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Giant Cell Arteritis: Practical Pearls and Updates

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Abstract
Purpose of Review The purpose of this review is to summarize recent updates and distill practical points from the literature which can be applied to the care of patients with suspected and confirmed giant cell arteritis (GCA).
Recent Findings Contemporary thinking implicates a fundamental failure of T regulatory cell function in GCA pathophysiology, representing opportunity for novel therapeutic avenues. Tocilizumab has become the first Food and Drug Administration-approved treatment for GCA following demonstration of efficacy and safety in a phase 3 clinical trial.
Summary There have been significant parallel advances in both our understanding of GCA pathophysiology and treatment. Tocilizumab, and other agents currently under investigation in phase 2 and 3 clinical trials, presents a new horizon of hope for both disease remission and avoidance of glucocorticoid-related complications.

Keywords Giant cell arteritis · Temporal arteritis · Secondary headache · Older adults · Tocilizumab · Pathophysiology

Introduction

Giant cell arteritis (GCA) also known as temporal arteritis is a medical emergency which if left untreated can result in visual loss [1]. It is the most common systemic vasculitis in the elderly with an estimated incidence of 27 cases in 100,000 people in those over 50 years old with peak incidence at age of 70–80 years [2]. GCA affects women three times more than it does men [2]. Ability to recognize GCA is critical considering that individuals 85 years and older represent the fastest-growing segment of the total population in most industrial countries. Additionally, with early treatment intervention, the occurrence of visual loss is significantly reduced. In a retrospective series, the 5-year probability of developing visual loss after starting steroids was 1% [3]. A recent meta-analysis and systemic review of mortality in GCA shows that compared to general population, mortality is not significantly increased [4]. The most frequent causes of death reported with GCA were cardiovascular disease, followed by cerebrovascular disease, infection, and malignancy [4].

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The classical clinical picture of GCA is systematically characterized by the American College of Rheumatology criteria which state that three out of the five following core features should be present: age of 50 or older at onset, new-onset headaches, temporal artery abnormality, elevated erythrocyte sedimentation rate (ESR) of at least 50 mm/h, and abnormal temporal artery biopsy (TAB) [5]. Unfortunately, many diagnostic nuances exist in the form of atypical clinical presentations, laboratory features, and pathologic findings. Further, the treatment course is commonly complicated by corticosteroid-related complications and a need for additional immunomodulatory agents. In these cases, the clinician may face both diagnostic and therapeutic challenges. In this narrative review, we aim to provide an updated perspective on GCA, with special attention to recent and important advances in both our understanding and management of this challenging patient population.

Autoimmunity in the Elderly and the Pathophysiology of Giant Cell Arteritis

GCA is a large and medium vessel vasculitis with granulomatous changes occurring most frequently in the aorta and the extracranial branches of the external carotid arteries. Temporal artery histopathology is characterized by segmental and focal

panarteritis with non-necrotizing granulomatous inflammation. Additionally, CD4+ T lymphocyte, macrophages, and giant cells are seen infiltrating the arterial wall. This vasculitic infiltration is thought to be dependent on activated antigen-presenting dendritic cells, which are present normally at the adventitia-media border of the arterial wall [6]. In polymyalgia rheumatic (PMR), which is present in up to 50% of patients with GCA, activated dendritic cells have been observed in temporal artery biopsies, in the absence of vasculitis. Interestingly, inflammatory T cells have been demonstrated experimentally to migrate from GCA to PMR arteries, suggesting the possibility of an existing antigen, although none have been identified to date [6]. Recently, it has been hypothesized that this disorder may fundamentally represent a defect in T cell regulation resulting in CD4+ T cell hyperimmunity, while explanation for the topography remains elusive [7]. CD8+ T regulatory cells, which are normally present in lymphoid organs and suppress CD4+ T cell activation, were recently shown to be deficient in patients with biopsy-proven GCA, independent of treatment [8]. This T regulatory failure was additionally shown to be dependent on NADPH oxidase 2 deficiency (NOX2) [8••]. Tocilizumab, a novel therapy for GCA (discussed below) was recently shown to correct the T regulatory failure, a mechanism of action not observed in a corticosteroid-treated control group [9]. Importantly, corticosteroids may also have limited efficacy in GCA as they have been shown through analysis of pre- and post-treatment temporal artery biopsies to preferentially suppress only certain subsets of activated T helper cells [10].

