REVIEW ARTICLE

Giant Cell Arteritis: State of the Art in Diagnosis, Monitoring, and Treatment

Abid Awisat, M.D.[1], Shiri Keret, M.D.[1], Amal Silawy, M.D.[2], Lisa Kaly, M.D.[1], Itzhak Rosner, M.D.[1], Michael Rozenbaum, M.D.[1], Nina Boulman, M.D.[1], Aniela Shouval, M.D.[1], Doron Rimar, M.D.[1], and Gleb Slobodin, M.D.[1]

[1]*Rheumatology Unit, Bnai Zion Medical Center, Haifa, Israel; and* [2]*Rheumatology Clinic, Maccabi Health Services, Haifa, Israel*

ABSTRACT

Giant cell arteritis (GCA) is the most prevalent subtype of vasculitis in adults. In recent years, there has been substantial improvement in the diagnosis and treatment of GCA, mainly attributed to the introduction of highly sensitive diagnostic tools, incorporation of modern imaging modalities for diagnosis and monitoring of large-vessel vasculitis, and introduction of highly effective novel biological therapies that have revolutionized the field of GCA. This article reviews state-of-the-art approaches for the diagnosis, monitoring, and treatment options of GCA.

KEY WORDS: Diagnosis, giant cell arteritis, monitoring, treatment

INTRODUCTION

Giant cell arteritis (GCA) is a granulomatous subtype of vasculitis involving large and medium-size arteries, both cranial and extra-cranial, e.g. aorta, temporal, subclavian, and axillary arteries. Giant cell arteritis is the most common form of vasculitis prevalent in adults after the age of 50, with the highest incidence observed in people from Northern Europe and of Scandinavian descent (14.6 to 43.6 per 100,000 aged >50 years)[1] compared to lower incidence rates in Asia, Africa, and other parts of the world.[2,3]

The recently published 2022 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for GCA have a sensitivity of 87.0% (95% CI 82.0%–91.0%) and a specificity of 94.8% (95% CI 91.0%–97.4%) as compared to a sensitivity of only 37.1% for the 1990 ACR criteria in the diagnosis of GCA with large vessel involvement.[4,5] However, to date, no diagnostic criteria for GCA have been officially established.

This impressive improvement in the diagnosis of GCA throughout the last decades can be attributed to the introduction of highly sensitive diagnostic tools (e.g. color Doppler ultrasound [CDUS]) and the incorporation of modern imaging modalities for diagnosis and monitoring of large-vessel vasculitis (computed tomography angiography [CTA] and positron emission tomography–computed tomography [PET-CT]).

Efficient and rapid diagnosis of GCA is crucial for preventing further morbidity and reducing the incidence of irreversible damage and complications, e.g. ischemic visual loss.[6]

In this article, we review state-of-the-art approaches for the diagnosis, monitoring, and treatment options of GCA.

DIAGNOSIS

Temporal Artery Biopsy

Given that GCA was previously considered limited to the inflammation of the cranial arteries, temporal artery biopsy (TAB) used to be considered the diagnostic "gold standard."

Temporal artery biopsy is an invasive procedure with a possible complication rate of up to 0.5%, including facial nerve injury,[7,8] ptosis,[9] and, rarely, stroke.[10] Even when optimally performed by a skilled surgeon, TAB lacks sensitivity compared to other diagnostic methods (39% versus 54% for CDUS),[11] probably as a result of skip lesions,[12] antecedent use of high-dose corticosteroids, or limitation of GCA to extracranial arteries with no cranial arteries involved.

Temporal artery biopsy should be obtained from the temporal artery on the more symptomatic side. The additional yield of contralateral artery biopsy ranges between 3% and 13%.[13,14] The optimal length of the biopsied specimen is a matter of debate as some studies recommend an optimal length cut-off of 0.7–1.5 cm,[15,16] while others concluded that there was no difference in the mean biopsy size between positive and negative samples.[17,18]

Several histological patterns of inflammatory changes can be suggestive of GCA, with panarteritis infiltrated by lymphocytes and macrophages being the most frequent (Figure 1), often with fragmented internal elastic lamina. Giant cells and histiocytes are found in 75% of specimens. Other less frequent inflammatory patterns in GCA include vasa vasorum vasculitis, in which inflammation is limited to the adventitial vasa vasorum without extension to the media.[19,20]

Interestingly, numerous studies reported giant cell presence in temporal artery biopsy as a strong predictor of ophthalmic complications and visual loss.[21–23]

Although the interpretation of histology findings in GCA seems straightforward, concerns were raised regarding poor inter-rater reliability among pathologists looking at the same TAB.[11] Nevertheless, and despite its limitations, TAB is still the preferred diagnostic method in North America, probably due to lack of expertise in other diagnostic modalities, e.g. CDUS.[24]

