marker of neuro-ophthalmic complications of giant cell arteritis? Rheumatology. 2008;47(4):488–90.

36. Vodopivec I, Rizzo JF. Ophthalmic manifestations of giant cell arteritis. Rheumatology (United Kingdom). 2018.

37. Hayreh SS. Giant cell arteritis: Its ophthalmic manifestations. Indian J Ophthalmol. 2021 Feb 1;69(2):227.

38. Patil P, Williams M, Maw WW, Achilleos K, Elsideeg S, Dejaco C, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015 Mar 1;33(2).

39. Kermani TA, Dasgupta B. Current and emerging therapies in large-vessel vasculitis. Rheumatology (United Kingdom). 2018 Sep 1;57(9):1513–24.

40. Nesher G, Nesher R, Mates M, Sonnenblick M, Breuer GS. Giant cell arteritis: intensity of the initial systemic inflammatory response and the course of the disease. Clin Exp Rheumatol. 2008 Jan;26(3 Suppl 49):S30-4.

41. Alba MA, García-Martínez A, Prieto-González S, Tavera-Bahillo I, Corbera-Bellalta M, Planas-Rigol E, et al. Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine. 2014 Jul;93(5):194–201.

42. Hamrin B, Jonsson N, Landberg T. INVOLVEMENT OF LARGE VESSELS IN POLYMYALGIA ARTERITICA. The Lancet. 1965 Jun 5;285(7397):1193–6.

43. Espitia O, Samson M, Le Gallou T, Connault J, Landron C, Lavigne C, et al. Comparison of idiopathic (isolated) aortitis and giant cell arteritis-related aortitis. A French retrospective multicenter study of 117 patients. Autoimmun Rev. 2016 Jun 1;15(6):571–6.

44. Dejaco C, Duftner C, Buttgereit F, Matteson EL, Dasgupta B. The spectrum of giant cell arteritis and polymyalgia rheumatica: Revisiting the concept of the disease. Rheumatology (United Kingdom). 2017.

45. Dejaco C, Duftner C, Dasgupta B, Matteson EL, Schirmer M. Polymyalgia rheumatica and giant cell arteritis: management of two diseases of the elderly. http://dx.doi.org/102217/ahe1150. 2011 Aug 12;7(4):633–45.

46. Blockmans D, De Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Rheum. 2006 Feb 15;55(1):131–7.

47. Blockmans D, De Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18-fluorodeoxyglucose positron emission tomography in isolated polymyalgia rheumatica: a prospective study in 35 patients. Rheumatology. 2007 Apr 1;46(4):672–7.

48. Muratore F, Kermani TA, Crowson CS, Green AB, Salvarani C, Matteson EL, et al. Large-vessel giant cell arteritis: A cohort study. Rheumatology (United Kingdom). 2015;54(3):463–70.

49. Hellmich B, Agueda A, Monti S, Buttgereit F, De Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020;

50. Monti S, Águeda AF, Luqmani RA, Buttgereit F, Cid M, Dejaco C, et al. Systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis: Focus on giant cell arteritis. RMD Open. 2019 Sep 1;5(2).

51. A Strong Initial Systemic Inflammatory Response is Associated With Higher Corticosteroid Requirements and Longer Duration of Therapy in Patients With Giant-Cell Arteritis. 2002;

52. Burja B, Feichtinger J, Lakota K, Thallinger GG, Sodin-Semrl S, Kuret T, et al. Utility of serological biomarkers for giant cell arteritis in a large cohort of treatment-naïve patients. Clin Rheumatol. 2019 Feb 14;38(2):317–29.

53. Hocevar A, Rotar Z, Jese R, Semrl SS, Pizem J, Hawlina M, et al. Do Early Diagnosis and Glucocorticoid Treatment Decrease the Risk of Permanent Visual Loss and Early Relapses in Giant Cell Arteritis. Medicine (United States). 2016 Apr 1;95(14):e3210.

54. Restuccia G, Boiardi L, Cavazza A, Catanoso M, Macchioni P, Muratore F, et al. Long-term remission in biopsy proven giant cell arteritis: A retrospective cohort study. J Autoimmun. 2017 Feb 1;77:39–44.

55. Bellan M, Puta E, Croce A, Sacchetti GM, Orsini F, Zecca E, et al. Role of positron emission tomography in the assessment of disease burden and risk of relapse in patients affected by giant cell arteritis. Clin Rheumatol. 2020 Apr 1;39(4):1277–81.

56. Martinez-Lado L, Calviño-Díaz C, Piñeiro A, Dierssen T, Vazquez-Rodriguez TR, Miranda-Filloy JA, et al. Relapses and recurrences in giant cell arteritis: A population-based study of patients with biopsy-proven disease from Northwestern Spain. Medicine. 2011;

57. van Sleen Y, Graver JC, Abdulahad WH, van der Geest KSM, Boots AMH, Sandovici M, et al. Leukocyte dynamics reveal a persistent myeloid dominance in giant cell arteritis and polymyalgia rheumatica. Front Immunol. 2019;10(AUG):1981.

58. Prieto-González S, Terrades-García N, Corbera-Bellalta M, Planas-Rigol E, Miyabe C, Alba MA, et al. Serum osteopontin: A biomarker of disease activity and predictor of relapsing course in patients with giant cell arteritis. Potential clinical usefulness in tocilizumab-treated patients. RMD Open. 2017;

59. Van Sleen Y, Sandovici M, Abdulahad WH, Bijzet J, Van Der Geest KSM, Boots AMH, et al. Markers of angiogenesis and macrophage products for predicting disease course and monitoring vascular inflammation in giant cell arteritis. Rheumatology. 2019 Aug 1;58(8):1383–92.

60. Nadkarni S, Dalli J, Hollywood J, Mason JC, Dasgupta B, Perretti M. Investigational analysis reveals a potential role for neutrophils in giant-cell arteritis disease progression. Circ Res. 2014;114(2):242–8.

61. Nesher G, Berkun Y, Mates M, Baras M, Nesher R, Rubinow A, et al. Risk Factors for Cranial Ischemic Complications in Giant Cell Arteritis. Medicine. 2004.

62. Cid MC, Hoffman MP, Hernández-Rodríguez J, Segarra M, Elkin M, Sánchez M, et al. Association between increased CCL2 (MCP-1) expression in lesions and persistence of disease activity in giant-cell arteritis. Rheumatology. 2006 Nov 1;45(11):1356–63.

63. Hernández-Rodríguez J, Segarra M, Vilardell C, Sánchez M, García-Martínez A, Esteban MJ, et al. Tissue production of pro-inflammatory cytokines (IL-1β, TNFα and IL-6) correlates with the intesity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. Rheumatology. 2004;

64. Samson M, Ly KH, Tournier B, Janikashvili N, Trad M, Ciudad M, et al. Involvement and prognosis value of CD8+ T cells in giant cell arteritis. J Autoimmun. 2016 Aug 1;72:73–83.

65. Espígol-Frigolé G, Corbera-Bellalta M, Planas-Rigol E, Lozano E, Segarra M, García-Martínez A, et al. Increased IL-17A expression in temporal artery lesions is a predictor of sustained response to glucocorticoid treatment in patients with giant-cell arteritis. Ann Rheum Dis. 2013 Sep 1;72(9):1481–7.

66. van der Geest KSM, Sandovici M, van Sleen Y, Sanders JS, Bos NA, Abdulahad WH, et al. Review: What Is the Current Evidence for Disease Subsets in Giant Cell Arteritis? Arthritis & Rheumatology. 2018 Sep 1;70(9):1366–76.

67. Esen I, Jiemy WF, Van Sleen Y, Bijzet J, De Jong DM, Nienhuis PH, et al. Plasma Pyruvate Kinase M2 as a marker of vascular inflammation in giant cell arteritis.

68. Muratore F, Crescentini F, Spaggiari L, Pazzola G, Casali M, Boiardi L, et al. Aortic dilatation in patients with large vessel vasculitis: A longitudinal case control study using PET/CT. Semin Arthritis Rheum. 2019;

69. Bilici Salman R, Koca G, Gülbahar Ateş S, Yapar D, Babaoglu H, Satış H, et al. Diagnostic utility of serum biomarkers in large vessel vasculitis and their correlation with positron emission tomography. Mod Rheumatol. 2022 Aug 20;32(5):938–45.

70. Van Sleen Y, Sandovici M, Abdulahad WH, Bijzet J, Van Der Geest KSM, Boots AMH, et al. Markers of angiogenesis and macrophage products for predicting disease course and monitoring vascular inflammation in giant cell arteritis. Rheumatology (United Kingdom). 2019;

71. Rodriguez-Pla A, Warner RL, Cuthbertson D, Carette S, Khalidi NA, Koening CL, et al. Evaluation of Potential Serum Biomarkers of Disease Activity in Diverse Forms of Vasculitis. J Rheumatol. 2020 Jul 1;47(7):1001.

72. Berger CT, Rebholz-Chaves B, Recher M, Manigold T, Daikeler T. Serial IL-6 measurements in patients with tocilizumab-treated large-vessel vasculitis detect infections and may predict early relapses. Ann Rheum Dis. 2019 Jul 1;78(7):1012–4.

73. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis. 2018 May 1;77(5):636–43.

74. Sugihara T, Hasegawa H, Uchida HA, Yoshifuji H, Watanabe Y, Amiya E, et al. Associated factors of poor treatment outcomes in patients with giant cell arteritis: Clinical implication of large vessel lesions. Arthritis Res Ther. 2020;22(1):1–12.

75. Czihal M, Piller A, Schroettle A, Kuhlencordt P, Bernau C, Schulze-Koops H, et al. Impact of cranial and axillary/subclavian artery involvement by color duplex sonography on response to treatment in giant cell arteritis. J Vasc Surg. 2015 May;61(5):1285–91.

76. De Boysson H, Liozon E, Lambert M, Parienti JJ, Artigues N, Geffray L, et al. 18 F-fluorodeoxyglucose positron emission tomography and the risk of subsequent aortic complications in giant-cell arteritis. Medicine (United States). 2016;

77. de Boysson H, Liozon E, Espitia O, Daumas A, Vautier M, Lambert M, et al. Different patterns and specific outcomes of large-vessel involvements in giant cell arteritis. J Autoimmun. 2019;

78. de Boysson H, Daumas A, Vautier M, Parienti JJ, Liozon E, Lambert M, et al. Large-vessel involvement and aortic dilation in giant-cell arteritis. A multicenter study of 549 patients. Vol. 17, Autoimmunity Reviews. Elsevier B.V.; 2018. p. 391–8.

79. Sammel AM, Hsiao E, Schembri G, Bailey E, Nguyen K, Brewer J, et al. Cranial and large vessel activity on positron emission tomography scan at diagnosis and 6 months in giant cell arteritis. Int J Rheum Dis. 2020;

80. Grayson PC, Alehashemi S, Bagheri AA, Civelek AC, Cupps TR, Kaplan MJ, et al. 18F-Fluorodeoxyglucose–Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis. Arthritis and Rheumatology. 2018 Mar 1;70(3):439–49.

81. Meller J, Strutz F, Siefker U, Scheel A, Sahlmann CO, Lehmann K, et al. Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI. Eur J Nucl Med Mol Imaging. 2003 May;30(5):730–6.

82. Sebastian A, Kayani A, Prieto-Pena D, Tomelleri A, Whitlock M, Mo J, et al. Efficacy and safety of tocilizumab in giant cell arteritis: A single centre NHS experience using imaging (ultrasound and PET-CT) as a diagnostic and monitoring tool. RMD Open. 2020;

83. Van Der Geest KSMM, Borg F, Kayani A, Paap D, Gondo P, Schmidt W, et al. Novel ultrasonographic Halo Score for giant cell arteritis: Assessment of diagnostic accuracy and association with ocular ischaemia. Ann Rheum Dis. 2019 Mar;79(3):393–9.

84. Hutchings A, Hollywood J, Lamping DL, Pease CT, Chakravarty K, Silverman B, et al. Clinical outcomes, quality of life, and diagnostic uncertainty in the first year of polymyalgia rheumatica. Arthritis Care Res (Hoboken). 2007 Jun 15;57(5):803–9.

85. Kermani TA, Warrington KJ. Polymyalgia rheumatica. The Lancet. 2013;381(9860):63–72.

86. Ramon A, Guillibert-Karras C, Milas-Julien L, Garrot JF, Maillefert JF, Ornetti P. The frequency of occult solid malignancy in patients with polymyalgia rheumatica-like symptoms. Ther Adv Musculoskelet Dis. 2021;13.

87. Lavado-Pérez C, Martínez-Rodríguez I, Martínez-Amador N, Banzo I, Quirce R, Jiménez-Bonilla J, et al. (18)F-FDG PET/CT for the detection of large vessel vasculitis in patients with polymyalgia rheumatica. Rev Esp Med Nucl Imagen Mol. 2015 Sep 1;34(5):275–81.

88. Prieto-Peña D, Martínez-Rodríguez I, Loricera J, Banzo I, Calderón-Goercke M, Calvo-Río V, et al. Predictors of positive 18 F-FDG PET/CT-scan for large vessel vasculitis in patients with persistent polymyalgia rheumatica Seminars in Arthritis and Rheumatism.

89. Hemmig AK, Gozzoli D, Werlen L, Ewald H, Aschwanden M, Blockmans D, et al. Subclinical giant cell arteritis in new onset polymyalgia rheumatica A systematic review and meta-analysis of individual patient data. Semin Arthritis Rheum. 2022 Aug 1;55.

90. Pease CT, Haugeberg G, Montague B, Hensor EMA, Bhakta BB, Thomson W, et al. Polymyalgia rheumatica can be distinguished from late onset rheumatoid arthritis at baseline: results of a 5-yr prospective study. Rheumatology (Oxford). 2009;48(2):123–7.

91. Karmacharya P, Donato A, Aryal M, Ghimire S, Pathak R, Shah K, et al. RS3PE revisited: A systematic review and meta-analysis of 331 cases. Clin Exp Rheumatol. 2016;34(3):404–15.

92. Dasgupta B, Cimmino MA, Maradit-Kremers H, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2012 Apr 1;71(4):484–92.

93. Salvarani C, Cantini F, Niccoli L, Macchioni P, Consonni D, Bajocchi G, et al. Acute-phase reactants and the risk of relapse/recurrence in polymyalgia rheumatica: A prospective followup study. Arthritis Care Res (Hoboken). 2005 Feb 15;53(1):33–8.

94. Noval Menéndez J, Serrano MTC, Nuño Mateo FJ, Morís de la Tassa J. Distal musculo-skeletal manifestations in rheumatic polymyalgia. Rev Clin Esp. 2002;202(7):385–7.

95. Noval Menéndez J, Serrano MTC, Nuño Mateo FJ, Morís de la Tassa J. Distal musculo-skeletal manifestations in rheumatic polymyalgia. Rev Clin Esp. 2002;202(7):385–7.

96. DISTAL MUSCULOSKELETAL MANIFESTATIONS IN POLYMYALGIA RHEUMATICA.

97. Kimura M, Tokuda Y, Oshiawa H, Yoshida K, Utsunomiya M, Kobayashi T, et al. Clinical Characteristics of Patients with Remitting Seronegative Symmetrical Synovitis with Pitting Edema Compared to Patients with Pure Polymyalgia Rheumatica. J Rheumatol. 2012 Jan 1;39(1):148–53.

98. Caporali R, Montecucco C, Epis O, Bobbio-Pallavicini F, Maio T, Cimmino MA. Presenting features of polymyalgia rheumatica (PMR) and rheumatoid arthritis with PMR-like onset: a prospective study. Ann Rheum Dis. 2001 Nov 1;60(11):1021–4.

99. Owen CE, McMaster C, Liew DFL, Leung JL, Scott AM, Buchanan RRC. Neutrophil to lymphocyte ratio predicts glucocorticoid resistance in polymyalgia rheumatica. Int J Rheum Dis. 2021 Jan 1;24(1):56–62.

100. Van Sleen Y, Boots AMH, Abdulahad WH, Bijzet J, Sandovici M, Van Der Geest KSM, et al. High angiopoietin-2 levels associate with arterial inflammation and long-term glucocorticoid requirement in polymyalgia rheumatica. Rheumatology. 2020 Jan 1;59(1):176–84.

101. van Sleen Y, Therkildsen P, Nielsen BD, van der Geest KSM, Hansen I, Heeringa P, et al. Angiopoietin-2/-1 ratios and MMP-3 levels as an early warning sign for the presence of giant cell arteritis in patients with polymyalgia rheumatica. Arthritis Res Ther. 2022 Dec 1;24(1).

102. Reitsema RD, Jiemy WF, Wekema L, Boots AMH, Heeringa P, Huitema MG, et al. Contribution of pathogenic T helper 1 and 17 cells to bursitis and tenosynovitis in polymyalgia rheumatica. Front Immunol. 2022;13(August):1–11.

103. Jiemy WF, Zhang A, Boots AMH, Heeringa P, Sandovici M, Diepstra A, et al. Expression of interleukin-6 in synovial tissue of patients with polymyalgia rheumatica. Ann Rheum Dis. 2022 Aug 12;annrheumdis-2022-222873.

104. van der Geest KSM, Treglia G, Glaudemans AWJM, Brouwer E, Jamar F, Slart RHJA, et al. Diagnostic value of [18F]FDG-PET/CT in polymyalgia rheumatica: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2021 Jun 1;48(6):1876–89.

105. Van Der Geest KSM, Van Sleen Y, Nienhuis P, Sandovici M, Westerdijk N, Glaudemans AWJM, et al. Comparison and validation of FDG-PET/CT scores for polymyalgia rheumatica. Rheumatology (United Kingdom). 2022;61(3):1072–82.

106. Camellino D, Duftner C, Dejaco C. New insights into the role of imaging in polymyalgia rheumatica. Rheumatology (United Kingdom). 2021;60(3):1016–33.

107. Rutigliano IM, Scirocco C, Ceccarelli F, Finucci A, Iagnocco A. Musculoskeletal ultrasound in the evaluation of Polymyalgia Rheumatica. Med Ultrason. 2015 Sep 1;17(3):361–6.

108. Huwart A, Garrigues F, Jousse-Joulin S, Marhadour T, Guellec D, Cornec D, et al. Ultrasonography and magnetic resonance imaging changes in patients with polymyalgia rheumatica treated by tocilizumab. Arthritis Res Ther. 2018 Jan 25;20(1):1–8.

109. Nakamura H, Kamada K, Tarumi M, Tanimura S, Shibata Y, Horita T. Gadolinium-enhanced magnetic resonance imaging in shoulders contributes accurate diagnosis and predicting recurrence to patients with polymyalgia rheumatica. Clin Exp Rheumatol. 2021;39(1):84–90.

110. Van Der Geest KSM, Van Sleen Y, Nienhuis P, Sandovici M, Westerdijk N, Glaudemans AWJM, et al. Comparison and validation of FDG-PET/CT scores for polymyalgia rheumatica. Rheumatology. 2022 Mar 2;61(3):1072–82.

111. Henckaerts L, Gheysens O, Vanderschueren S, Goffin K, Blockmans D. Use of 18F-fluorodeoxyglucose positron emission tomography in the diagnosis of polymyalgia rheumatica-A prospective study of 99 patients. Rheumatology (Oxford). 2018 Nov 1;57(11):1908–16.

112. Miceli MC, Zoli A, Peluso G, Bosello S, Gremese E, Ferraccioli G. Baseline Shoulder Ultrasonography Is Not a Predictive Marker of Response to Glucocorticoids in Patients with Polymyalgia Rheumatica: A 12-month Followup Study. J Rheumatol. 2017 Feb 1;44(2):241–7.

113. Ayano M, Arinobu Y, Tsukamoto H, Ota S ichiro, Misaki K, Nishimura K, et al. Shoulder ultrasound and serum lactate dehydrogenase predict inadequate response to glucocorticoid treatment in patients with polymyalgia rheumatica. Rheumatol Int. 2020 Jul 1;40(7):1101–9.

114. Macchioni PL, Catanoso MG, Pipitone N, Boiardi L, Salvarani C. Longitudinal examination with shoulder ultrasound of patients with polymyalgia rheumatica. Rheumatology. 2009;48(12):1566–9.

115. Mackie SL, Pease CT, Fukuba E, Harris E, Emery P, Hodgson R, et al. Whole-body MRI of patients with polymyalgia rheumatica identifies a distinct subset with complete patient-reported response to glucocorticoids. Ann Rheum Dis. 2015;74(12):2188–92.

116. Giraud N, Prati C, Wendling D, Verhoeven F. Prognostic value of 18F-fluorodeoxyglucose PET-CT score at baseline on the therapeutic response to prednisone in patients with polymyalgia rheumatica. Joint Bone Spine. 2021;88(1):2020–1.

117. Gonzalez-Gay MA, Martinez-Dubois C, Agudo M, Pompei O, Blanco R, Llorca J. Giant cell arteritis: Epidemiology, diagnosis, and management. Current Rheumatology Reports. 2010.

118. Mackie SL, Taylor JC, Haroon-Rashid L, Martin S, Dasgupta B, Gough A, et al. Association of <Emphasis Type=Italic>HLA-DRB1</Emphasis> amino acid residues with giant cell arteritis: Genetic association study, meta-analysis and geo-epidemiological investigation. Arthritis Res Ther. 2015 Jul 30;17(1):1–14.

119. Weyand CM, Hunder NNH, Hicok KC, Hunder GG, Goronzy JJ. Hla–drb1 alleles in polymyalgia rheumatica, giant cell arteritis, and rheumatoid arthritis. Arthritis Rheum. 1994 Dec 1;37(4):514–20.

120. Carmona FD, González-Gay MA, Martín J. Genetic component of giant cell arteritis. Rheumatology (Oxford). 2014 Jan;53(1):6–18.

121. González-Gay MA, Amoli MM, Garcia-Porrua C, Ollier WER. Genetic markers of disease susceptibility and severity in giant cell arteritis and polymyalgia rheumatica. Semin Arthritis Rheum. 2003 Aug 1;33(1):38–48.

122. Ma-Krupa W, Jeon MS, Spoerl S, Tedder TF, Goronzy JJ, Weyand CM. Activation of Arterial Wall Dendritic Cells and Breakdown of Self-tolerance in Giant Cell Arteritis. Journal of Experimental Medicine. 2004 Jan 19;199(2):173–83.

123. Deng J, Ma-Krupa W, Gewirtz AT, Younge BR, Goronzy JJ, Weyand CM. Toll-Like Receptors 4 and 5 Induce Distinct Types of Vasculitis. Circ Res. 2009 Feb 27;104(4):488–95.

124. Pryshchep O, Ma-Krupa W, Younge BR, Goronzy JJ, Weyand CM. Vessel-Specific Toll-Like Receptor Profiles in Human Medium and Large Arteries. Circulation. 2008 Sep 16;118(12):1276–84.

125. Knab K, Chambers D, Krönke G. Synovial Macrophage and Fibroblast Heterogeneity in Joint Homeostasis and Inflammation. Front Med (Lausanne). 2022 Apr 25;9:930.

126. Akbar M, MacDonald L, Crowe LAN, Carlberg K, Kurowska-Stolarska M, Ståhl PL, et al. Single cell and spatial transcriptomics in human tendon disease indicate dysregulated immune homeostasis. Ann Rheum Dis. 2021 Nov 1;80(11):1494–7.

127. Mackie SL, Owen CE, Buchanan RRC, McGonagle D. A shared basis for overlapping immunopathologies in giant cell arteritis and polymyalgia rheumatica. Lancet Rheumatol. 2021 Dec 1;3(12):e826–9.

128. Samson M, Audia S, Fraszczak J, Trad M, Ornetti P, Lakomy D, et al. Th1 and Th17 Lymphocytes Expressing CD161 Are Implicated in Giant Cell Arteritis and Polymyalgia Rheumatica Pathogenesis. Arthritis Rheum. 2012;64(11):3788–98.

129. Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in giant cell arteritis. Arthritis Rheum. 2012 Jun;64(6):2001–11.

130. Deng J, Younge BR, Olshen RA, Goronzy JJ, Weyand CM. Th17 and Th1 T-Cell Responses in Giant Cell Arteritis. 2010;

131. Van der Geest KSM, Abdulahad WH, Rutgers A, Horst G, Bijzet J, Arends S, et al. Serum markers associated with disease activity in giant cell arteritis and polymyalgia rheumatica. Rheumatology. 2015 Aug 1;54(8):1397–402.

132. Dasgupta B, Panayi GS. INTERLEUKIN-6 IN SERUM OF PATIENTS WITH POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS. Rheumatology. 1990 Dec 1;29(6):456–8.

133. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of tocilizumab in giant-cell arteritis. New England Journal of Medicine. 2017;

134. Bonelli M, Radner H, Kerschbaumer A, Mrak D, Durechova M, Stieger J, et al. Tocilizumab in patients with new onset polymyalgia rheumatica (PMR-SPARE): a phase 2/3 randomised controlled trial. Ann Rheum Dis. 2022 Feb 24;annrheumdis-2021-221126.

135. Devauchelle-Pensec V, Carvajal-Alegria G, Dernis E, Richez C, Truchetet ME, Wendling D, et al. Effect of Tocilizumab on Disease Activity in Patients With Active Polymyalgia Rheumatica Receiving Glucocorticoid Therapy: A Randomized Clinical Trial. JAMA. 2022 Sep 20;328(11):1053–62.

136. Jiemy WF, van Sleen Y, van der Geest KSM, ten Berge HA, Abdulahad WH, Sandovici M, et al. Distinct macrophage phenotypes skewed by local granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) are associated with tissue destruction and intimal hyperplasia in giant cell arteritis. Clin Transl Immunology. 2020 Jan 1;9(9):e1164.

137. van Sleen Y, Jiemy WF, Pringle S, van der Geest KSM, Abdulahad WH, Sandovici M, et al. A Distinct Macrophage Subset Mediating Tissue Destruction and Neovascularization in Giant Cell Arteritis: Implication of the YKL-40/Interleukin-13 Receptor α2 Axis. Arthritis and Rheumatology. 2021 Dec 1;73(12):2327–37.

138. Meliconi R, Facchini A, Salvarani C, Macchioni P, Nuova ASM, Emilia R, et al. LEUKOCYTE INFILTRATION IN SYNOVIAL TISSUE FROM THE SHOULDER OF PATIENTS WITH POLYMYALGIA RHEUMATICA Quantitative Analysis and Influence of Corticosteroid Treatment RICCARDO MELICONI, LIA PULSATELLI, MARIAGRAZIA UGUCCIONI, CARL0 SALVARANI, PIERLUIGI MACCHIONI, CINZIA MELCHIORRI, MARIA CRISTINA FOCHERINI, LUIGI FRIZZIERO, and ANDREA FACCHINI. Vol. 39, ARTHRITIS & RHEUMATISM. 1996.

139. Ma-Krupa W, Jeon MS, Spoerl S, Tedder TF, Goronzy JJ, Weyand CM. Activation of Arterial Wall Dendritic Cells and Breakdown of Self-tolerance in Giant Cell Arteritis. Journal of Experimental Medicine. 2004 Jan 19;199(2):173–83.

140. Szekanecz Z, McInnes IB, Schett G, Szamosi S, Benkő S, Szűcs G. Autoinflammation and autoimmunity across rheumatic and musculoskeletal diseases. Nature Reviews Rheumatology 2021 17:10. 2021 Aug 2;17(10):585–95.

141. Maz M, Chung SA, Abril A, Langford CA, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis and Rheumatology. 2021 Aug 1;73(8):1349–65.

142. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis. Arthritis and Rheumatology. 2017;69(4):837–45.

143. Cid MC, Unizony SH, Blockmans D, Brouwer E, Dagna L, Dasgupta B, et al. Efficacy and safety of mavrilimumab in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2022 May 1;81(5):653–61.

144. Venhoff N, Schmidt WA, Lamprecht P, Tony HP, App C, Sieder C, et al. Efficacy and safety of secukinumab in patients with giant cell arteritis: study protocol for a randomized, parallel group, double-blind, placebo-controlled phase II trial. Trials. 2021 Dec 1;22(1).

145. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 2002;46(5):1309–18.

146. Spiera RF, Mitnick HJ, Kupersmith M, Richmond M, Spiera H, Peterson MGE, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin Exp Rheumatol. 2001;

147. Mahr AD, Jover JA, Spiera RF, Hernández-García C, Fernández-Gutiérrez B, Lavalley MP, et al. Adjunctive Methotrexate for Treatment of Giant Cell Arteritis An Individual Patient Data Meta-Analysis. Arthritis Rheum. 2007;56(8):2789–97.

148. Tomelleri A, Coath F, Sebastian A, Prieto-Peña D, Kayani A, Mo J, et al. Long-Term Efficacy and Safety of Leflunomide in Large-Vessel Giant-Cell Arteritis: A Single Centre Ten-Year Experience. Journal of Clinical Rheumatology. 2021;In press.

149. Hočevar A, Ješe R, Rotar Ž, Tomšič M. Does leflunomide have a role in giant cell arteritis? An open-label study. Clin Rheumatol. 2019 Feb 14;38(2):291–6.

150. Das S, Goswami RP, Sinha D, Ghosal A, Datta A, Sarkar S. Efficacy of leflunomide as a steroid-sparing agent in treatment of Indian giant cell arteritis patients: A 2-year follow-up study. Int J Rheum Dis. 2022 Mar 29;

151. Coath F, Gillbert K, Griffiths B, Hall F, Kay L, Lanyon P, et al. Giant cell arteritis: New concepts, treatments and the unmet need that remains. Rheumatology (United Kingdom). 2019;58(7):1123–5.

152. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. The Lancet. 2008.

153. Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis: A population-based study. Ann Intern Med. 1995;

154. Salvarani C, Cimino L, Macchioni P, Consonni D, Cantini F, Bajocchi G, et al. Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. Arthritis Care Res (Hoboken). 2005;

155. Baig IF, Pascoe AR, Kini A, Lee AG. Giant cell arteritis: Early diagnosis is key. Vol. 11, Eye and Brain. Dove Medical Press Ltd.; 2019. p. 1–12.

156. Lie JT. Aortic and extracranial large vessel giant cell arteritis: A review of 72 cases with histopathologic documentation. Semin Arthritis Rheum. 1995;24(6):422–31.

157. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. Arthritis Rheum. 1999 Feb;42(2):311–7.

158. Prieto-González S, Arguis P, García-Martínez A, Espígol-Frigolé G, Tavera-Bahillo I, Butjosa M, et al. Large vessel involvement in biopsy-proven giant cell arteritis: Prospective study in 40 newly diagnosed patients using CT angiography. Ann Rheum Dis. 2012;71(7):1170–6.

159. González-Gay MA, Prieto-Peña D, Calderón-Goercke M, Atienza-Mateo B, Castañeda S. Giant cell arteritis: more than a cranial disease. Clin Exp Rheumatol. 2020;38(Suppl 124(2)):15–7.

160. Tomelleri A, Campochiaro C, Sartorelli S, Farina N, Baldissera E, Dagna L. Presenting features and outcomes of cranial-limited and large-vessel giant cell arteritis: a retrospective cohort study. Scand J Rheumatol. 2021 Apr 29;1–8.

161. Prieto-Peña D, Remuzgo-Martínez S, Ocejo-Vinyals JG, Atienza-Mateo B, Muñoz-Jiménez A, Ortiz-Sanjuán F, et al. Cranial and extracranial giant cell arteritis share similar HLA-DRB1 association. Semin Arthritis Rheum. 2020 Oct 1;50(5):897–901.

162. Diamantopoulos AP, Haugeberg G, Lindland A, Myklebust G. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: towards a more effective strategy to improve clinical outcome in giant cell arteritis?

163. Hocevar A, Rotar Z, Jese R, Semrl SS, Pizem J, Hawlina M, et al. Do Early Diagnosis and Glucocorticoid Treatment Decrease the Risk of Permanent Visual Loss and Early Relapses in Giant Cell Arteritis. Medicine (United States). 2016 Apr 1;95(14).

164. MacKie SL, Dejaco C, Appenzeller S, Camellino D, Duftner C, Gonzalez-Chiappe S, et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. Rheumatology (United Kingdom). 2020;

165. Ponte C, Rodrigues AF, O'Neill L, Luqmani RA. Giant cell arteritis: Current treatment and management. World J Clin Cases. 2015;3(6):484.