Color Doppler Ultrasound

Color Doppler ultrasound was introduced as a diagnostic modality for GCA in 1997 by Schmidt et al., who reported sonographic signs of inflammation in the temporal artery in 22 of 30 GCA patients.[25] Being feasible and non-invasive, in the last two decades, CDUS has become the imaging modality of choice for diagnosing GCA in many centers worldwide. Moreover, dedicated, cost-effective fast-track GCA clinics utilizing CDUS for rapid diagnosis and, subsequently, treatment initiation of GCA have been proven to reduce the risk of visual complications significantly.[6,26,27] In keeping with this, the trend towards visual loss has decreased considerably in
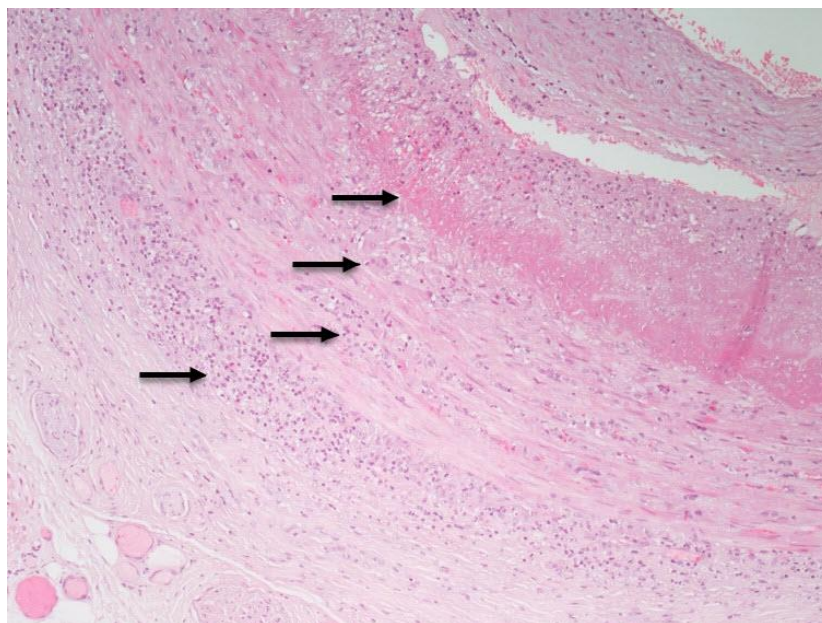
Figure 1. Transmural Inflammatory Infiltrate, Lymphohistiocytic Involving Intima, Elastic Internal Membrane, Media, and Adventitia (Arrows).

Photo courtesy of Michael Lurie, M.D.

the last decade, thanks to the early diagnosis of GCA and the early introduction of targeted treatments.[28]

Color Doppler ultrasound allows inspection of the complete course of each temporal artery and other arteries, including axillary, facial, occipital, and vertebral arteries, which contributes vastly to the accuracy and the yield of the diagnostics with an estimated sensitivity of 54%−94%.[11,29]

In patients suspected of GCA, CDUS of the temporal artery tree on both sides should be performed as soon as possible by an experienced examiner using a machine equipped with a high-frequency linear or hockey stick probe (15 MHz or more). Scanning axillary and subclavian arteries adds about 10% to the diagnostic yield of ultrasound because some patients with GCA have isolated extracranial vasculitis.[30]

In earlier reports, the cutoff of intima-media thickness of the artery wall representing active inflammation in the temporal and axillary artery was 0.35 mm and 1.0 mm, respectively (Figure 2A),[31] but a recent large study proposed intima-media thickness cut-off values ≥0.4 mm for temporal, facial, and occipital arteries in order to further improve the diagnostic utility of CDUS.[32] An additional and unique finding seen in CDUS, indicative of active inflammation, is the "halo" sign (Figure 2B),

which is a hypoechoic halo around the lumen of the temporal artery.[33]

A low percentage (4%) of false positive halo signs has been reported in the literature in patients eventually diagnosed with amyloidosis, T cell lymphoma, atherosclerosis, and other forms of vasculitis as well.[34−36]

ADVANCED IMAGING MODALITIES

The utility and importance of computerized tomography angiography (CTA), magnetic resonance angiography (MRA), and fluorodeoxyglucose positron emission tomography (FDG-PET) for the diagnosis of large-vessel vasculitis (LVV) were acknowledged in the new 2022 EULAR/ACR GCA classification criteria.[4] A substantial percentage, from one-third and up to half of GCA patients, have extracranial LVV, depending on the imaging modality used.[37−39]

Large-vessel vasculitis involvement includes the aorta and major branches, e.g. axillary, subclavian, and, less frequently, mesenteric and iliac arteries.