166. Birkhead NC, Wagener HP, Shick RM. Treatment of temporal arteritis with adrenal corticosteroids: Results in fifty-five cases in which lesion was proved at biopsy. J Am Med Assoc. 1957;

167. Mazlumzadeh M, Hunder GG, Easley KA, Calamia KT, Matteson EL, Griffing WL, et al. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: A double-blind, placebo-controlled, randomized prospective clinical trial. Arthritis Rheum. 2006 Oct;54(10):3310–8.

168. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of tocilizumab in giant-cell arteritis. New England Journal of Medicine. 2017;

169. Chatterjee S, Flamm SD, Tan CD, Rodriguez ER. Clinical diagnosis and management of large vessel vasculitis: Giant cell arteritis. Curr Cardiol Rep. 2014;

170. Caylor TL, Perkins A. Recognition and management of polymyalgia rheumatica and giant cell arteritis. Am Fam Physician. 2013;

171. Chan CCK, Paine M, O'Day J. Steroid management in giant cell arteritis. British Journal of Ophthalmology. 2001;

172. Chevalet P, Barrier JH, Pottier P, Magadur-Joly G, Pottier MA, Hamidou M, et al. A randomized, multicenter, controlled trial using intravenous pulses of methylprednisolone in the initial treatment of simple forms of giant cell arteritis: A one year followup study of 164 patients. Journal of Rheumatology. 2000 Jun 1;27(6):1484–91.

173. Eberhardt RT, Dhadly M. Giant cell arteritis: Diagnosis, management, and cardiovascular implications. Cardiology in Review. 2007.

174. Ness T, Bley TA, Schmidt WA, Lamprecht P. The diagnosis and treatment of giant cell arteritis. Dtsch Arztebl Int. 2013;

175. Saleh M, Turesson C, Englund M, Merkel PA, Mohammad AJ. Visual complications in patients with biopsy-proven giant cell arteritis: A population-based study. Journal of Rheumatology. 2016 Aug 1;43(8):1559–65.

176. Gonzalez-Gay MA, Castaneda S, Llorca J. Giant cell arteritis: Visual loss is our major concern. Vol. 43, Journal of Rheumatology. Journal of Rheumatology; 2016. p. 1458–61.

177. de Boysson H, Daumas A, Vautier M, Parienti JJ, Liozon E, Lambert M, et al. Large-vessel involvement and aortic dilation in giant-cell arteritis. A multicenter study of 549 patients. Vol. 17, Autoimmunity Reviews. Elsevier B.V.; 2018. p. 391–8.

178. Espitia O, Néel A, Leux C, Connault J, Espitia-Thibault A, Ponge T, et al. Giant cell arteritis with or without aortitis at diagnosis. A retrospective study of 22 patients with longterm followup. Journal of Rheumatology. 2012 Nov;39(11):2157–62.

179. Schönau V, Roth J, Tascilar K, Corte G, Manger B, Rech J, et al. Resolution of vascular inflammation in patients with new-onset giant cell arteritis: data from the RIGA study. Rheumatology. 2021 Apr 8;

180. Alberts M. Temporal arteritis: improving patient evaluation with a new protocol. Perm J. 2013;

181. Boscaro M, Barzon L, Fallo F, Sonino N. Cushing's syndrome. In: Lancet. 2001.

182. Nesher G, Sonnenblick M, Friedlander Y. Analysis of steroid related complications and mortality in temporal arteritis: A 15-year survey of 43 patients. Journal of Rheumatology. 1994;

183. Gale S, Wilson JC, Chia J, Trinh H, Tuckwell K, Collinson N, et al. Risk Associated with Cumulative Oral Glucocorticoid Use in Patients with Giant Cell Arteritis in Real-World Databases from the USA and UK. Rheumatol Ther. 2018;

184. Strehl C, Bijlsma JWJ, De Wit M, Boers M, Caeyers N, Cutolo M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: Viewpoints from an EULAR task force. Annals of the Rheumatic Diseases. 2016.

185. Strehl C, Bijlsma JWJ, De Wit M, Boers M, Caeyers N, Cutolo M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: Viewpoints from an EULAR task force. Annals of the Rheumatic Diseases. 2016.

186. Low C, Conway R. Current advances in the treatment of giant cell arteritis: the role of biologics. Therapeutic Advances in Musculoskeletal Disease. 2019.

187. Rüegg S, Engelter S, Jeanneret C, Hetzel A, Probst A, Steck AJ, et al. Bilateral vertebral artery occlusion resulting from giant cell arteritis: Report of 3 cases and review of the literature. Medicine. 2003;

188. Nesher G, Berkun Y, Mates M, Baras M, Rubinow A, Sonnenblick M. Low-Dose Aspirin and Prevention of Cranial Ischemic Complications in Giant Cell Arteritis. Arthritis and Rheumatism. 2004.

189. Lee MS, Smith SD, Galor A, Hoffman GS. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. Vol. 54, Arthritis and Rheumatism. John Wiley & Sons, Ltd; 2006. p. 3306–9.

190. Fraser JA, Weyand CM, Newman NJ, Biousse V. The treatment of giant cell arteritis. Vol. 5, Reviews in Neurological Diseases. NIH Public Access; 2008. p. 140–52.

191. Berger CT, Wolbers M, Meyer P, Daikeler T, Hess C. High incidence of severe ischaemic complications in patients with giant cell arteritis irrespective of platelet count and size, and platelet inhibition. Rheumatology. 2009;

192. Narváez FJG, Bernad B, Gómez-Vaquero C, García-Gómez C, Roig-Vilaseca D, Juanola X, et al. Impact of antiplatelet therapy in the development of severe ischemic complications and in the outcome of patients with giant cell arteritis. Clin Exp Rheumatol. 2008;

193. Martínez-Taboada VM, López-Hoyos M, Narvaez J, Muñoz-Cacho P. Effect of antiplatelet/anticoagulant therapy on severe ischemic complications in patients with giant cell arteritis: A cumulative meta-analysis. Autoimmunity Reviews. 2014.

194. Mollan SP, Sharrack N, Burdon MA, Denniston AK. Aspirin as adjunctive treatment for giant cell arteritis. Cochrane Database of Systematic Reviews. 2014.

195. Rajagopalan PTR, Zhang Z, McCourt L, Dwyer M, Benkovic SJ, Hammes GG. Interaction of dihydrofolate reductase with methotrexate: Ensemble and single-molecule kinetics. Proc Natl Acad Sci U S A. 2002;

196. Goodsell DS. The molecular perspective: Methotrexate. Stem Cells. 1999.

197. Wessels JAM, Huizinga TWJ, Guchelaar HJ. Recent insights in the pharmacological actions of methotrexate in the treatment of rheumatoid arthritis. Rheumatology. 2008.

198. Böhm I. Increased peripheral blood B-cells expressing the CD5 molecules in association to autoantibodies in patients with lupus erythematosus and evidence to selectively down-modulate them. Biomedicine and Pharmacotherapy. 2004;

199. Brody M, Böhm I, Bauer R. Mechanism of Action of Methotrexate: Experimental Evidence that Methotrexate Blocks the Binding of Interleukin 1 β to the Interleukin 1 Receptor on Target Cells. Clin Chem Lab Med. 1993;

200. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 2002;

201. Jover JA, Hernández-García C, Morado IC, Vargas E, Bañares A, Fernàndez-Gutiérrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone: A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2001;

202. Koster MJ, Yeruva K, Crowson CS, Muratore F, Labarca C, Warrington KJ. Efficacy of methotrexate in real-world management of giant cell arteritis: A case-control study. Journal of Rheumatology. 2019 May;46(5):501–8.

203. Mahr AD, Jover JA, Spiera RF, Hernández-García C, Fernández-Gutiérrez B, LaValley MP, et al. Adjunctive methotrexate for treatment of giant cell arteritis: An individual patient data meta-analysis. Arthritis Rheum. 2007;

204. De Silva M, Hazleman BL. Azathioprine in giant cell arteritis/polymyalgia rheumatica: A double-blind study. Ann Rheum Dis. 1986;

205. Gossec L, Smolen JS, Ramiro S, De Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. 2016;

206. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;

207. Adizie T, Christidis D, Dharmapaliah C, Borg F, Dasgupta B. Efficacy and tolerability of leflunomide in difficult-to-treat polymyalgia rheumatica and giant cell arteritis: A case series. Int J Clin Pract. 2012;66(9):906–9.

208. Diamantopoulos AP, Hetland H, Myklebust G. Leflunomide as a corticosteroid-sparing agent in giant cell arteritis and polymyalgia rheumatica: A case series. Biomed Res Int. 2013;2013(1):10–2.

209. Hočevar A, Ješe R, Rotar Ž, Tomšič M. Does leflunomide have a role in giant cell arteritis? An open-label study. Clin Rheumatol. 2019;38(2):291–6.

210. Tengesdal S, Diamantopoulos AP, Myklebust G. Leflunomide versus methotrexate in treatment of giant cell arteritis: comparison of efficacy, safety, and drug survival. Scand J Rheumatol. 2019;48(4):333–5.

211. Sciascia S, Piras D, Baldovino S, Russo A, Naretto C, Rossi D, et al. Mycophenolate mofetil as steroid-sparing treatment for elderly patients with giant cell arteritis: Report of three cases. Aging Clin Exp Res. 2012;

212. Loock J, Henes J, Kötter I, Witte T, Lamprecht P, Schirmer M, et al. Treatment of refractory giant cell arteritis with cyclophosphamide: A retrospective analysis of 35 patients from three centres. Clin Exp Rheumatol. 2012;

213. de Boysson H, Boutemy J, Creveuil C, Ollivier Y, Letellier P, Pagnoux C, et al. Is there a place for cyclophosphamide in the treatment of giant-cell arteritis? A case series and systematic review. Semin Arthritis Rheum. 2013 Aug;43(1):105–12.

214. Sailler L, Lapeyre-Mestre M, Geffray L, Letellier P, Liozon E, De La Roque PM, et al. Adding hydroxychloroquine to prednisone does not improve the outcome in giant cell arteritis: A double blind randomized controlled trial. Arthritis Rheum. 2009;

215. Schaufelberger C, Möllby H, Uddhammar A, Bratt J, Nordborg E. No additional steroid-sparing effect of cyclosporine A in giant cell arteritis [4]. Scandinavian Journal of Rheumatology. 2006.

216. Schaufelberger C, Andersson R, Nordborg E. No additive effect of cyclosporin a compared with glucocorticoid treatment alone in giant cell arteritis: Results of an open, controlled, randomized study [4]. British Journal of Rheumatology. 1998.

217. Field M, Cook A, Gallagher G. Immuno-localisation of tumour necrosis factor and its receptors in temporal arteritis. Rheumatol Int. 1997;

218. Visvanathan S, Rahman MU, Hoffman GS, Xu S, García-Martínez A, Segarra M, et al. Tissue and serum markers of inflammation during the follow-up of patients with giant-cell arteritis--a prospective longitudinal study. Rheumatology (Oxford). 2011;

219. Seror R, Baron G, Hachulla E, Debandt M, Larroche C, Puéchal X, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: Results of a multicentre randomised controlled trial. Ann Rheum Dis. 2014;

220. Leydet-Quilici H, Luc M, Armingeat T, Pham T, Lafforgue P. Giant cell arteritis during adalimumab treatment for rheumatoid arthritis. Joint Bone Spine. 2007.

221. Seton M. Giant cell arteritis in a patient taking etanercept and methotrexate [6]. Journal of Rheumatology. 2004.

222. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998;

223. Cantini F, Niccoli L, Salvarani C, Padula A, Olivieri I. Treatment of longstanding active giant cell arteritis with infliximab: Report of four cases. Arthritis Rheum. 2001;

224. Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis a randomized trial. Ann Intern Med. 2007;

225. Andonopoulos AP, Meimaris N, Daoussis D, Bounas A, Giannopoulos G. Experience with infliximab (anti-TNFα monoclonal antibody) as monotherapy for giant cell arteritis. Ann Rheum Dis. 2003;

226. Martínez-Taboada VM, Rodríguez-Valverde V, Carreño L, López-Longo J, Figueroa M, Belzunegui J, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. Ann Rheum Dis. 2008;

227. Roche NE, Fulbright JW, Wagner AD, Hunder GG, Goronzy JJ, Weyand CM. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum. 1993;

228. Dasgupta B, Panayi GS. Interleukin-6 in serum of patients with polymyalgia rheumatica and giant cell arteritis. Rheumatology. 1990;

229. Weyand CM, Fulbright JW, Hunder GG, Evans JM, Goronzy JJ. Treatment of giant cell arteritis: Interleukin-6 as a biologic marker of disease activity. Arthritis Rheum. 2000;

230. González-Gay MA, Pina T, Prieto-Peña D, Calderon-Goercke M, Blanco R, Castañeda S. The role of biologics in the treatment of giant cell arteritis. Vol. 19, Expert Opinion on Biological Therapy. Taylor and Francis Ltd; 2019. p. 65–72.

231. González-Gay M, Pina T, Prieto-Peña D, Calderon-Goercke M, Gualillo O, Castañeda S. Treatment of giant cell arteritis. Vol. 165, Biochemical Pharmacology. Elsevier Inc.; 2019. p. 230–9.

232. Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: A phase 2, randomised, double-blind, placebo-controlled trial. The Lancet. 2016;

233. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of Tocilizumab in Giant-Cell Arteritis. New England Journal of Medicine. 2017 Jul 27;377(4):317–28.

234. Stone JH, Han J, Aringer M, Blockmans D, Brouwer E, Cid MC, et al. Long-term effect of tocilizumab in patients with giant cell arteritis: open-label extension phase of the Giant Cell Arteritis Actemra (GiACTA) trial. Lancet Rheumatol. 2021 May 1;3(5):e328–36.

235. Seitz M, Reichenbach S, Bonel HM, Adler S, Wermelinger F, Villiger PM. Rapid induction of remission in large vessel vasculitis by IL-6 blockade: A case series. Swiss Med Wkly. 2011;

236. Evans J, Steel L, Borg F, Dasgupta B. Long-term efficacy and safety of tocilizumab in giant cell arteritis and large vessel vasculitis. RMD Open. 2016;

237. Calderón-Goercke M, Castañeda S, Aldasoro V, Villa I, Prieto-Peña D, Atienza-Mateo B, et al. Tocilizumab in giant cell arteritis: differences between the GiACTA trial and a multicentre series of patients from the clinical practice. Clin Exp Rheumatol. 2020 Mar 1;38(2):112–9.

238. Calderón-Goercke M, Castañeda S, Aldasoro V, Villa I, Moriano C, Romero-Yuste S, et al. Tocilizumab in refractory giant cell arteritis. Monotherapy versus combined therapy with conventional immunosuppressive drugs. Observational multicenter study of 134 patients. Semin Arthritis Rheum. 2021 Apr 1;51(2):387–94.

239. Unizony S, McCulley TJ, Spiera R, Pei J, Sidiropoulos PN, Best JH, et al. Clinical outcomes of patients with giant cell arteritis treated with tocilizumab in real-world clinical practice: decreased incidence of new visual manifestations. Arthritis Res Ther. 2021 Dec 1;23(1).

240. Clément J, Duffau P, Constans J, Schaeverbeke T, Viallard JF, Barcat D, et al. Real-world risk of relapse of giant cell arteritis treated with tocilizumab: A retrospective analysis of 43 patients. J Rheumatol. 2021 Feb 15;jrheum.200952.

241. Schönau V, Roth J, Tascilar K, Corte G, Manger B, Rech J, et al. Resolution of vascular inflammation in patients with new-onset giant cell arteritis: data from the RIGA study. Rheumatology. 2021 Apr 8;

242. 1 Recommendations | Tocilizumab for treating giant cell arteritis | Guidance | NICE.

243. Xu Z, Bouman-Thio E, Comisar C, Frederick B, Van Hartingsveldt B, Marini JC, et al. Pharmacokinetics, pharmacodynamics and safety of a human anti-IL-6 monoclonal antibody (sirukumab) in healthy subjects in a first-in-human study. Br J Clin Pharmacol. 2011;

244. Aletaha D, Bingham CO, Tanaka Y, Agarwal P, Kurrasch R, Tak PP, et al. Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): a randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3 study. The Lancet. 2017;

245. Schmidt WA, Dasgupta B, Luqmani R, Unizony SH, Blockmans D, Lai Z, et al. A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Sirukumab in the Treatment of Giant Cell Arteritis. Rheumatol Ther. 2020;

246. Schmidt WA, Dasgupta B, Luqmani R, Unizony SH, Blockmans D, Lai Z, et al. A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Sirukumab in the Treatment of Giant Cell Arteritis. Rheumatol Ther. 2020;

247. Boyce EG, Rogan EL, Vyas D, Prasad N, Mai Y. Sarilumab: Review of a Second IL-6 Receptor Antagonist Indicated for the Treatment of Rheumatoid Arthritis. Annals of Pharmacotherapy. 2018.

248. Weyand CM, Goronzy AJ. Giant cell arteritis as an antigen-driven disease. Rheumatic Disease Clinics of North America. 1995.

249. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. Nat Rev Rheumatol. 2013;9(12):731–40.

250. Weyand CM, Goronzy JJ. Medium- and Large-Vessel Vasculitis. New England Journal of Medicine. 2003;

251. Masteller EL, Chuang E, Mullen AC, Reiner SL, Thompson CB. Structural Analysis of CTLA-4 Function In Vivo. The Journal of Immunology. 2000;

252. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of Rheumatoid Arthritis by Selective Inhibition of T-Cell Activation with Fusion Protein CTLA4Ig. New England Journal of Medicine. 2003;

253. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor α Inhibition. New England Journal of Medicine. 2005;

254. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis. Arthritis and Rheumatology. 2017;69(4):837–45.

255. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis. Arthritis and Rheumatology. 2017;69(4):837–45.

256. Deng J, Younge BR, Olshen RA, Goronzy JJ, Weyand CM. Th17 and th1 T-cell responses in giant cell arteritis. Circulation. 2010;

257. Deng J, Younge BR, Olshen RA, Goronzy JJ, Weyand CM. Th17 and th1 T-cell responses in giant cell arteritis. Circulation. 2010;

258. Weyand CM, Liao YJ, Goronzy JJ. The immunopathology of giant cell arteritis: Diagnostic and therapeutic implications. Journal of Neuro-Ophthalmology. 2012.

259. Luo J, Wu SJ, Lacy ER, Orlovsky Y, Baker A, Teplyakov A, et al. Structural Basis for the Dual Recognition of IL-12 and IL-23 by Ustekinumab. J Mol Biol. 2010;

260. Benson JM, Sachs CW, Treacy G, Zhou H, Pendley CE, Brodmerkel CM, et al. Therapeutic targeting of the IL-12/23 pathways: Generation and characterization of ustekinumab. Nature Biotechnology. 2011.

261. Conway R, O'Neill L, Gallagher P, McCarthy GM, Murphy CC, Veale DJ, et al. Ustekinumab for refractory giant cell arteritis: A prospective 52-week trial. Semin Arthritis Rheum. 2018;48(3):523–8.

262. Matza MA, Fernandes AD, Stone JH, Unizony SH. Ustekinumab for the Treatment of Giant Cell Arteritis. Arthritis Care Res (Hoboken). 2020;0–1.

263. Conway R, O'Neill L, Gallagher P, McCarthy GM, Murphy CC, Veale DJ, et al. Ustekinumab for refractory giant cell arteritis: A prospective 52-week trial. Semin Arthritis Rheum. 2018;48(3):523–8.

264. Matza MA, Fernandes AD, Stone JH, Unizony SH. Ustekinumab for the Treatment of Giant Cell Arteritis. Arthritis Care Res (Hoboken). 2020;0–1.

265. Nakamura M, Lee K, Jeon C, Sekhon S, Afifi L, Yan D, et al. Guselkumab for the Treatment of Psoriasis: A Review of Phase III Trials. Vol. 7, Dermatology and Therapy. Springer Healthcare; 2017. p. 281–92.

266. Cada DJ, Baker DE, Panther SG, Ingram K. Secukinumab. Hospital Pharmacy. 2015.

267. Torchinsky MB, Blander JM. T helper 17 cells: Discovery, function, and physiological trigger. Cellular and Molecular Life Sciences. 2010.

268. Rotar Ž, Tomšič M, Hočevar A. Secukinumab for the maintenance of glucocorticoid-free remission in a patient with giant cell arteritis and psoriatic arthritis. Rheumatology. 2018 Jan 30;

269. Rotar Ž, Tomšič M, Hočevar A. Secukinumab for the maintenance of glucocorticoid-free remission in a patient with giant cell arteritis and psoriatic arthritis. Rheumatology. 2018 Jan;

270. Nair JR, Edwards SW, Moots RJ. Mavrilimumab, a human monoclonal GM-CSF receptor-α antibody for the management of rheumatoid arthritis: A novel approach to therapy. Expert Opinion on Biological Therapy. 2012.

271. Burmester GR, McInnes IB, Kremer J, Miranda P, Korkosz M, Vencovsky J, et al. A randomised phase IIb study of mavrilimumab, a novel GM-CSF receptor alpha monoclonal antibody, in the treatment of rheumatoid arthritis. Ann Rheum Dis. 2017;

272. Dougan M, Dranoff G, Dougan SK. GM-CSF, IL-3, and IL-5 Family of Cytokines: Regulators of Inflammation. Immunity. 2019.

273. Dougan M, Dranoff G, Dougan SK. GM-CSF, IL-3, and IL-5 Family of Cytokines: Regulators of Inflammation. Immunity. 2019.

274. Cid MC, Gandhi R, Corbera-Bellalta M, Muralidharan S, Paolini JF. GM-CSF pathway signature identified in temporal artery biopsies of patients with giant-cell arteritis. In Ann Rheum Dis 2019;78:145–6.;

275. Mavrilimumab (anti GM-CSF Receptor α Monoclonal Antibody) Reduces Time to Flare and Increases Sustained Remission in a Phase 2 Trial of Patients with Giant Cell Arteritis - ACR Meeting Abstracts [Internet]. [cited 2021 Apr 22]. Available from: https://acrabstracts.org/abstract/mavrilimumab-anti-gm-csf-receptor-α-monoclonal-antibody-reduces-time-to-flare-and-increases-sustained-remission-in-a-phase-2-trial-of-patients-with-giant-cell-arteritis/

276. Shuai K, Liu B. Regulation of JAK-STAT signalling in the immune system. Nature Reviews Immunology. 2003.

277. Villarino A V., Kanno Y, O'Shea JJ. Mechanisms and consequences of Jak-STAT signaling in the immune system. Nature Immunology. 2017.

278. Rawlings JS, Rosler KM, Harrison DA. The JAK/STAT signaling pathway. J Cell Sci. 2004;

279. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nature Reviews Drug Discovery. 2017.

280. Zhang H, Watanabe R, Berry GJ, Tian L, Goronzy JJ, Weyand CM. Inhibition of JAK-STAT signaling suppresses pathogenic immune responses in medium and large vessel vasculitis. Circulation. 2018;

281. Zhang H, Watanabe R, Berry GJ, Tian L, Goronzy JJ, Weyand CM. Inhibition of JAK-STAT signaling suppresses pathogenic immune responses in medium and large vessel vasculitis. Circulation. 2018;

282. Li J, Li M, Tian X, Zeng X. Tofacitinib in patients with refractory Takayasu's arteritis. Rheumatology (Oxford). 2020;59(11):e95–8.

283. Yamamura Y, Matsumoto Y, Asano Y, Katayama Y, Hayashi K, Ohashi K, et al. Refractory Takayasu arteritis responding to the oral Janus kinase inhibitor, tofacitinib. Rheumatology Advances in Practice. 2020.

284. Kuwabara S, Tanimura S, Matsumoto S, Nakamura H, Horita T, Horita T. Successful remission with tofacitinib in a patient with refractory Takayasu arteritis complicated by ulcerative colitis. Annals of the Rheumatic Diseases. 2020.

285. Sato S, Matsumoto H, Temmoku J, Fujita Y, Matsuoka N, Furuya M, et al. A case of Takayasu arteritis complicated by refractory ulcerative colitis successfully treated with tofacitinib. Rheumatology (United Kingdom). 2020.

286. Palermo A, Marvisi C, Casali M, Pipitone N, Muratore F, Salvarani C. Tofacitinib for the treatment of refractory Takayasu's arteritis: description of 2 cases. Clinical and experimental rheumatology. 2020.

287. Monti S, Bartoletti A, Bellis E, Delvino P, Montecucco C. Fast-Track Ultrasound Clinic for the Diagnosis of Giant Cell Arteritis Changes the Prognosis of the Disease but Not the Risk of Future Relapse. Front Med (Lausanne). 2020 Dec 8;7.

288. Sebastian A, van der Geest KSM, Coath F, Gondo P, Kayani A, Mackerness C, et al. Halo score (temporal artery, its branches and axillary artery) as a diagnostic, prognostic and disease monitoring tool for Giant Cell Arteritis (GCA). BMC Rheumatol. 2020;

289. Nielsen BD, Gormsen LC, Hansen IT, Keller KK, Therkildsen P, Hauge EM. Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. Eur J Nucl Med Mol Imaging. 2018;

290. Grayson PC, Alehashemi S, Bagheri AA, Civelek AC, Cupps TR, Kaplan MJ, et al. 18F-Fluorodeoxyglucose–Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis. Arthritis and Rheumatology. 2018;

291. Blockmans D, De Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: A prospective study of 35 patients. Arthritis Care Res (Hoboken). 2006 Feb 15;55(1):131–7.

292. Reichenbach S, Adler S, Bonel H, Cullmann JL, Kuchen S, Bütikofer L, et al. Magnetic resonance angiography in giant cell arteritis: Results of a randomized controlled trial of tocilizumab in giant cell arteritis. Rheumatology (United Kingdom). 2018 Jun 1;57(6):982–6.

293. Prieto-González S, García-Martínez A, Tavera-Bahillo I, Hernández-Rodríguez J, Gutiérrez-Chacoff J, Alba MA, et al. Effect of glucocorticoid treatment on computed tomography angiography detected large-vessel inflammation in giant-cell arteritis. A prospective, longitudinal study. Medicine (United States). 2015 Feb 13;94(5):e486.

294. Coath F, Gillbert K, Griffiths B, Hall F, Kay L, Lanyon P, et al. Giant cell arteritis: New concepts, treatments and the unmet need that remains. Rheumatology (United Kingdom). 2019;58(7):1123–5.

295. Van Der Geest KSM, Borg F, Kayani A, Paap D, Gondo P, Schmidt W, et al. Novel ultrasonographic Halo Score for giant cell arteritis: Assessment of diagnostic accuracy and association with ocular ischaemia. Ann Rheum Dis. 2019;79(3).

296. Chrysidis S, Lage-Hansen PR, Svendsen N, Diamantopoulos AP. The fast-track outpatient clinic significantly decreases hospitalisation rates among polymyalgia rheumatica patients. BMC Rheumatol. 2021 Dec 1;5(1).

297. Nguyen JT, Roberts C, Thorpe CT, Thorpe JM, Hogan SL, McGregor J, et al. Economic and objective burden of caregiving on informal caregivers of patients with systemic vasculitis. Musculoskeletal Care. 2019 Jun 1;17(2):282–7.

298. De Smit E, Palmer AJ, Hewitt AW. Projected Worldwide Disease Burden from Giant Cell Arteritis by 2050. J Rheumatol. 2015 Jan 1;42(1):119–25.

299. Sarnes E, Crofford L, Watson M, Dennis G, Kan H, Bass D. Incidence and US Costs of Corticosteroid-Associated Adverse Events: A Systematic Literature Review. Clin Ther. 2011 Oct 1;33(10):1413–32.

300. Robson JC, Kiran A, Maskell J, Hutchings A, Arden N, Dasgupta B, et al. The relative risk of aortic aneurysm in patients with giant cell arteritis compared with the general population of the UK. Ann Rheum Dis. 2015 Jan 1;74(1):129–35.

301. Stone WM, Fankhauser GT. Inflammatory Aneurysms Treated with EVAR. Semin Vasc Surg. 2012 Dec 1;25(4):227–31.

302. Broder MS, Sarsour K, Chang E, Collinson N, Tuckwell K, Napalkov P, et al. Corticosteroid-related adverse events in patients with giant cell arteritis: A claims-based analysis. Semin Arthritis Rheum. 2016 Oct 1;46(2):246–52.

303. Petri H, Nevitt A, Sarsour K, Napalkov P, Collinson N. Incidence of giant cell arteritis and characteristics of patients: Data-driven analysis of comorbidities. Arthritis Care Res (Hoboken). 2015 Mar 1;67(3):390–5.

304. Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. Respir Med. 2009 Jul 1;103(7):975–94.

305. Tuckwell K, Collinson N, Dimonaco S, Klearman M, Blockmans D, Brouwer E, et al. Newly diagnosed vs. relapsing giant cell arteritis: Baseline data from the GiACTA trial. Semin Arthritis Rheum. 2017 Apr 1;46(5):657–64.

306. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss: An update of the 1997 American Heart Association Scientific Statement on obesity and heart disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2006 Feb 14;113(6):898–918.

307. Van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology. 2000 Dec 1;39(12):1383–9.

308. Kanis JA, Stevenson M, McCloskey E V., Davis S, Lloyd-Jones M. Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis. Health Technol Assess (Rockv). 2007 Mar 6;11(7).

309. Diamantopoulos AP, Haugeberg G, Lindland A, Myklebust G. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: Towards a more effective strategy to improve clinical outcome in giant cell arteritis? Rheumatology (United Kingdom). 2016;

310. Monti S, Bartoletti A, Bellis E, Delvino P, Montecucco C. Fast-Track Ultrasound Clinic for the Diagnosis of Giant Cell Arteritis Changes the Prognosis of the Disease but Not the Risk of Future Relapse. Front Med (Lausanne). 2020;

311. Patil P, Williams M, Maw WW, Achilleos K, Elsideeg S, Dejaco C, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015;

312. Laskou F, Coath F, Mackie SL, Banerjee S, Aung T, Dasgupta B. A probability score to aid the diagnosis of suspected giant cell arteritis. Clin Exp Rheumatol. 2019;

313. Sebastian A, Tomelleri A, Kayani A, Prieto-Pena D, Ranasinghe C, Dasgupta B. Probability-based algorithm using ultrasound and additional tests for suspected GCA in a fast-track clinic. RMD Open. 2020;

314. Fernández-Fernández E, Monjo I, Peiteado D, Balsa A, De Miguel E. Validity of the EULAR recommendations on the use of ultrasound in the diagnosis of giant cell arteritis. RMD Open. 2022 Apr 5;8(1):e002120.

315. Melville AR, Donaldson K, Dale J, Ciechomska A. Validation of the Southend giant cell arteritis probability score in a Scottish single-centre fast-track pathway. Rheumatol Adv Pract. 2022 Jan 4;6(1).

316. Lazarewicz K, Watson P. Giant cell arteritis. The BMJ. 2019.

317. Younger DS. Giant Cell Arteritis. Neurologic Clinics. 2019.

318. van der Geest KSM, Wolfe K, Borg F, Sebastian A, Kayani A, Tomelleri A, et al. Ultrasonographic Halo Score in giant cell arteritis: association with intimal hyperplasia and ischaemic sight loss. Rheumatology. 2020;

319. Smith JH, Swanson JW. Giant cell arteritis. Headache. 2014.

320. Soriano A, Muratore F, Pipitone N, Boiardi L, Cimino L, Salvarani C. Visual loss and other cranial ischaemic complications in giant cell arteritis. Nat Rev Rheumatol. 2017;

321. Caselli RJ, Hunder GG. Neurologic complications of giant cell (temporal) arteritis. Seminars in Neurology. 1994.

322. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia rheumatica and giant cell arteritis a systematic review. JAMA - Journal of the American Medical Association. 2016 Jun;315(22):2442–58.

323. Patil P, Williams M, Maw WW, Achilleos K, Elsideeg S, Dejaco C, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015;

324. Smetana GW, Shmerling RH. Does this patient have temporal arteritis? J Am Med Assoc. 2002 Jan;287(1):92–101.

325. Wilson JC, Sarsour K, Collinson N, Tuckwell K, Musselman D, Klearman M, et al. Serious adverse effects associated with glucocorticoid therapy in patients with giant cell arteritis (GCA): A nested case–control analysis. Semin Arthritis Rheum. 2017;

326. Coath F, Gillbert K, Griffiths B, Hall F, Kay L, Lanyon P, et al. Giant cell arteritis: New concepts, treatments and the unmet need that remains. Rheumatology (United Kingdom). 2019.