Both CTA and MRA provide detailed information about the arterial lumen and wall. They can provide valuable input regarding the extent of involvement in medium and large vessels manifesting as concentric thickening of the arterial wall, dilatations, or potentially fatal aneurysms (Figure 3).
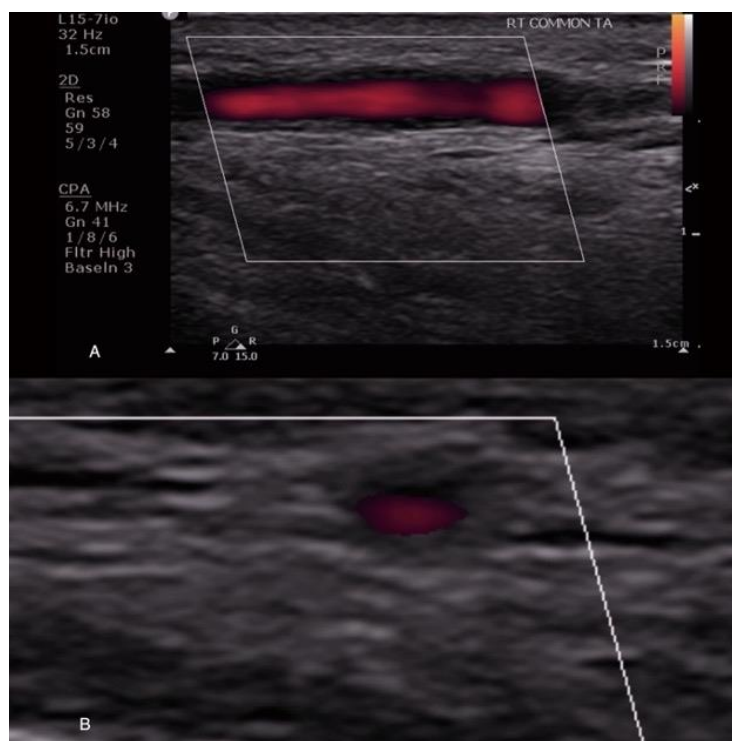
Figure 2. Longitudinal (A) and Transectional "Halo Sign" (B) of Frontal Branch of Right Temporal Artery in a 76-Year-Old Patient with GCA Showing Thickening of Arterial Wall.

Magnetic resonance angiography is potentially more sensitive than CTA as it demonstrates vessel wall edema/contrast enhancement of inflamed arteries. Moreover, without an experienced vascular sonographer, high-resolution MRA can be utilized as an alternative for CDUS of temporal arteries since both modalities have comparable sensitivity and specificity (69%–73% and 88%–91%, respectively).[40,41]

Three-dimensional MRI black blood is a newer sequence with multiplanar and curved reconstructions designed to evaluate better the tortuous intracranial arteries[42] and has a high spatial resolution for diagnosis of both cranial and extracranial vasculitis, harvesting promising results with reported sensitivity and specificity of 80% and 100%, respectively.[43–45]

Often combined with CT for optimal anatomic allocation, FDG-PET detects glucose reuptake in the walls of inflamed arteries (Figure 4). The imaging tool PET-CT is helpful for diagnosing and monitoring LVV[46] and has been most recently proven valuable in detecting vasculitis in relatively small cranial arteries.[47] When compared to CTA in 24 patients with GCA, PET-CT had comparable sensitivity but higher specificity and positive predictive value (66.7% versus 73.3%, 100% versus 84.6%, 100% versus 84.6%, respectively).[48] The main pitfalls in PET-CT remain the lack of standardization criteria for assessing LVV,[49] high radiation dose, and low availability. Moreover, specificity may be influenced by atherosclerotic lesions in elderly patients being misinterpreted as active vasculitis. However, this may be the population that mostly benefits from PET-CT as it is the modality of choice for ruling out malignancies that are not unusual in GCA patients.

The best imaging modality for assessment of LVV in GCA remains a matter of debate and depends on the clinical situation, local availability, and expertise.[50]

DISEASE MONITORING

Once considered a disease resolving in 1–2 years in most patients,[51] GCA has evolved to be a chronic and multisystem disease in which more than half of the patients experience flares.[52,53] Hence, monitoring disease activity and response to treatment, along with identifying vascular complications, e.g.
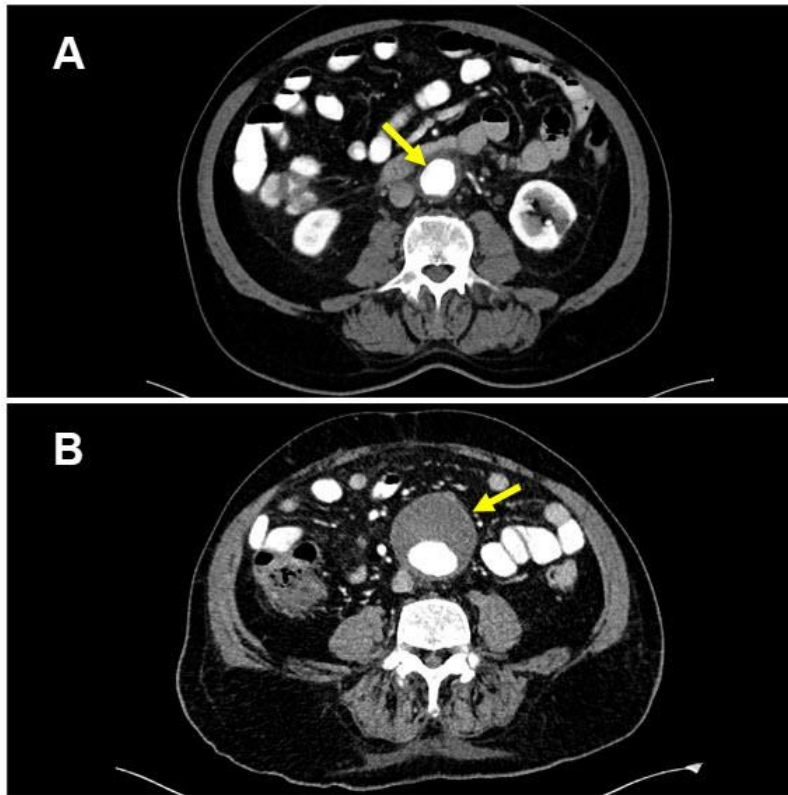
Figure 3. Color Doppler Ultrasound (CTA) Images of a Giant Cell Arteritis Patient.

(A) A 2017 CTA showing active vasculitis of the abdominal aorta with aortic wall thickening (arrow); patient age 68 years. **(B)** The same patient in 2021 showing an aortic aneurysm (arrow); patient age 72 years.

an aneurysm, is more vital than ever. Monitoring inflammatory markers and clinical state is not satisfactory since the introduction of biological therapies can potentially normalize the laboratory findings without achieving remission. Moreover, the activity of LVV can be indolent and subclinical.
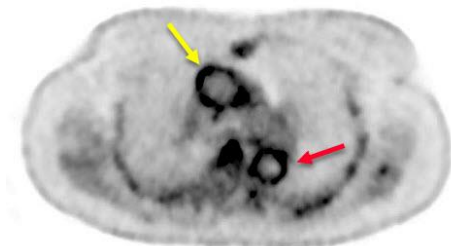

Figure 4. A PET-CT Image of GCA Patient with Active Vasculitis of Thoracic Aorta Showing Increased FDG Uptake in Arterial Wall of Both the Ascending (Yellow Arrow) and Descending (Red Arrow) Aorta.

Color Doppler ultrasound has been validated as a reliable modality and should be the tool of choice for monitoring cranial GCA considering its accessible, radiation-free, and non-invasive nature. Once treatment is initiated, the halo sign and intima-media thickness are reported to shrink within seven days, eventually disappearing after eight weeks in most patients,[54–56] while recurrence of halo predicts flare with a high inter-rater agreement of 0.91.[57] Moreover, the number of temporal artery segments with halo correlates with erythrocyte sedimentation rate, C reactive protein, and Birmingham Vasculitis Activity Score.[58]

The data concerning the role of MRA and CTA for monitoring GCA activity have been rather confusing since structural changes in vessel walls do not always indicate active disease but rather fibrotic and regenerative changes.[59] Data from small studies showed that imaging characteristics in MRA often did not parallel that of laboratory or clinical parameters, although wall thickness significantly

decreased at follow-up in 12 patients with LVV treated with biological therapies.[60]

Repetitive PET-CT scans are associated with a substantial dose of radiation, but when attempted in treated GCA patients it showed a decline in FDG uptake compared with pre-treatment uptake.[61] Meanwhile, data from patients with clinically controlled GCA revealed long-term persistent vascular uptake on repeated PET-CT in >80% of our GCA patients with large-vessel inflammation and clinical-biological controlled disease.[62] Similar results were reproduced in a prospective study of patients with LVV allegedly in clinical remission who underwent serial PET-CT scans that were interpreted as active vasculitis in 58% of patients and those who were more likely to relapse.[63] These data support the hypothesis that persistent FDG uptake may reflect smoldering inflammatory activity, but we are yet to articulate specific criteria to guide treatment decisions.

Future novel biomarkers may aid in ameliorating GCA disease activity monitoring. Serum amyloid A1 and A2 and complement factor H were higher in patients with active disease and receiving prednisolone therapy. In addition, the haptoglobin blood test level seems to be higher and fibrinogen levels lower in patients with active disease taking tocilizumab.[64,65]

TREATMENT

Vascular complications of GCA can be abrupt and irreversible, e.g. visual loss and cerebrovascular accidents, but these are not inevitable if GCA is diagnosed early and treated appropriately. Data from several studies have pointed out that when a visual loss occurs due to GCA, real visual improvement occurs only rarely, in an estimated 5% of patients.[66,67]

Patients with suspected GCA should be referred to fast-track GCA clinics to facilitate rapid diagnosis and, subsequently, full-dose treatment. In contrast, patients can discontinue steroids at once, avoiding needless treatment if GCA is excluded.

Although treatment of giant cell arteritis has evolved in recent years from glucocorticoids (GC) and broad-spectrum immunosuppressive agents to targeted therapies, the cornerstone of treatment in GCA remains GC.