327. de Boysson H, Liozon E, Ly KH, Dumont A, Delmas C, Aouba A. The different clinical patterns of giant cell arteritis. Clin Exp Rheumatol. 2019;

328. Dejaco C, Brouwer E, Mason JC, Buttgereit F, Matteson EL, Dasgupta B. Giant cell arteritis and polymyalgia rheumatica: Current challenges and opportunities. Vol. 13, Nature Reviews Rheumatology. Nature Publishing Group; 2017. p. 1–15.

329. Tuckwell K, Collinson N, Dimonaco S, Klearman M, Blockmans D, Brouwer E, et al. Newly diagnosed vs. relapsing giant cell arteritis: Baseline data from the GiACTA trial. Semin Arthritis Rheum. 2017;

330. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;

331. Starling AJ. Diagnosis and Management of Headache in Older Adults. Mayo Clin Proc. 2018;93:252–62.

332. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;

333. Murchison AP, Gilbert ME, Bilyk JR, Eagle RC, Pueyo V, Sergott RC, et al. Validity of the American college of rheumatology criteria for the diagnosis of giant cell arteritis. Am J Ophthalmol. 2012;

334. Rao JK, Allen NB, Pincus T. Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. Ann Intern Med. 1998;

335. Hellmich B, Agueda A, Monti S, Buttgereit F, De Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020;

336. Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. New England Journal of Medicine. 1997;

337. Chrysidis S, Duftner C, Dejaco C, Schäfer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: A study from the OMERACT large vessel vasculitis ultrasound working group. RMD Open. 2018;

338. Aschwanden M, Daikeler T, Kesten F, Baldi T, Benz D, Tyndall A, et al. Temporal artery compression sign - A novel ultrasound finding for the diagnosis of giant cell arteritis. Ultraschall in der Medizin. 2013;

339. Aschwanden M, Imfeld S, Staub D, Baldi T, Walker UA, Berger CT, et al. The ultrasound compression sign to diagnose temporal giant cell arteritis shows an excellent interobserver agreement. Clin Exp Rheumatol. 2015;

340. Schäfer VS, Juche A, Ramiro S, Krause A, Schmidt WA. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. Rheumatology (United Kingdom). 2017;

341. Van Der Geest KSM, Borg F, Kayani A, Paap D, Gondo P, Schmidt W, et al. Novel ultrasonographic Halo Score for giant cell arteritis: Assessment of diagnostic accuracy and association with ocular ischaemia. Ann Rheum Dis. 2019;

342. Luqmani R, Lee E, Singh S, Gillett M, Schmidt WA, Bradburn M, et al. The role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis (TABUL): A diagnostic accuracy and cost-effectiveness study. Health Technol Assess (Rockv). 2016;

343. Huizinga TWJ, Machold KP, Breedveld FC, Lipsky PE, Smolen JS. Criteria for early rheumatoid arthritis: From Bayes' law revisited to new thoughts on pathogenesis. Arthritis Rheum. 2002 May;46(5):1155–9.

344. Higgins JPT GS (editors). The Cochrane Collaboration . 2011. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 .

345. Monti S, Ponte C, Pereira C, Manzoni F, Klersy C, Rumi F, et al. The impact of disease extent and severity detected by quantitative ultrasound analysis in the diagnosis and outcome of giant cell arteritis. Rheumatology. 2019;

346. Terslev L, Naredo E, Aegerter P, Wakefield RJ, Backhaus M, Balint P, et al. Scoring ultrasound synovitis in rheumatoid arthritis: A EULAR-OMERACT ultrasound taskforce-Part 2: Reliability and application to multiple joints of a standardised consensus-based scoring system. RMD Open. 2017;

347. Chaurasia BD. Human anatomy Regional and applied. CBS Publishers and distributers. 2006.

348. Snell R. Clinical Anatomy by Regions. Clinical Anatomy by Regions, Ninth Edition. 2012.

349. DiFiore's. Atlas of Histology with functional correlations. Vasa. 2008.

350. Wang AL, Raven ML, Surapaneni K, Albert DM. Studies on the Histopathology of Temporal Arteritis. Ocul Oncol Pathol. 2017;

351. Bowling K, Rait J, Atkinson J, Srinivas G. Temporal artery biopsy in the diagnosis of giant cell arteritis: Does the end justify the means? Annals of Medicine and Surgery. 2017;

352. Maleszewski JJ, Younge BR, Fritzlen JT, Hunder GG, Goronzy JJ, Warrington KJ, et al. Clinical and pathological evolution of giant cell arteritis: A prospective study of follow-up temporal artery biopsies in 40 treated patients. Modern Pathology. 2017;

353. González Porto SA, Silva Díaz MT, Reguera Arias A, Pombo Otero J, González Rodríguez A, Valero Gasalla J, et al. A comparative study of Doppler ultrasound against temporal artery biopsy in the diagnosis of giant cell arteritis. Reumatología Clínica (English Edition) [Internet]. 2020;16(5):313–8. Available from: https://doi.org/10.1016/j.reumae.2018.08.008

354. Deyholos C, Sytek MC, Smith S, Cardella J, Orion KC. Impact of Temporal Artery Biopsy on Clinical Management of Suspected Giant Cell Arteritis. Ann Vasc Surg. 2020;

355. Aghdam KA, Sanjari MS, Manafi N, Khorramdel S, Alemzadeh SA, Navahi RAA. Temporal Artery Biopsy for Diagnosing Giant Cell Arteritis: A Ten-year Review. Journal of Ophthalmic and Vision Research. 2020.

356. Rubenstein E, Maldini C, Gonzalez-Chiappe S, Chevret S, Mahr A. Sensitivity of temporal artery biopsy in the diagnosis of giant cell arteritis: A systematic literature review and meta-analysis. Rheumatology (United Kingdom). 2020.

357. Cristaudo AT, Mizumoto R, Hendahewa R. The impact of temporal artery biopsy on surgical practice. Annals of Medicine and Surgery. 2016 Nov;11:47–51.

358. Alberts M. Temporal Arteritis: Improving Patient Evaluation with a New Protocol. Perm J. 2013 Mar;17(1):56–62.

359. González-Gay MA, Prieto-Peña D, Martínez-Rodríguez I, Calderon-Goercke M, Banzo I, Blanco R, et al. Early large vessel systemic vasculitis in adults. Vol. 33, Best Practice and Research: Clinical Rheumatology. 2019.

360. Quinn KA, Grayson PC. The Role of Vascular Imaging to Advance Clinical Care and Research in Large-Vessel Vasculitis. Curr Treatm Opt Rheumatol. 2019;5(1).

361. Duftner C, Dejaco C, Sepriano A, Falzon L, Schmidt WA, Ramiro S. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: A systematic literature review and meta-Analysis informing the EULAR recommendations. RMD Open. 2018;

362. Bley TA, Uhl M, Carew J, Markl M, Schmidt D, Peter HH, et al. Diagnostic value of high-resolution MR imaging in giant cell arteritis. American Journal of Neuroradiology. 2007;

363. Geiger J, Bley T, Uhl M, Frydrychowicz A, Langer M, Markl M. Diagnostic value of T2-weighted imaging for the detection of superficial cranial artery inflammation in giant cell arteritis. Journal of Magnetic Resonance Imaging. 2010;31(2).

364. Klink T, Geiger J, Both M, Ness T, Heinzelmann S, Reinhard M, et al. Giant cell arteritis: Diagnostic accuracy of mr imaging of superficial cranial arteries in initial diagnosis-results from a multicenter trial. Radiology. 2014;273(3).

365. Rhéaume M, Rebello R, Pagnoux C, Carette S, Clements-Baker M, Cohen-Hallaleh V, et al. High-Resolution Magnetic Resonance Imaging of Scalp Arteries for the Diagnosis of Giant Cell Arteritis: Results of a Prospective Cohort Study. Arthritis and Rheumatology. 2017;69(1).

366. Yip A, Jernberg ET, Bardi M, Geiger J, Lohne F, Schmidt WA, et al. Magnetic resonance imaging compared to ultrasonography in giant cell arteritis: a cross-sectional study. Arthritis Res Ther. 2020;22(1).

367. Sommer NN, Treitl KM, Coppenrath E, Kooijman H, Dechant C, Czihal M, et al. Three-Dimensional High-Resolution Black-Blood Magnetic Resonance Imaging for Detection of Arteritic Anterior Ischemic Optic Neuropathy in Patients With Giant Cell Arteritis. Invest Radiol. 2018 Nov;53(11):698–704.

368. Mournet S, Sené T, Charbonneau F, Poillon G, Vignal C, Clavel G, et al. High-resolution MRI demonstrates signal abnormalities of the 3rd cranial nerve in giant cell arteritis patients with 3rd cranial nerve impairment. Eur Radiol. 2021;31(7).

369. Schäfer VS, Jin L, Schmidt WA. Imaging for Diagnosis, Monitoring, and Outcome Prediction of Large Vessel Vasculitides. Vol. 22, Current Rheumatology Reports. 2020.

370. de Boysson H, Dumont A, Liozon E, Lambert M, Boutemy J, Maigné G, et al. Giant-cell arteritis: Concordance study between aortic CT angiography and FDG-PET/CT in detection of large-vessel involvement. Eur J Nucl Med Mol Imaging. 2017;44(13).

371. Moragas Solanes M, Andreu Magarolas M, Martín Miramon JC, Caresia Aróztegui AP, Monteagudo Jiménez M, Oliva Morera JC, et al. Comparative study of 18F-FDG PET/CT and CT angiography in detection of large vessel vasculitis. Rev Esp Med Nucl Imagen Mol. 2019;38(5).

372. Vaidyanathan S, Chattopadhyay A, Mackie SL, Scarsbrook AF. Comparative effectiveness of 18F-FDG PeT-CT and contrast-enhanced CT in the diagnosis of suspected large-vessel vasculitis. British Journal of Radiology. 2018;91(1089).

373. Slart RHJA. FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET Interest Group (PIG), and endorsed by the ASNC. Eur J Nucl Med Mol Imaging. 2018 Jul 11;45(7):1250–69.

374. Emamifar A, Ellingsen T, Hess S, Gerke O, Hviid Larsen R, Ahangarani Farahani Z, et al. The Utility of 18F-FDG PET/CT in Patients With Clinical Suspicion of Polymyalgia Rheumatica and

Giant Cell Arteritis: A Prospective, Observational, and Cross-sectional Study. ACR Open Rheumatol. 2020;2(8).

375. Martínez-Rodríguez I, Del Castillo-Matos R, Quirce R, Banzo I, Jiménez-Bonilla J, Martínez-Amador N, et al. Aortic 18F-FDG PET/CT uptake pattern at 60 min (early) and 180 min (delayed) acquisition in a control population: A visual and semiquantitative comparative analysis. Nucl Med Commun. 2013;34(9).

376. Martínez-Rodríguez I, Martínez-Amador N, Banzo I, Quirce R, Jiménez-Bonilla J, De Arcocha-Torres M, et al. Assessment of aortitis by semiquantitative analysis of 180-min 18F-FDG PET/CT acquisition images. Eur J Nucl Med Mol Imaging. 2014;41(12).

377. Rosenblum JS, Quinn KA, Rimland CA, Mehta NN, Ahlman MA, Grayson PC. Clinical Factors Associated with Time-Specific Distribution of 18F-Fluorodeoxyglucose in Large-Vessel Vasculitis. Sci Rep. 2019;9(1).

378. Besson FL, Parienti JJ, Bienvenu B, Prior JO, Costo S, Bouvard G, et al. Diagnostic performance of 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: A systematic review and meta-analysis. Vol. 38, European Journal of Nuclear Medicine and Molecular Imaging. 2011.

379. Soussan M, Nicolas P, Schramm C, Katsahian S, Pop G, Fain O, et al. Management of large-vessel vasculitis with FDG-PET: a systematic literature review and meta-analysis. Medicine. 2015;94(14).

380. Lee YH, Choi SJ, Ji JD, Song GG. Diagnostic accuracy of 18F-FDG PET or PET/CT for large vessel vasculitis. Z Rheumatol. 2016;75(9).

381. Van Der Geest KSM, Treglia & G, Glaudemans AWJM, Brouwer E, Sandovici & M, Jamar & F, et al. Diagnostic value of [18F]FDG-PET/CT for treatment monitoring in large vessel vasculitis: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging [Internet]. 2021;48:3886–902. Available from: https://doi.org/10.1007/s00259-021-05362-8

382. Prieto-Peña D, Martínez-Rodríguez I, Loricera J, Banzo I, Calderón-Goercke M, Calvo-Río V, et al. Predictors of positive 18F-FDG PET/CT-scan for large vessel vasculitis in patients with persistent polymyalgia rheumatica. Semin Arthritis Rheum. 2019 Feb;48(4):720–7.

383. Nielsen BD, Hansen IT, Kramer S, Haraldsen A, Hjorthaug K, Bogsrud TV, et al. Simple dichotomous assessment of cranial artery inflammation by conventional 18F-FDG PET/CT shows high accuracy for the diagnosis of giant cell arteritis: a case-control study. Eur J Nucl Med Mol Imaging. 2019;46(1).

384. Sammel AM, Hsiao E, Schembri G, Nguyen K, Brewer J, Schrieber L, et al. Diagnostic Accuracy of Positron Emission Tomography/Computed Tomography of the Head, Neck, and Chest for Giant Cell Arteritis: A Prospective, Double-Blind, Cross-Sectional Study. Arthritis and Rheumatology. 2019;

385. Nielsen BD, Gormsen LC, Hansen IT, Keller KK, Therkildsen P, Hauge EM. Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. Eur J Nucl Med Mol Imaging. 2018;

386. Nienhuis PH, van Praagh GD, Glaudemans AWJM, Brouwer E, Slart RHJA. A review on the value of imaging in differentiating between large vessel vasculitis and atherosclerosis. Vol. 11, Journal of Personalized Medicine. 2021.

387. Stellingwerff MD, Brouwer E, Lensen KJDF, Rutgers A, Arends S, Van Der Geest KSM, et al. Different scoring methods of FDG PET/CT in Giant cell arteritis need for standardization. Medicine (United States). 2015;94(37).

388. Nienhuis PH, Sandovici M, Glaudemans AW, Slart RH, Brouwer E. Visual and semiquantitative assessment of cranial artery inflammation with FDG-PET/CT in giant cell arteritis. Semin Arthritis Rheum. 2020;50(4).

389. de Miguel E, Andreu JL, Naredo E, Möller I. Ultrasound in Rheumatology: Where Are We and Where Are We Going? Reumatología Clínica (English Edition). 2014;10(1).

390. Mahr A, Belhassen M, Paccalin M, Devauchelle-Pensec V, Nolin M, Gandon S, et al. Characteristics and management of giant cell arteritis in France: A study based on national health insurance claims data. Rheumatology (United Kingdom). 2020;59(1).

391. Ing E, Xu Q, Chuo J, Kherani F, Landau K. Practice Preferences: Temporal Artery Biopsy versus Doppler Ultrasound in the Work-Up of Giant Cell Arteritis. Neuro-Ophthalmology. 2020;44(3).

392. Schmidt WA. Ultrasound in the diagnosis and management of giant cell arteritis. Rheumatology (United Kingdom). 2018;

393. Schmidt WA, Kraft HE, Völker L, Vorpahl K, Gromnica-Ihle EJ. Colour doppler sonography to diagnose temporal arteritis. The Lancet. 1995.

394. Chrysidis S, Duftner C, Dejaco C, Schäfer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. Open [Internet]. 2018;4:598. Available from: http://rmdopen.bmj.com/

395. Karassa FB, Matsagas MI, Schmidt WA, Ioannidis JPA. Meta-analysis: Test performance of ultrasonography for giant-cell arteritis. Annals of Internal Medicine. 2005.

396. De Miguel E, Castillo C, Rodríguez A, De Agustín JJ, Alvarez F, Babio J, et al. Learning and reliability of colour Doppler ultrasound in giant cell arteritis. Clin Exp Rheumatol. 2009;27(1 SUPPL. 52).

397. Vicente-Rabaneda EF, Acebes C, Castañeda S. Usefulness of extra-articular ultrasound applied to systemic inflammatory diseases in clinical practice. Reumatología Clínica (English Edition). 2021;17(4).