When started at a high dose of 1 mg/kg, GC induces rapid improvement in both clinical symptoms and inflammatory markers, minimizing the odds of GCA complications. Hence, GC should be initiated once GCA is suspected and prior to a definite diagnosis. The main goal of high-dose GC is to induce remission and should be maintained for four weeks or until symptoms subside.[68] Glucocorticoids should be slowly tapered after that, by 10 mg every two weeks until 20 mg/day is reached, then reduced by 2.5 mg every 2–4 weeks to 10 mg and afterward by 1 mg every 1–2 months according to clinical response. Despite controversies about whether intravenous GC are more effective than the oral route when ischemic ophthalmic involvement is suspected, patients are frequently treated with a high dose of 1000 mg i.v. methylprednisolone for three consecutive days to prevent further visual damage.[69]

About half of GCA patients experience at least one flare in the first year,[70] even with optimal high-dose GC tapering protocol. Relapses are usually treated by escalating GC doses 10–15 mg above the previous effective dose, thus increasing the cumulative GC dose and the likelihood of GC long-term side effects, e.g. osteoporosis, diabetes mellitus, cataract, and cardiovascular events. The burden of GC in GCA patients is so substantial that an estimated 86% of patients suffer at least one GC-related side effect and 58% more than one when followed for a median of 10 years.[71]

The toxicity of long-term GC treatment in GCA led to studies evaluating several disease-modifying antirheumatic drugs (DMARDs) showing modest impact, if any. A meta-analysis of three small randomized, double-blind, placebo-controlled trials (RCTs) found that when treated with methotrexate, GCA patients experienced relative reduction in the risk of a first and second GCA relapse and were exposed to lower cumulative GC doses.[72] Nevertheless, methotrexate should be preferred over other DMARDs as recommended by ACR[24] and French[73] guidelines for management of GCA and LVV. Retrospective case series showed the potential benefit of leflunomide in patients with refractory GCA, with partial or complete remission.[74,75] Azathioprine demonstrated a modest effect on disease activity in GCA patients when evaluated in a retrospective study in 18/28 patients; 10 patients experienced azathioprine's serious side effects, leading to treatment discontinuation in 7 cases.[76]

When evaluated, RCTs of tumor necrosis factor-alpha antagonists failed to show efficacy in GCA.[77–79]

An essential role is played by interleukin-6 (IL6) in the pathogenesis of GCA, and elevated circulating levels of IL6 have been reported in patients with active disease.[80] Nevertheless, studies of small series of patients with successfully treated GCA were published only in 2011, in parallel to the introduction of targeted anti-IL6 therapies.[81–83] In 2017, a 52-week GiACTA study demonstrated significant clinical responses and cumulative GC dose reduction following weekly and every-other-week administration of subcutaneous tocilizumab (TCZ) compared to placebo arms where GC were tapered within 26 and 52 weeks.[70] The GiACTA extension study reports prolonged remission in about half of the patients previously receiving TCZ during the subsequent follow-up period compared to placebo.

Interestingly, despite clinical differences between real-life patients undergoing TCZ treatment and those included in the GiACTA trial (real-life patients were older with longer disease duration and higher values of erythrocyte sedimentation rate (ESR), TCZ was equally effective in both GiACTA trial and clinical practice patients.[84]

As a result of these studies, tocilizumab became the first biologic to receive US Food and Drug Administration approval for GCA. Subsequently, ACR recommends tocilizumab with GC as first-line treatment for GCA, while EULAR recommends it as second-line therapy.[24,68]

We recommend starting GCA patients initially with GC and reserving TCZ for relapsing disease or GC toxicity. Once on remission with TCZ and GC treatment, GC should be tapered within 26 weeks and discontinued. If remission is maintained, tocilizumab is often continued as monotherapy for 18–24 months. Given the fact that GCA relapse is still frequent following discontinuation of TCZ (about half of the patients),[85] we recommend tapering TCZ to once every other week for an additional year before complete discontinuation.

An open-label, single-arm study performed with relapsing patients with GCA suggested the clinical benefit of ustekinumab.[86] Granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor antagonist mavrilimumab showed efficacy in 42 GCA patients compared to GC for time to flare and sustained remission after 26 weeks.[87]

Abatacept blocks the engagement of CD28 with its ligand thereby inhibiting T cell activation. When administered to newly diagnosed or relapsing GCA patients, relapse-free survival at 12 months was 48% for those receiving abatacept (anti CTLA-4) and GC and 31% for those receiving GC alone (P=0.049).[84]

New promising targeted therapies, e.g. Janus-activated kinase inhibitors and IL17/IL23 pathway inhibitors, are under investigation in ongoing trials.

CONCLUDING REMARKS

Giant cell arteritis is a chronic disease in which relapses are common and long-term monitoring is required. The diagnosis and treatment of GCA has been revolutionized with the utilization of innovative imaging modalities and the introduction of IL6 blockage with TCZ. Despite the obvious advantages of PET-CT and MRA in GCA, these methods lack accuracy when used to distinguish active LVV from remission, especially when TCZ treatment significantly reduces acute phase reactants (erythrocyte sedimentation rate and C-reactive protein) regardless of clinical remission. Consequently, the clinical judgement of the treating rheumatologist will still have the major role in assessing disease activity in LVV.

REFERENCES

1. Sharma A, Mohammad AJ, Turesson C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: a systematic literature review. Semin Arthritis Rheum 2020;50:1040–8. CrossRef

2. Catanoso M, Macchioni P, Boiardi L, et al. Incidence, prevalence and survival of biopsy-proven giant cell arteritis in Northern Italy during a 26-year period. Arthritis Care Res (Hoboken) 2017;69:430–8. CrossRef

3. Kobayashi S, Yano T, Matsumoto Y, 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 Rheum 2003;49:594–8. CrossRef

4. Ponte C, Grayson PC, Robson JC, et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. Ann Rheum Dis 2022; 81:1647–53. CrossRef

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

6. 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 (Oxford) 2016;55:66–70. CrossRef

7. Yoon MK, Horton JC, McCulley TJ. Facial nerve injury: a complication of superficial temporal artery biopsy. Am J Ophthalmol 2011;152:251–5. CrossRef

8. Rison RA. Branch facial nerve trauma after superficial temporal artery biopsy: a case report. J Med Case Rep 2011;5:34. CrossRef

9. Murchison AP, Bilyk JR. Brow ptosis after temporal artery biopsy: incidence and associations. Ophthalmology 2012;119:2637–42. CrossRef

10. Haist SA. Stroke after temporal artery biopsy. Mayo Clin Proc 1985;60:538. CrossRef

11. Luqmani R, Lee E, Singh S, 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 2016;20:1–238. CrossRef

12. Klein RG, Campbell RJ, Hunder GG, Carney JA. Skip lesions in temporal arteritis. Mayo Clin Proc 1976;51:504–10. PMID: 950804.

13. Boyev LR, Miller NR, Green WR. Efficacy of unilateral versus bilateral temporal artery biopsies for the diagnosis of giant cell arteritis. Am J Ophthalmol 1999;128:211–15. CrossRef

14. Ponge T, Barrier JH, Grolleau JY, Ponge A, Vlasak AM, Cottin S. The efficacy of selective unilateral temporal artery biopsy versus bilateral biopsies for diagnosis of giant cell arteritis. J Rheumatol 1988;15:997–1000. PMID: 2971112

15. Ypsilantis E, Courtney ED, Chopra N, et al. Importance of specimen length during temporal artery biopsy. Br J Surg 2011;98:1556–60. CrossRef

16. Oh LJ, Wong E, Gill AJ, McCluskey P, Smith JEH. Value of temporal artery biopsy length in diagnosing giant cell arteritis. ANZ J Surg 2018;88:191–5. CrossRef

17. Papadakis M, Kaptanis S, Kokkori-Steinbrecher A, Floros N, Schuster F, Hübner G. Temporal artery biopsy in the diagnosis of giant cell arteritis: bigger is not always better. Am J Surg 2018;215:647–50. CrossRef

18. Kaptanis S, Perera JK, Halkias C, Caton N, Alarcon L, Vig S. Temporal artery biopsy size does not matter. Vascular 2014;22:406–10. CrossRef

19. Cavazza A, Muratore F, Boiardi L, et al. Inflamed temporal artery: histologic findings in 354 biopsies, with clinical correlations. Am J Surg Pathol 2014;38:1360–70. CrossRef

20. McDonald HM, Farmer JP, Blanco PL. Periadventitial tissue examination in temporal artery biopsies for suspected giant cell arteritis: a case series and literature review. Can J Ophthalmol 2019;54:615–20. CrossRef

21. Schmidt D, Löffler KU. Temporal arteritis. Comparison of histological and clinical findings. Acta Ophthalmol (Copenh) 1994;72:319–25. CrossRef

22. Chatelain D, Duhaut P, Schmidt J, et al. Pathological features of temporal arteries in patients with giant cell arteritis presenting with permanent visual loss. Ann Rheum Dis 2009;68:84–8. CrossRef

23. Armstrong AT, Tyler WB, Wood GC, Harrington TM. Clinical importance of the presence of giant cells in temporal arteritis. J Clin Pathol 2008;61:669–71. CrossRef

24. Maz M, Chung SA, Abril A, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Care Res (Hoboken) 2021;73:1071–87. CrossRef

25. Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. N Engl J Med 1997;337:1336–42. CrossRef

26. Lyons HS, Quick V, Sinclair AJ, Nagaraju S, Mollan SP. A new era for giant cell arteritis. Eye (Lond) 2020;34:1013–26. CrossRef

27. 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;7:589794. CrossRef

28. Gonzalez-Gay MA, Castañeda S, Llorca J. Giant cell arteritis: visual loss is our major concern. J Rheumatol 2016;43:1458–61. CrossRef

29. Chrysidis S, Døhn UM, Fredberg U, et al. Diagnostic accuracy of vascular ultrasound in patients with suspected giant cell arteritis (EUREKA): a prospective, multicentre, non-interventional, cohort study. Lancet Rheumatol 2021;3:e865–73. CrossRef

30. 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 (Oxford) 2008;47:96–101. CrossRef