398. Arida A, Kyprianou M, Kanakis M, Sfikakis PP. The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: A second meta-analysis. BMC Musculoskelet Disord. 2010;

399. Aranda-Valera IC, García Carazo S, Monjo Henry I, De Miguel Mendieta E. Diagnostic validity of Doppler ultrasound in giant cell arteritis. Clin Exp Rheumatol. 2017;35(1).

400. Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ. Color Duplex Ultrasonography in the Diagnosis of Temporal Arteritis. New England Journal of Medicine. 1997;

401. Sebastian A, Coath F, Innes S, Jackson J, Van Der Geest KSM, Dasgupta B. Role of the halo sign in the assessment of giant cell arteritis: A systematic review and meta-analysis. Vol. 5, Rheumatology Advances in Practice. 2021.

402. Schmidt WA, Seifert A, Gromnica-ihle E, Krause A, Natusch A. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. Rheumatology. 2008;

403. Hop H, Mulder DJ, Sandovici M, Glaudemans AWJM, van Roon AM, Slart RHJA, et al. Diagnostic value of axillary artery ultrasound in patients with suspected giant cell arteritis. Rheumatology. 2020;1–9.

404. Nielsen BD, Hansen IT, Keller KK, Therkildsen P, Gormsen LC, Hauge EM. Diagnostic accuracy of ultrasound for detecting large-vessel giant cell arteritis using FDG PET/CT as the reference. Rheumatology. 2019;

405. Gehlen M, Schaefer N, Schwarz-Eywill M, Maier A. Ultrasound to detect involvement of vertebral artery in giant cell arteritis. Vol. 36, Clinical and Experimental Rheumatology. 2018.

406. Czihal M, Zanker S, Rademacher A, Tatò F, Kuhlencordt PJ, Schulze-Koops H, et al. Sonographic and clinical pattern of extracranial and cranial giant cell arteritis. Scand J Rheumatol. 2012;41(3).

407. Ješe R, Rotar Ž, Tomšič M, Hočevar A. The role of colour doppler ultrasonography of facial and occipital arteries in patients with giant cell arteritis: A prospective study. Eur J Radiol. 2017;95.

408. Diamantopoulos AP, Haugeberg G, Hetland H, Soldal DM, Bie R, Myklebust G. Diagnostic value of color doppler ultrasonography of temporal arteries and large vessels in giant cell arteritis: A consecutive case series. Arthritis Care Res (Hoboken). 2014;

409. Zachrisson H, Svensson C, Dremetsika A, Eriksson P. An extended high-frequency ultrasound protocol for detection of vessel wall inflammation. Clin Physiol Funct Imaging. 2018;38(4).

410. Agard C, Hamidou MA, Said L, Ponge T, Connault J, Chevalet P, et al. Screening of abdominal aortic involvement using Doppler sonography in active giant cell (temporal) arteritis at the time of diagnosis. A prospective study of 30 patients. Revue de Medecine Interne. 2007;28(6).

411. Sundholm JKM, Paetau A, Albäck A, Pettersson T, Sarkola T. Non-Invasive Vascular Very-High Resolution Ultrasound to Quantify Artery Intima Layer Thickness: Validation of the Four-Line Pattern. Ultrasound Med Biol. 2019;45(8).

412. Bergner R, Splitthoff J, Wadsack D. Use of Contrast-Enhanced Ultrasound Sonography in Giant Cell Arteritis: A Proof-of-Concept Study. Ultrasound Med Biol. 2022;48(1).

413. Schinkel AFL, Van Den Oord SCH, Van Der Steen AFW, Van Laar JAM, Sijbrands EJG. Utility of contrast-enhanced ultrasound for the assessment of the carotid artery wall in patients with Takayasu or giant cell arteritis. Eur Heart J Cardiovasc Imaging. 2014;15(5).

414. Germanò G, Macchioni P, Possemato N, Boiardi L, Nicolini A, Casali M, et al. Contrast-Enhanced Ultrasound of the Carotid Artery in Patients With Large Vessel Vasculitis: Correlation With Positron Emission Tomography Findings. Arthritis Care Res (Hoboken). 2017;69(1).

415. Roncato C, Perez L, Brochet-Guégan A, Allix-Béguec C, Raimbeau A, Gautier G, et al. Colour Doppler ultrasound of temporal arteries for the diagnosis of giant cell arteritis: a multicentre deep learning study. Clin Exp Rheumatol. 2020;38(2).

416. Czihal M, Schröttle A, Baustel K, Lottspeich C, Dechant C, Treitl KM, et al. B-mode sonography wall thickness assessment of the temporal and axillary arteries for the diagnosis of giant cell arteritis: a cohort study. Clin Exp Rheumatol. 2017;35(1).

417. Czihal M, Köhler A, Lottspeich C, Prearo I, Hoffmann U, Schulze-Koops H, et al. Temporal artery compression sonography for the diagnosis of giant cell arteritis in elderly patients with acute ocular arterial occlusions. Rheumatology (United Kingdom). 2021;60(5).

418. De Miguel E, Beltran LM, Monjo I, Deodati F, Schmidt WA, Garcia-Puig J. Atherosclerosis as a potential pitfall in the diagnosis of giant cell arteritis. Rheumatology (United Kingdom). 2018;57(2).

419. Martire MV, Cipolletta E, Di Matteo A, Di Carlo M, Jesus D, Grassi W, et al. Is the intima-media thickness of temporal and axillary arteries influenced by cardiovascular risk? Rheumatology (United Kingdom). 2021;60(11).

420. Schmidt WA, Natusch A, Möller DE, Vorpahl K, Gromnica-Ihle E. Involvement of peripheral arteries in giant cell arteritis: A color Doppler sonography study. Clin Exp Rheumatol. 2002;20(3).

421. Lauwerys BR, Puttemans T, Houssiau FA, Devogelaer JP. Color Doppler sonography of the temporal arteries in giant cell arteritis and polymyalgia rheumatica. Journal of Rheumatology. 1997;24(8).

422. Karahaliou M, Vaiopoulos G, Papaspyrou S, Kanakis MA, Revenas K, Sfikakis PP. Colour duplex sonography of temporal arteries before decision for biopsy: A prospective study in 55 patients with suspected giant cell arteritis. Arthritis Res Ther. 2006;

423. Santoro L, D'Onofrio F, Bernardi S, Gremese E, Ferraccioli G, Santoliquido A. Temporal ultrasonography findings in temporal arteritis: Early disappearance of halo sign after only 2 days of steroid treatment. Vol. 52, Rheumatology (United Kingdom). 2013.

424. Diamantopoulos AP, Myklebust G. Long-term inflammation in the temporal artery of a giant cell arteritis patient as detected by ultrasound. Vol. 6, Therapeutic Advances in Musculoskeletal Disease. 2014.

425. Aschwanden M, Kesten F, Stern M, Thalhammer C, Walker UA, Tyndall A, et al. Vascular involvement in patients with giant cell arteritis determined by duplex sonography of 2x11 arterial regions. Ann Rheum Dis. 2010;69(7).

426. Pérez López J, Solans Laqué R, Bosch Gil JA, Molina Cateriano C, Huguet Redecilla P, Vilardell Tarrés M. Colour-duplex ultrasonography of the temporal and ophthalmic arteries in the diagnosis and follow-up of giant cell arteritis. Clin Exp Rheumatol. 2009;

427. Ford JA, DiIorio MA, Huang W, Sobiesczcyk P, Docken WP, Tedeschi SK. Follow-up vascular ultrasounds in patients with giant cell arteritis. Clin Exp Rheumatol. 2020;38(2).

428. De Miguel E, Roxo A, Castillo C, Peiteado D, Villalba A, Martín-Mola E. The utility and sensitivity of colour Doppler ultrasound in monitoring changes in giant cell arteritis. Clin Exp Rheumatol. 2012;

429. Monti S, Floris A, Ponte CB, Schmidt WA, Diamantopoulos AP, Pereira C, et al. The proposed role of ultrasound in the management of giant cell arteritis in routine clinical practice. Rheumatology (United Kingdom). 2018;

430. Aschwanden M, Schegk E, Imfeld S, Staub D, Rottenburger C, Berger CT, et al. Vessel wall plasticity in large vessel giant cell arteritis: An ultrasound follow-up study. Rheumatology (United Kingdom). 2019;

431. Ponte C, Monti S, Scirè CA, Delvino P, Khmelinskii N, Milanesi A, et al. Ultrasound halo sign as a potential monitoring tool for patients with giant cell arteritis: A prospective analysis. Ann Rheum Dis. 2021;80(11).

432. Patil P, Williams M, Maw WW, Achilleos K, Elsideeg S, Dejaco C, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015;

433. Van Der Geest KSM, Sandovici M, Brouwer E, MacKie SL. Diagnostic Accuracy of Symptoms, Physical Signs, and Laboratory Tests for Giant Cell Arteritis: A Systematic Review and Meta-analysis. JAMA Intern Med. 2020;

434. Mackie SL, Dasgupta B, Hordon L, Gough A, Green M, Hollywood J, et al. Ischaemic manifestations in giant cell arteritis are associated with area level socio-economic deprivation, but not cardiovascular risk factors. Rheumatology (Oxford). 2011;

435. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Glucocorticoid Dosages and Acute-Phase Reactant Levels at Giant Cell Arteritis Flare in a Randomized Trial of Tocilizumab. Arthritis and Rheumatology. 2019;

436. Mackie SL, Dejaco C, Appenzeller S, Camellino D, Duftner C, Gonzalez-Chiappe S, et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. Rheumatology. 2020;

437. Bley TA, Wieben O, Uhl M, Thiel J, Schmidt D, Langer M, et al. Vascular Imaging Bley et al. MRI of Vessel Wall in Giant Cell Arteritis High-Resolution MRI in Giant Cell Arteritis: Imaging of the Wall of the Superficial Temporal Artery. AJR. 2005;

438. Pouncey AL, Yeldham G, Magan T, Lucenteforte E, Musonda P, Jaffer U, et al. Temporal artery ultrasound versus temporal artery biopsy for giant cell arteritis. Cochrane Database of Systematic Reviews. 2018;

439. Sebastian A, van der Geest KSM, Coath F, Gondo P, Kayani A, Mackerness C, et al. Halo score (temporal artery, its branches and axillary artery) as a diagnostic, prognostic and disease monitoring tool for Giant Cell Arteritis (GCA). BMC Rheumatol. 2020;

440. Dasgupta B, Borg FA, Hassan N, Alexander L, Barraclough K, Bourke B, et al. BSR and BHPR guidelines for the management of giant cell arteritis. Rheumatology. 2010.

441. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. Arthritis Rheum. 1999;

442. Ball EL, Walsh SR, Tang TY, Gohil R, Clarke JMF. Role of ultrasonography in the diagnosis of temporal arteritis. British Journal of Surgery. 2010;

443. Schäfer VS, Chrysidis S, Dejaco C, Duftner C, Iagnocco A, Bruyn GA, et al. Assessing vasculitis in giant cell arteritis by ultrasound: Results of OMERACT patient-based reliability exercises. Journal of Rheumatology. 2018;

444. Schäfer VS, Juche A, Ramiro S, Krause A, Schmidt WA. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. Rheumatology. 2017;

445. Isaac CA, Franceschi A. EBM: Evidence to practice and practice to evidence. J Eval Clin Pract. 2008;

446. Salameh JP, Bossuyt PM, McGrath TA, Thombs BD, Hyde CJ, MacAskill P, et al. Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): Explanation, elaboration, and checklist. The BMJ. 2020.

447. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies The PRISMA-DTA Statement. JAMA - Journal of the American Medical Association. 2018;

448. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. Quadas-2: A revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine. 2011.

449. Hooft L, Scholten RJPM. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Inleiding in evidence-based medicine. 2018;

450. Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. New England Journal of Medicine. 1997;

451. Salvarani C, Silingardi M, Ghirarduzzi A, Lo Scocco G, Macchioni PL, Bajocchi GL, et al. Is duplex ultrasonography useful for the diagnosis of giant-cell arteritis? Ann Intern Med. 2002;

452. Reinhard M, Schmidt D, Hetzel A. Color-coded sonography in suspected temporal arteritis-experiences after 83 cases. Rheumatol Int. 2004;

453. Nesher G, Shemesh D, Mates M, Sonnenblick M, Abramowitz HB. The predictive value of the halo sign in color Doppler ultrasonography of the temporal arteries for diagnosing giant cell arteritis. Journal of Rheumatology. 2002;

454. Mukhtyar C, Myers H, Scott DGI, Misra A, Jones C. Validating a diagnostic GCA ultrasonography service against temporal artery biopsy and long-term clinical outcomes. Clin Rheumatol. 2020;

455. Maldini C, Dépinay-Dhellemmes C, Tra TTS, Chauveau M, Allanore Y, Gossec L, et al. Limited value of temporal artery ultrasonography examinations for diagnosis of giant cell arteritis: Analysis of 77 subjects. Journal of Rheumatology. 2010;

456. Croft AP, Thompson N, Duddy MJ, Barton C, Khattak F, Mollan SP, et al. Cranial ultrasound for the diagnosis of giant cell arteritis. A retrospective cohort study. Journal of the Royal College of Physicians of Edinburgh. 2015;

457. Black R, Roach D, Rischmueller M, Lester SL, Hill CL. The use of temporal artery ultrasound in the diagnosis of giant cell arteritis in routine practice. Int J Rheum Dis. 2013;

458. Bilyk JR, Murchison AP, Leiby BT, Sergott RC, Eagle RC, Needleman L, et al. The Utility of Color Duplex Ultrasonography in the Diagnosis of Giant Cell Arteritis: A Prospective, Masked Study. (An American Ophthalmological Society Thesis). Trans Am Ophthalmol Soc. 2017;

459. Sommer F, Spörl E, Herber R, Pillunat LE, Terai N. Predictive value of positive temporal artery biopsies in patients with clinically suspected giant cell arteritis considering temporal artery ultrasound findings. Graefe's Archive for Clinical and Experimental Ophthalmology. 2019;

460. Romera-Villegas A, Vila-Coll R, Poca-Dias V, Cairols-Castellote MA. The role of color duplex sonography in the diagnosis of giant cell arteritis. Journal of Ultrasound in Medicine. 2004;

461. Pfenninger L, Horst A, Stuckmann G, Flury R, Stürmer J. Comparison of histopathological findings with duplex sonography of the temporal arteries in suspected giant cell arteritis. Klin Monbl Augenheilkd. 2012;

462. Muratore F, Boiardi L, Restuccia G, Macchioni P, Pazzola G, Nicolini A, et al. Comparison between colour duplex sonography findings and different histological patterns of temporal artery. Rheumatology (United Kingdom). 2013;

463. LeSar CJ, Meier GH, DeMasi RJ, Sood J, Nelms CR, Carter KA, et al. The utility of color duplex ultrasonography in the diagnosis of temporal arteritis. J Vasc Surg. 2002;

464. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. BMJ (Online). 2015.

465. Moher D, Liberati A, Tetzlaff J AD. PRISMA 2009 Flow Diagram. The PRISMA statement. 2009.

466. Aschwanden M, Imfeld S, Staub D, Baldi T, Walker UA, Berger CT, et al. The ultrasound compression sign to diagnose temporal giant cell arteritis shows an excellent interobserver agreement. Clin Exp Rheumatol. 2015;

467. Rinagel M, Chatelus E, Jousse-Joulin S, Sibilia J, Gottenberg JE, Chasset F, et al. Diagnostic performance of temporal artery ultrasound for the diagnosis of giant cell arteritis: a systematic review and meta-analysis of the literature. Autoimmunity Reviews. 2019.

468. Schmidt WA. Doppler ultrasonography in the diagnosis of giant cell arteritis. In: Clinical and Experimental Rheumatology. 2000.

469. Reinhard M, Schmidt D, Hetzel A. Color-coded sonography in suspected temporal arteritis-experiences after 83 cases. Rheumatol Int. 2004;

470. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. The Lancet. 2008.

471. Machado EBV, Michet CJ, Ballard DJ, Hunder GG, Beard CM, Chu C -P, et al. Trends in incidence and clinical presentation of temporal arteritis in olmsted county, minnesota, 1950–1985. Arthritis Rheum. 1988;

472. Hunder GG. The use and misuse of classification and diagnostic criteria for complex diseases. Annals of Internal Medicine. 1998.