31. Schmidt WA, Möller DE, Gromnica-Ihle E. Color duplex ultrasound of the temporal artery: replacement for biopsy in temporal arteritis. Ophthalmologica 2003;217:164–5. CrossRef

32. Ješe R, Rotar Ž, Tomšič M, Hočevar A. The cut-off values for the intima-media complex thickness

assessed by colour Doppler sonography in seven cranial and aortic arch arteries. Rheumatology (Oxford) 2021;60:1346–52. CrossRef

33. Salvarani C, Silingardi M, Ghirarduzzi A, et al. Is duplex ultrasonography useful for the diagnosis of giant-cell arteritis? Ann Intern Med 2002;137:232–8. CrossRef

34. Fernández-Fernández E, Monjo-Henry I, Bonilla G, et al. False positives in the ultrasound diagnosis of giant cell arteritis: some diseases can also show the halo sign. Rheumatology (Oxford) 2020;59:2443–7. CrossRef

35. 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 2018;57:318–21. CrossRef

36. 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;8:R116–18. CrossRef

37. Muratore F, Boiardi L, Mancuso P, et al. Incidence and prevalence of large vessel vasculitis (giant cell arteritis and Takayasu arteritis) in northern Italy: a population-based study. Semin Arthritis Rheum 2021;51:786–92. CrossRef

38. Bossert M, Prati C, Balblanc JC, Lohse A, Wendling D. Aortic involvement in giant cell arteritis: current data. Joint Bone Spine 2011;78:246–51. CrossRef

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

40. Bley TA, Reinhard M, Hauenstein C, et al. Comparison of duplex sonography and high-resolution magnetic resonance imaging in the diagnosis of giant cell (temporal) arteritis. Arthritis Rheum 2008;58:2574–8. CrossRef

41. 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;4:e000612. CrossRef

42. Mandell DM, Mossa-Basha M, Qiao Y, et al. Vessel Wall Imaging Study Group of the American Society of Neuroradiology. Intracranial vessel wall MRI: principles and expert consensus recommendations of the American Society of Neuroradiology. AJNR Am J Neuroradiol 2017;38:218–29. CrossRef

43. Vynckier J, Demeestere J, Lambert J. Black-blood magnetic resonance imaging in giant cell arteritis. J Rheumatol 2021;48:301–2. CrossRef

44. Guggenberger KV, Vogt ML, Song JW, et al. Intraorbital findings in giant cell arteritis on black blood MRI. Eur Radiol 2023;33:2529–35. CrossRef

45. Treitl KM, Maurus S, Sommer NN, et al. 3D-black-blood 3T-MRI for the diagnosis of thoracic large vessel vasculitis: a feasibility study. Eur Radiol 2017;27:2119–28. CrossRef

46. Muratore F, Pipitone N, Salvarani C, Schmidt WA. Imaging of vasculitis: state of the art. Best Pract Res Clin Rheumatol 2016;30:688–706. CrossRef

47. Nielsen BD, Hansen IT, Kramer S, 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;46:184–93. CrossRef

48. Lariviere D, Benali K, Coustet B, et al. Positron emission tomography and computed tomography angiography for the diagnosis of giant cell arteritis: a real-life prospective study. Medicine (Baltimore) 2016;95:e4146. CrossRef

49. Muratore F, Pazzola G, Soriano A, et al. Unmet needs in the pathogenesis and treatment of vasculitides. Clin Rev Allergy Immunol 2018;54:244–60. CrossRef

50. Dejaco C, Ramiro S, Duftner C, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis 2018;77:636–43. CrossRef

51. Bengtsson BA, Malmvall BE. Prognosis of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. A follow-up study on ninety patients treated with corticosteroids. Acta Med Scand 1981;209:337–45. CrossRef

52. Restuccia G, Boiardi L, Cavazza A, et al. Flares in biopsy-proven giant cell arteritis in Northern Italy: characteristics and predictors in a long-term follow-up study. Medicine (Baltimore) 2016;95:e3524. CrossRef

53. Alba MA, García-Martínez A, Prieto-González S, et al. Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine (Baltimore) 2014;93:194–201. CrossRef

54. 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;27(1 Suppl 52):S77–82. PMID: 19646351

55. 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;30(1 Suppl 70):S34-8. PMID: 22410311

56. Monti S, Floris A, Ponte CB, et al. The proposed role of ultrasound in the management of giant cell arteritis in routine clinical practice. Rheumatology (Oxford) 2018;57:112–19. CrossRef

57. Dejaco C, Ponte C, Monti S, et al. The provisional OMERACT ultrasonography score for giant cell arteritis. Ann Rheum Dis 2022:ard-2022-223367. CrossRef

58. Ponte C, Monti S, Scirè CA, et al. Ultrasound halo sign as a potential monitoring tool for patients with giant cell arteritis: a prospective analysis. Ann Rheum Dis 2021;80:1475–82. CrossRef

59. Muratore F, Pazzola G, Pipitone N, Boiardi L, Salvarani C. Large-vessel involvement in giant cell arteritis and polymyalgia rheumatica. Clin Exp Rheumatol 2014;32(3 Suppl 82):S106–11. PMID: 24854380