473. Bley TA, Reinhard M, Hauenstein C, Markl M, Warnatz K, Hetzel A, et al. Comparison of duplex sonography and high-resolution magnetic resonance imaging in the diagnosis of giant cell (temporal) arteritis. Arthritis Rheum. 2008;

474. Weyand CM, Goronzy JJ, Sherwin JC, De Smit E, Hewitt AW, CM W, et al. Giant-cell arteritis and polymyalgia rheumatica...N Engl J Med. 2014 Oct 23;371(17):1652; N Engl J Med. 2014 Oct 23;371(17):1652-3; N Engl J Med. 2014 Jul 3;371(1):50-7. New England Journal of Medicine. 2014;

475. Danesh-Meyer H V. Temporal artery biopsy: Skip it at your patient's peril. American Journal of Ophthalmology. 2012;

476. Khan A, Dasgupta B. Imaging in Giant Cell Arteritis. Current Rheumatology Reports. 2015.

477. Muratore F, Pipitone N, Salvarani C, Schmidt WA. Imaging of vasculitis: State of the art. Best Practice and Research: Clinical Rheumatology. 2016.

478. Arida A, Kyprianou M, Kanakis M, Sfikakis PP. The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: A second meta-analysis. BMC Musculoskelet Disord. 2010;

479. Mazlumzadeh M, Hunder GG, Easley KA, Calamia KT, Matteson EL, Griffing WL, et al. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: A double-blind, placebo-controlled, randomized prospective clinical trial. Arthritis Rheum. 2006;

480. Chandran A, Udayakumar PD, Kermani TA, Warrington KJ, Crowson CS, Matteson EL. Glucocorticoid usage in giant cell arteritis over six decades (1950 to 2009). Clin Exp Rheumatol. 2015;

481. Planas-Rigol E, Terrades-Garcia N, Corbera-Bellalta M, Lozano E, Alba MA, Segarra M, et al. Endothelin-1 promotes vascular smooth muscle cell migration across the artery wall: A mechanism contributing to vascular remodelling and intimal hyperplasia in giant-cell arteritis. Ann Rheum Dis. 2017;76(9).

482. Sundholm JKM, Pettersson T, Paetau A, Albäck A, Sarkola T. Diagnostic performance and utility of very high-resolution ultrasonography in diagnosing giant cell arteritis of the temporal artery. Rheumatol Adv Pract. 2019;3(2).

483. Bosch P, Dejaco C, Schmidt WA, Schlüter KD, Pregartner G, Schäfer VS. Ultrasound for diagnosis and follow-up of chronic axillary vasculitis in patients with long-standing giant cell arteritis. Ther Adv Musculoskelet Dis. 2021;13.

484. Hop H, Mulder DJ, Sandovici M, Glaudemans A, Roon A Van, Slart R, et al. OP0211 ULTRASONOGRAPHY CAN POTENTIALLY BE THE FIRST CHOICE OF IMAGING IN SUSPECTED EXTRA-CRANIAL GCA. In 2019.

485. Oglat AA, Matjafri MZ, Suardi N, Oqlat MA, Abdelrahman MA, Oqlat AA. A review of medical doppler ultrasonography of blood flow in general and especially in common carotid artery. J Med Ultrasound. 2018;

486. Conway R, O'Neill L, McCarthy GM, Murphy CC, Veale DJ, Fearon U, et al. Performance characteristics and predictors of temporal artery ultrasound for the diagnosis of giant cell arteritis in routine clinical practice in a prospective cohort. Clin Exp Rheumatol. 2019;

487. Czihal M, Piller A, Schroettle A, Kuhlencordt P, Bernau C, Schulze-Koops H, et al. Impact of cranial and axillary/subclavian artery involvement by color duplex sonography on response to treatment in giant cell arteritis. J Vasc Surg. 2015;

488. Evans J, Steel L, Borg F, Dasgupta B. Long-term efficacy and safety of tocilizumab in giant cell arteritis and large vessel vasculitis. RMD Open. 2016;

489. Deshayes S, Ly KH, Rieu V, Maigne G, Martin Silva N, Manrique A, et al. Steroid-sparing effect of anakinra in giant-cell arteritis: A case series with clinical, biological and iconographic long-term assessments. Rheumatology (United Kingdom). 2022;61(1).

490. Berman M, Ben-Ami R, Berliner S, Anouk M, Kaufman I, Broyde A, et al. The effect of tocilizumab on inflammatory markers in patients hospitalized with serious infections. Case series and review of literature. Life. 2021;11(3).

491. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Vol. 395, The Lancet. Lancet Publishing Group; 2020. p. 470–3.

492. Reference Method for the Erythrocyte Sedimentation Rate (ESR) Test on Human Blood. Br J Haematol. 1973;24(5).

493. Kratz A, Plebani M, Peng M, Lee YK, McCafferty R, Machin SJ. ICSH recommendations for modified and alternate methods measuring the erythrocyte sedimentation rate. Int J Lab Hematol. 2017;39(5).

**APPENDIX-1: Data entry form (CRF)**

# HAS GCA

| | |
|---|---|
| **Chief Investigator:** | **Professor Bhaskar Dasgupta** |
| **IRAS Project number:** | **264294** |
| **REC reference:** | **19/LO/1375** |
| **Protocol version number & Date:** | **4.3 (08 AUG 2019)** |
| **Sponsor:** | **R&D Southend University hospital** |

Site Name:☐☐☐☐☐☐☐☐☐☐☐☐

Participant ID:☐☐☐☐☐☐☐☐

Visit Date: ☐☐/☐☐☐/☐☐☐☐

Visit Time point: ☐☐☐☐☐☐☐☐

Visit Number:☐☐

GCA☐ CONTROL ☐(tick as appropriate)

| Demographics | |
|---|---|
| Patient ID | |
| NHS Number | |
| Age | |
| Sex | |
| GCA Diagnosis Type | |
| Date of GCA Diagnosis | |
| [redacted] | |
| Ophthalmology R/v | |
| Ophthalmology Report | |
| Weight (Kg) | |
| Height (cm) | |
| Probability score | |
| Other/Comments | |
| **checked by** | |
| **date** | |

| Confirmatory Ix | | |
|---|---|---|
| | Investigations | Date |
| US TA | | |
| US Axillary | | |
| TAB | | |
| PET-CT | | |
| MRA | | |
| CTA | | |
| Ophthalmology | | |
| DEXA | | |
| Other Imaging | | |

| HALO thickness (mm) | | | |
|---|---|---|---|
| Right | | Left | |
| Common | | Common | |
| Parietal | | Parietal | |
| Frontal | | Frontal | |
| Axillary | | Axillary | |
| Checked By | | | |
| Date | | | |

| Symptoms at time of Assessment | | | |
|---|---|---|---|
| Ocular Involvement | | Temporal Headache (R/L) | |
| Visual Loss in One Eye (R/L) | | Generalised Headache | |
| Visual Loss in Both Eyes | | Scalp Tenderness (R/L) | |
| Partial Sight Impairment (R/L) | | Fever/pyrexia | |
| Amaurosis Fugax | | Night Sweats | |
| Diplopia | | Weight Loss | |
| Blurred Vision | | Tongue Claudication | |
| Other Pre-existing Eye Disease | | Jaw Claudication | |
| Ophthalmology Report | | Limb Claudication | |
| PMR symptoms | | Other Symptoms | |

| Signs | | |
|---|---|---|
| | Y/N | Side |
| Ischaemic | | |
| AION | | |
| CRAO | | |
| PION | | |
| Tongue Necrosis | | |
| Scalp Necrosis | | |
| Oculomotor Nerve Palsy | | |
| Cranial Artery Abnormality | | |
| TA Swelling | | |
| TA Tenderness | | |
| TA Reduced/Absent Pulse | | |
| Peripheral Involvement | | |
| Carotid Bruit | | |
| Axillary Bruit | | |
| Brachial Bruit | | |
| Brachial Absent/Reduced Pulse | | |
| Radial Absent/Reduced Pulse | | |
| Femoral Bruit | | |
| Femoral Absent/Reduced Pulse | | |
| BP Pressure (Right) | | |
| BP Pressure (Left) | | |
| Heart Rate | | |
| Temperature | | |
| Other Signs | | |

| Co-Morbidities | | |
|---|---|---|
| | Y/N | Date of Dg |
| CNS | | |
| TIA | | |
| Haemorrhagic CVA | | |
| Ischaemic CVA | | |
| Cardiac | | |
| IHD | | |
| CCF | | |
| HTN | | |
| Adrenal insufficiency | | |
| Cushing's | | |
| DM | | |
| Thyroid disease | | |
| Other endocrine | | |
| Osteoporosis | | |
| GIT | | |
| PUD | | |
| GI Perforation | | |
| Diverticulitis | | |
| Infections | | |
| TB | | |
| Hep B/C | | |
| HIV | | |
| VZV | | |
| Malignancy | | |
| Other sys/Rheum disease | | |
| Head & Neck path | | |
| Other | | |

| Laboratory | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Results | Sample Collection Date | | Results | Sample Collection Date | | Sample Collection Date | Results |
| CRP | | | TC | | | U. Leu | | |
| ESR | | | LDL | | | U.Protein | | |
| Hb | | | HDL | | | U.Blood | | |
| PLT | | | TG | | | Other | | |
| WBC | | | Blood sugar | | | | | |
| Neu | | | HbA1c | | | | | |
| ALT | | | Creatinine | | | | | |
| ALP | | | eGFR | | | | | |

| Disease Activity | | |
|---|---|---|
| | Value | Comments |
| Patient's Global Assessment (out of 10) | | |
| Evaluator's Global Assessment (out of 10) | | |
| HAQ (if PMR) | | |
| Patient Reported outcome (EQ5D) | | |
| | | |
| Checked by | | |
| Checked Date | | |

| Treatment | | | |
|---|---|---|---|
| | Treatment | Current Use | Historic Use |
| Oral Glucocorticosteroids | | | |
| IV Steroids Given | | | |
| Methotrexate | | | |
| Leflunomide | | | |
| Azathioprin | | | |
| Tocilizumab | | | |
| Other | | | |
| Biologic DMARDs | | | |
| Antiplatelet | | | |
| | | | |

| **Steroid Dose (mg)** | |
|---|---|
| Daily Dose | |
| Cumulative Dose | |

| **GCA Outcome** | | |
|---|---|---|
| | Outcome | Comments |
| GCA Disease Activity Well Controlled? | | |
| Any Flares since the Last visit? | | |
| Vascular Damage | | |
| Is Patient Steroid Dependent? | | |
| Any Contraindications to Steroid Therapy? | | |
| Need for Step Up Treatment? | | |
| Any Contraindications to Step Up Therapy? | | |

**APPENDIX-2: Patient consent form**

Southend University Hospital NHS
NHS Foundation Trust

Southend University Hospital
Prittlewell Chase, Westcliff-on-Sea,Essex SS0 0RY
Tel: 01702 385252
Fax: 01702 385909

IRAS Project number: 264294
Centre Number: Study Number:
Participant Identification Number for this trial:

**CONSENT FORM**

Title of Project: **Halo Score (Temporal artery, it's branches and Axillary artery) as a diagnostic, prognostic and disease monitoring tool for Giant Cell Arteritis (GCA)**

Name of Researcher: Prof. Dasgupta

| | Please initial box |
|---|---|
| 1. I confirm that I have read the information sheet dated 20th August 2019 (version 2.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. | ☐ |
| 2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. | ☐ |
| 3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. | ☐ |
| 4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. | ☐ |
| 5. I agree to my General Practitioner being informed of my participation in the study, including any necessary exchange of information about me between my GP and the research team. | ☐ |
| 6. I understand that the information held and maintained by the Rheumatology research department and NHS trust may be used to help contact me or provide information about my health status. | ☐ |
| 7. I agree for my anonymised samples to be used in future research, here or abroad, which has ethics approval. | ☐ |
| 8. I agree to take part in the above study. | ☐ |

| Name of Participant | Date | Signature |
|---|---|---|

| Name of Person taking consent | Date | Signature |
|---|---|---|

**When completed: 1 for participant; 1 for Researcher site file; 1 to be kept in medical notes**

## APPENDIX-3: GCA probability score Performa

| Weightage | | -3 | 0 | 1 | 2 | 3 |
|---|---|---|---|---|---|---|
| Demographics | **Age** | | ≤ 49 | 50-60 | 60-65 | ≥ 66 |
| | **Sex** | | | M | F | |
| Onset | | | >24 weeks | 12-24 weeks | 6-12 weeks | <6 weeks |
| Laboratory | **CRP** | | 0-5 mg/L | 6-10mg/L | 11-25 mg/L | ≥ 25 mg/L |
| symptoms | **Cranial** | | N | Y | | |
| | **Polymyalgic** | | N | | Y | |
| | **Constitutional** | | N | single | | Combine |
| | **Ischemic** | | N | | | Y |
| Signs | **Visual (AION, CRAO, Field loss, RAPD)** | | N | | | |
| | **TA abnormality** | | N | Tenderness | Thickness | Pulse loss |
| | **Extra-cranial artery abnormality** | | N | Thickness | | Pulse loss |
| | **Cranial nerve palsy** | | N | | | Y |
| Alternative diagnosis | **Infection** | Y | | | | |
| | **Cancer** | Y | | | | |
| | **Systemic Rheumatological disease** | Y | | | | |
| | **Head and neck pathology** | Y | | | | |
| | **Other** | Y | | | | |
| Total Score | | | | | | |

## APPENDIX-4: Patient information sheet

**Department of Rheumatology**

**PATIENT INFORMATION SHEET (PIS)**

**Study Title: Halo Score (Temporal artery, its branches and Axillary artery) as a diagnostic, prognostic and disease monitoring tool for Giant Cell Arteritis (GCA). (HAS-GCA study)**

We are inviting you to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information, and discuss it with others if you wish. **One of our team will go through the information leaflet with you, explain the study in more detail, and answer any questions you have**. If there is anything that is not clear, or if you would like more information, please ask us (see contact details on the last page) Talk to others about the study if you wish, such as friends or relatives, and take time to decide. If you would like to take part, you will be asked to confirm by signing a separate consent form and will be given a copy of this for your records.

**1. What is the purpose of this study?**

Giant cell arteritis (GCA) is a condition causing inflammation of blood vessels, termed vasculitis. GCA is also sometimes called temporal arteritis. In GCA, arteries around the scalp and head become inflamed. This frequently includes the temporal artery, which is a small blood vessel under the skin at the temples. GCA occurs in adults over 50 years of age, more commonly affects women, and occurs in Caucasians more often than non-Caucasians. Its cause is unknown. Symptoms can include a new, persistent headache, often at the temples, but may occur around the head. Other symptoms are fatigue, fevers, flu-like symptoms, weight loss, loss of appetite and pain in the jaw or tongue when chewing. Inflammation can spread to vessels that supply blood to the eyes. People may therefore notice blurring of vision, double vision or blindness. Permanent, sudden loss of eyesight is a rare complication that could be prevented if GCA is recognised and treated promptly. A Rheumatologist should diagnose and treat GCA. GCA treatment should commence immediately when the doctor recognises it is GCA, to prevent further complications. Usually the doctor will prescribe high dose steroids as a standard treatment for GCA. This is an appropriate treatment for GCA, but unfortunately steroids have several side effects including bone loss, weight gain, mood changes diabetes and cataracts. Therefore, making a correct diagnosis is vital to minimise inappropriate steroid use and prevent the side effects.

GCA is diagnosed using clinical symptoms and blood tests showing inflammation. Increasingly, centres may also use ultrasound scans of the temporal and axillary arteries (under-arms) to diagnose GCA. Some patients may also need to go on to have a biopsy of the temporal artery to aid diagnosis. A biopsy is where a sample of tissue, in this case a

small section of the temporal artery, is taken under local anaesthetic so it can be examined in more detail.

This study was designed to assess whether ultrasound scans of the temporal arteries and axillary arteries helps to make a prompt diagnosis of GCA, and if it can help predict response to treatment, as demonstrated on repeat scans at follow-up appointments.

**2. Why have I been chosen?**

You have been chosen because you are 50 years of age or older and referred to our clinic with the suspicious of having GCA.

**3. Do I have to take part?**

It is up to you to decide whether or not to take part. You are free to withdraw at any time and without giving a reason.

**4. What will happen if I take part?**

Your treatment plan will be the same as for any other patient diagnosed with GCA. In addition to standard care we will check extra blood tests and call you for follow-up appointments more frequently. At these appointments we will assess you, check your bloods and perform repeat ultrasound scans of the temporal and axillary arteries. You will also be asked to fill out a structured questionnaire about your quality of life following your diagnosis. The scheduled appointments will occur at 1, 3, 6 and 12 months.
If you are tested negative for GCA we will refer you back to the referring physician or team to continue your care. However, we would like to have a telephone interview at 6 months to check how you did in this time period.

**5. What do I have to do?**

During your first consultation if you are diagnosed with GCA and you agree to participate in this study, you will be asked to sign a consent form and fill out a questionnaire. You will need to attend 4 more follow up appointments for this study (1, 3, 6 and 12 months). During each follow up visit you will be seen by a member of the research team and they will take history, examination, blood tests (blood volume of approximately one teaspoon) and an Ultrasound scan of the temporal and axillary arteries. Each visit lasts between 30-45 minutes. You can continue to take your regular prescribed medication and the over the counter medications. If you are already involved with another research study, you can continue to be part of that study. Total duration of this study will be 12 months. After this period, you will be followed in our clinic as any other patient has this condition.

During the first consultation if you are not diagnosed with GCA then we will discharge you back to the referring physician. However, we would like to have a telephone interview in 6 months' time to check how you did during this time. We will ask you set of questions related to your initial presentation and some additional questions to check any changes in this time period.

**6. What are the possible benefits of taking part?**

You will be seen and assessed in our clinic for follow up more frequently with Ultrasound examination. The information we get from this study will help improve the future treatment of people with GCA.

**7. What are the possible risks of taking part?**

There is no radiation or risk associate with the ultrasound scan. However, there are some minor risks associated with giving blood, for example, infection, excessive bleeding, bruising, fainting or dizziness, haematoma (a collection of blood under the skin similar to bruising). The research nurse is trained to take appropriate action if any of these things occur.

**8. Will my taking part be kept confidential?**

You will be allocated a study number. Responsible members of the Southend University Hospitals NHS Foundation Trust, regulatory authorities, the Sponsor of the study, and NHS Trust(s)] may be given access to data collected during the study for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

This means that your medical notes will need to be seen by authorised members of the hospital research team so they can collect information needed for this research study. With your consent, your GP will also be informed that you are taking part in the research study. Your GP may be asked to provide information from your records which is required for the research. Occasionally, other members of NHS staff or research staff may need to check your medical records. This will be done by NHS staff or by researchers who are bound by the same rules of confidentiality as all NHS staff. Regulatory authorities and the hospital trust overseeing the research may also need to look at your notes but the confidentiality of your medical records will be respected at all times.
All information which is collected about you during the course of this research will be kept strictly confidential. The information that will be collected includes personal information such as your name, address and NHS number. This will allow us to keep in touch with you during your participation in this research, enabling us to collect information about your quality of life.

Electronic information collected by the hospital where you are normally treated for other conditions may be securely transferred within the NHS to Southend University Hospital Foundation Trust. The information collected will be stored in a secure database held at the co-ordinating centre (University Hospitals NHS Foundation Trust,) and will only be accessed by authorised members of staff involved in the research.

The findings from the study may be reported in medical journals or presented at meetings but your identity will not be disclosed. During the course of the study we will ask you if you would like to receive a summary of the results by post after the research has finished.
Under no circumstances will you be identified in any way in any report arising from the study.

**9. What if I change my mind about taking part?**

If you decide to withdraw from the study, your standard of care will not be affected. You will still be asked to attend the usual follow-up clinics required by your doctor. These will not be part of the study.

**10. What if there is a problem?**

If you have any concerns or questions about this study, please contact the research team listed at the end of this leaflet. Please feel free to ask any further questions before deciding to take part in the trial, or at any time during the study. If you have concerns about the way you have been approached or treated during the course of the study, you may wish to contact the Patient Advice and Liaison Service (PALS) on Email: PALs@southend.nhs.uk or Phone: 01702 385333.

**11. Will my GP be informed of my involvement in the study?**

Your GP will be informed about your involvement in this study.

**12. What will happen to any samples I give?**

Your anonymised samples will be used mainly by local researchers but ethically approved research projects may take place in hospitals, universities, non-profit institutions or commercial laboratories worldwide. If you agree to your samples being used in future research, your consent form will be held until the samples have been used up. If you withdraw from the study, unless you state otherwise, any blood or tissue samples which have been collected whilst you have been in the study will be used for research as detailed in this participant information sheet. You are free to request that your blood or tissue samples are destroyed at any time during or after the study. Your blood sample will be assigned a code and your data will also be identified only by this number. The material given to researchers will not have information that identifies you.

**13. How will the information I provide be used?**

We will be using information from you and your medical records in order to undertake this study. Research is a task that we perform in the public interest. Southend University Hospitals NHS Foundation Trust, as sponsor, is the data controller. This means that we, as Southend University Hospitals NHS Foundation Trust researchers, are responsible for looking after your information and using it properly. We will use the minimum personally-identifiable information possible. We will keep identifiable information about you for 15 years after the study has finished. We will store the anonymised research data and any research documents with personal information, such as consent forms, securely at the Southend University Hospitals NHS Foundation Trust archive centre for 15 years after the end of the study as part of the research record. Your rights to access, change, or move your personal information may be limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. You can find out more about how we use your information by contacting the research team listed at the end of this leaflet.

**14. Who is organising the research?**

This study is organized by the Rheumatology department at Southend University Hospital

**15. Who has reviewed this study?**

A Research Ethics Committee in NHS trust and your local rheumatology Consultant have reviewed this study.

**16. Further Information**

If you require more information about this study please talk to one of our clinical members of the research team.

**Dr. Alwin Sebastian**
Bresnihan-Malloy International Fellow
Rheumatology Research Fellow
Southend University Hospital
Tel: 01702385254

**Thank you for reading this.**
**Please keep this information sheet for your records.**

**If you agree to enter the study, please sign the enclosed consent form and we will return a copy to you**
Further contacts:

**Prof. Bhaskar Dasgupta – MD, FRCP**
Consultant Rheumatologist
Southend University Hospital NHS Foundation Trust
Prittlewell Chase, Westcliff on Sea
Essex, SS0 0RY
Tel: 01702 385254

**Independent point of contact for complaints**
Patient Advice & Liaison Services (PALs)
Southend University Hospital NHS Foundation Trust
Prittlewell Chase, Westcliff on Sea
Essex, SS0 0RY
Telephone: 01702 385333,
Email: PALs@southend.nhs.uk

## APPENDIX-5: Preliminary Results presented at the international conferences at different stages of the study

### one month follow up- American college of Rheumatologist 2020 Conference

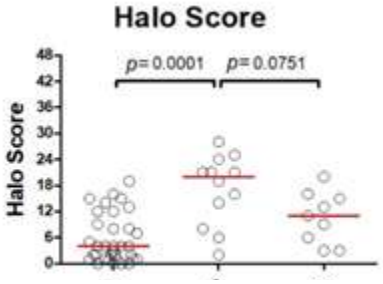
**Results**

Total of 47 patients have been recruited so far into HAS GCA with 1 month follow up assessments. Demographics, clinical features and US results are shown (Table 1).

Twelve (26%) were confirmed GCA (9 cranial, 2 large vessel and 1 cranial plus large vessel) and 35 (74%) confirmed non-GCA. Median age 72 years in GCA and 71.5 years in controls (42% females in GCA and 77% non GCA). GCA patients stratified by PTPS to Low risk (0%), Intermediate risk (33%) and High risk (66%) whereas the 35 non GCA were categorised by PTPS as Low risk 51%. Intermediate risk 37% and High risk 11%.

In High risk 1 LV GCA patient had negative US and FDG PET/CT confirmed bilateral vertebral arteritis. Another patient with axillary artery US positive LV-GCA had a negative FDG PET/CT without other pathologies. In the Intermediate risk, one patient had negative US and negative MRA.

Jaw claudication (42%) and polymyalgic symptoms (33%) were the dominant features in GCA patients contrast to controls. 4 had permanent visual loss prior to the assessment. a Median Total Halo Score in GCA was 20 and control group was 4 (p=0.0001). 9/12 patients with GCA have completed at least 1 month follow up (Table 2). Median TA Halo Score and Total Halo Score was reduced from 8 to 3 and 16 to 11 respectively (Image). AA Halo Score increased from 6 to 9 in 1 month. All the GCA patients were on glucocorticoids (GC) (prednisolone 40-60 mg daily) at presentation compare to 43% (15) in control group (in all GC discontinued after the assessment).



## Three month follow up- EULAR 2021 conference

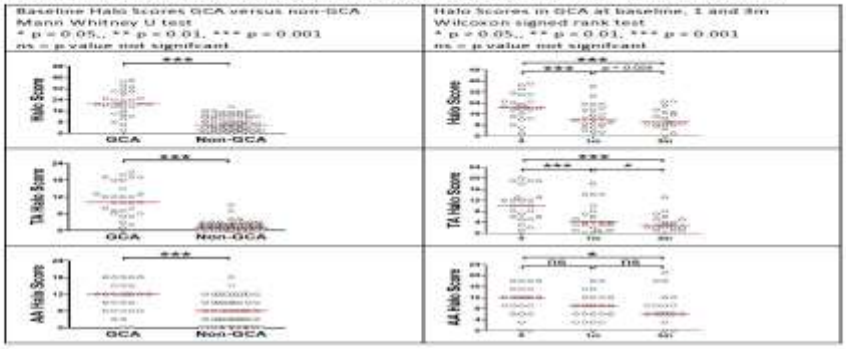
Ninety-three patients (29 GCA, 64 controls) have been recruited thus far: 18 completed 3-month follow up assessment; 4 were lost to follow up (2 died, 2 withdrew consent due to pandemic). Demographics, clinical features, and US results are shown (Table).

Among GCA patients, 23 had cranial, 2 large-vessel and 4 mixed phenotypes (cranial plus large vessel) disease.

Jaw claudication (66%) and polymyalgic symptoms (55%) were the dominant features in GCA patients. Median age 75 years in GCA (42% females) and 67 years in controls (78% females). GCA and controls were stratified by SPTPS to Low risk (0% vs 48%; Sn-undefined, Sp-97), Intermediate risk (24% vs 39%; Sn-100, Sp-100) and High risk (76% vs 13%; Sn-95, Sp-88). Optimal SPTPS cut-off point was ≥12 (Sn-93, Sp-86); ≥10 (Sn-100 & Sp-69).

Median THS was 21 in GCA and 6 in controls. Optimal cut-off Halo Score in diagnosis was TAHS ≥5 (Sn-90, Sp-98), AAHS ≥11 (Sn-55, Sp-80), THS ≥18 (Sn-72%, Sp-98%). Among the 18 patients who completed 3-months follow up, median TAHS, AAHS and THS reduced from 10 to 2.5, 12 to 6 and 21 to 10, respectively (Figure)

**Figure: HS comparing GCA vs non GCA and baseline Halo Score vs 1 and 3 months follow up**




AA; Axillary artery; GCA; Giant cell arteritis; TA; Temporal artery

**Twelve month follow up- EULAR 2022 conference**

**Reults:**

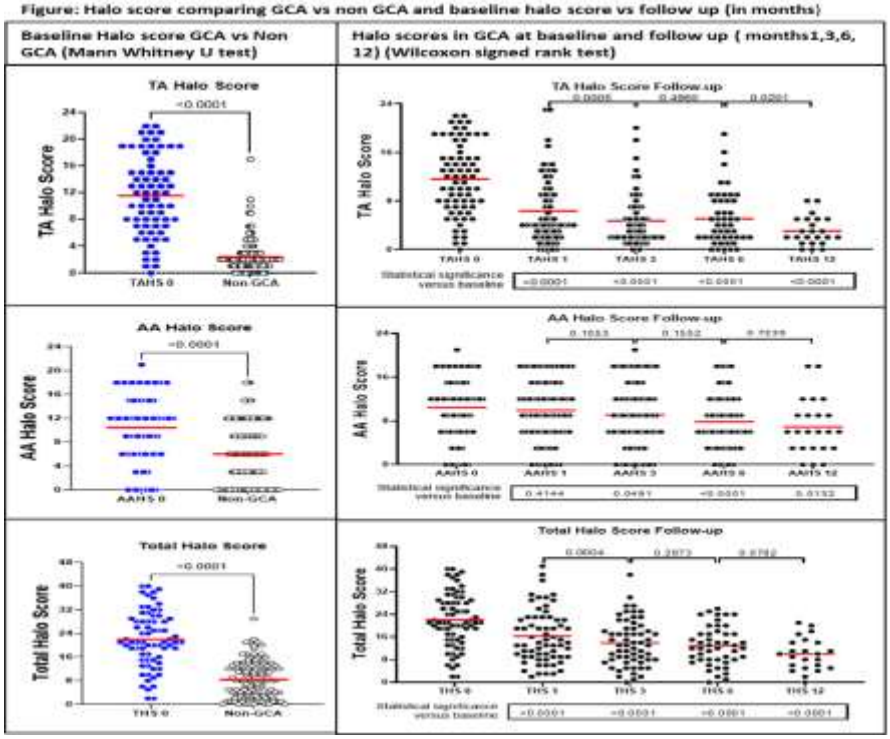
202 patients (71 GCA, 131 controls) have been recruited thus far: 23 completed 12-month follow up assessment; 6 were lost to follow up (4 died, 2 withdrew consent due to pandemic). Demographics, clinical features, and US results are shown (**Table**).

Among GCA patients, 50 had cranial, 5 large-vessel and 16 mixed phenotypes. Diseases were diagnosed by US and additional tests such as PET CT.

Jaw claudication (54%) and constitutional symptoms (59%) were the dominant features in GCA patients. Median age was 75 years in GCA (54% females) and 68 years in controls (68% females). GCA and controls were stratified by SPTPS to Low risk (0% vs 45%; Sn-undefined, Sp-98), Intermediate risk (23% vs 37%; Sn-81, Sp-98) and High risk (77% vs 18%; Sn-98, Sp-91). Optimal SPTPS cut-off point was ≥12 (Sn-89, Sp-76).

Median THS was 21 in GCA and 8 in controls. Optimal cut-off Halo Score in diagnosis was TAHS ≥5 (Sn-89, Sp-86), AAHS ≥11 (Sn-55, Sp-75), THS ≥15 (Sn-79%, Sp-86%). Baseline Halo Score and CRP levels showed positive correlation (spearman rank correlation). Among the 23 patients who completed 12-months follow up, median TAHS, AAHS and THS reduced from 12 to 2, 12 to 6 and 21 to 10, respectively (**Figure**).

Figure: Halo score comparing GCA vs non GCA and baseline halo score vs follow up (in months)



## Southend probability score (GCAPS) Probability based diagnostic algorithm in suspected Giant Cell Arteritis: A prospective, multicentre validity data from HAS GCA study- ACR 2022 conference- oral presentation

**Methods:**

This is a prospective, multicentre, observational study including consecutive patients with suspected, new onset GCA that were recruited at 7 European centres participating in the HAS GCA study. SPTPS was calculated and patients were stratified into the three risk categories: low-risk <9, intermediate-risk 9-12 and high-risk >12. All patients underwent vascular ultrasonography (bilateral common, parietal, frontal temporal arteries, and axillary arteries). Vascular ultrasonography was considered positive for GCA when the intimal medial thickness is >0.42mm in common temporal, >0.29mm in Parietal, >0.34mm in frontal and >1.0mm in axillary arteries. Additional tests such as temporal artery biopsy, FDG-PET/CT, or CTA were performed at the discretion of the treating physician. Final diagnosis was confirmed after 6 months of follow up.

**Results:**

A total of 226 patients were included in the study. A diagnosis of GCA was confirmed in 83 (36.73%) patients. SPTPS was low-risk in 66 (29.2%) patients, intermediate-risk in71 (31.4%) patients and high-risk in 89 (39.4%) patients (Image). The number of patients with GCA among patients in distinct risk categories was 0 (0%) in low-risk patients, 17 (20.5%) in intermediate-risk patients and 66 (79.5%) in high-risk patients. A high diagnostic accuracy was observed for ultrasonography among the three risk categories (table).

**Conclusion:**

The SPTPS is a useful tool for assessing the clinical probability of GCA among patients with suspected, new onset GCA. A combination of the SPTPS and vascular ultrasonography accurately discriminated between patients with and without GCA in our prospective, multicentre study.