60. Spira D, Xenitidis T, Henes J, Horger M. MRI parametric monitoring of biological therapies in primary large vessel vasculitides: a pilot study. Br J Radiol 2016;89:20150892. CrossRef

61. Puppo C, Massollo M, Paparo F, et al. Giant cell arteritis: a systematic review of the qualitative and semiquantitative methods to assess vasculitis with 18F-fluorodeoxyglucose positron emission tomography. Biomed Res Int 2014;2014:574248. CrossRef

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

63. Grayson PC, Alehashemi S, Bagheri AA, et al. 18 F-fluorodeoxyglucose-positron emission tomography as an imaging biomarker in a prospective, longitudinal cohort of patients with large vessel vasculitis. Arthritis Rheumatol 2018;70:439–49. CrossRef

64. Unizony S, Morris R, Kreuzer J, et al. Mass spectrometry identifies novel biomarkers in giant cell arteritis, useful in patients on interleukin-6 receptor blockade. Ann Rheum Dis 2020;79:207–8. Available at: https://acrabstracts.org/abstract/mass-spectrometry-identifies-novel-biomarkers-in-giant-cell-arteritis-useful-in-patients-on-interleukin-6-receptor-blockade/ (accessed April 10, 2023).

65. González-Gay MA, Vicente-Rabaneda EF, Martínez-López JA, Largo R, Heras-Recuero E, Castañeda S.

Challenges in the diagnosis of polymyalgia rheumatica and related giant cell arteritis. Expert Rev Clin Immunol 2023:1–10. CrossRef

66. Hayreh SS, Zimmerman B, Kardon RH. Visual improvement with corticosteroid therapy in giant cell arteritis. Report of a large study and review of literature. Acta Ophthalmol Scand 2002;80:355–67. CrossRef

67. Danesh-Meyer H, Savino PJ, Gamble GC. Poor visual outcome after visual loss from giant cell arteritis. Ophthalmology 2005;112:1098–103. CrossRef

68. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19–30. CrossRef

69. Monti S, Agueda A, Luqmani R, et al. Diagnosis, general management, drug and surgical treatment for large vessel vasculitis (with a focus on giant cell arteritis): a systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis. RMD Open 2019;5:e001003. CrossRef

70. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017; 377:317–28. CrossRef

71. Proven A, Gabriel SE, Orces C, O'Fallon WM, Gene G, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum 2003;49:703–8. CrossRef

72. Mahr AD, Jover JA, Spiera RF, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum 2007;56:2789–97. CrossRef

73. Bienvenu B, Ly KH, Lambert M, et al. Management of giant cell arteritis: recommendations of the French Study Group for Large Vessel Vasculitis (GEFA). Rev Med Interne 2016;37:154–65. CrossRef

74. 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; 66:906–9. CrossRef

75. 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;2013:120638. CrossRef

76. Boureau AS, de Faucal P, Espitia O, De Decker L, Agard C. Utilisation de l'azathioprine dans le traitement de l'artérite à cellules géantes [Place of azathioprine in the treatment of giant cell arteritis]. Rev Med Interne 2016;37:723–9. [Article in French]. CrossRef

77. Seror R, Baron G, Hachulla E, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial. Ann Rheum Dis 2014;73:2074–81. CrossRef

78. Hoffman GS, Cid MC, Rendt-Zagar KE, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Ann Intern Med 2007;146:621–30. CrossRef

79. Martinez-Taboada VM, Rodriguez-Valverde V, Carreno L, et al. A double-blind placebo-controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. Ann Rheum Dis 2008; 67:625–30. CrossRef

80. 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;36:1286–94. CrossRef

81. Salvarani C, Magnani L, Catanoso M, et al. Tocilizumab: a novel therapy for patients with large-vessel vasculitis. Rheumatology (Oxford) 2012;51:151–6. CrossRef

82. 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;141:w13156. CrossRef

83. Christidis D, Jain S, Gupta BD. Successful use of tocilizumab in polymyalgic onset biopsy positive GCA with large vessel involvement. BMJ Case Rep 2011; 2011:bcr0420114135. CrossRef

84. Calderón-Goercke M, Castañeda S, Aldasoro V, 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;38(Suppl 124):112–19. PMID: 32441643

85. Stone JH, Han J, Aringer M, 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. The Lancet Rheumatology 2021;3:e328–36. CrossRef

86. Conway R, O'Neill L, Gallagher P, et al. Ustekinumab for refractory giant cell arteritis: a prospective 52-week trial. Semin Arthritis Rheum 2018;48:523–8. CrossRef

87. Cid MC, Unizony SH, Blockmans D, et al. Efficacy and safety of mavrilimumab in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Ann Rheum Dis 2022;81:653–61. CrossRef

88. Langford CA, Cuthbertson D, Ytterberg SR, et al. A randomized, double-blind trial of abatacept (CTLA-4Ig) for the treatment of giant cell arteritis. Arthritis Rheumatol 2017;69:837–45. CrossRef