Although the specific etiology and pathogenesis of GCA remain elusive, aging, genetics, and infections have all been thought to play a role [11]. Aging is accompanied by physiological changes that impact the immune system, a process termed immunosenescence. Immunosenescence includes three major events: an overall reduction in immune response, increases in inflammation and oxidation, and an increased production of auto-antibodies [12]. Overtime, the balance between regulation of immune cells, specifically pro-inflammatory and anti-inflammatory makers, are disrupted. Aging also modifies the vascular wall resulting in calcium deposition, wall thickening, and biochemical modifications that could also trigger auto-antigens [13, 14].

Strong associations between genes and GCA have been discovered and the high frequency of GCA in Scandinavian ethnic groups suggests a genetic component, especially for polymorphisms of human leukocyte antigen-DR4. Most recently, an unbiased genome-wide association study comparing 2134 cases and 9125 unaffected controls from individuals of European ancestry identified HLA class II, *PLG*, and *P4HA2* as GCA genetic risk variants [15]. The latter two genes have identified roles in vascular remodeling and angiogenesis [15]. Additionally, some studies have noted a seasonal or cyclic pattern suggesting an infectious trigger. Recently, a study demonstrated varicella-zoster virus antigens in 78% of temporal artery biopsy (TAB)-positive patients, but this has not been validated by other studies [16]. It has been hypothesized that an infectious agent could activate dendritic cells located in the adventitia of medium and large vessels initiating an immune response. The dynamic relationship between genetic predisposition, epigenetic modifications, and dysregulation of immune system is being explored and may lead to a more holistic understanding of the disorder.

Pearls and Pitfalls in GCA Diagnosis

Diagnosis of GCA may be challenging as symptoms can be transient, fluctuating, and protean. A recent meta-analysis assessed a mean delay in diagnosis of 9 weeks (95% CI, 6.5 to 11.4) from the time of onset of symptoms [17]. Delay of diagnosis has been observed to be greatest in patients with non-cranial as opposed to cranial presentations [17]. Discussed below include a description of features that may aid in more accurate and rapid diagnosis of GCA in addition to the classical paradigm.

Headache

The neurologist must have a high index of suspicion: any new or changed pattern of headache in individuals aged 50 years or older is sufficient to consider a diagnosis of GCA. Only 32% of patients report headache as being the initial symptom despite being the most common symptom overall reported by 72% of patients [18]. Headache in GCA can be acute or subacute in onset, associated with scalp tenderness, and can resemble many other primary headache disorders including migraine, cluster headaches, or stabbing headache [19, 20]. Although, classically, the headache is isolated to the temples, this is reported only 25–50% of the time [21], and the headache most often involves other localizations. Pain can also be experienced in the jaw or tongue, in addition to chest pain and odynophagia due to aortitis. Jaw claudication refers to mandibular pain that develops only after repetitive and/or vigorous chewing of food, as opposed to temporomandibular joint pain that occurs at the onset of chewing, most often localizing to the joint itself. If jaw claudication is identified, this increases the probability of a positive temporal artery biopsy result [22].

Neuro-Ophthalmologic

Visual loss is the feared complication of GCA unfortunately occurring in up to 15–20% of patients [3]. Visual loss is commonly painless, sudden, can be partial or complete and may be unilateral or bilateral. Posterior ciliary artery is the most commonly affected vessel. Visual loss is rarely reversible. There is not a reliable or safe way to identify the subset of patients at

risk for visual compromise. The most common cause of visual loss in GCA is anterior ischemic optic neuropathy, but central or branch retinal arterial occlusion, posterior ischemic optic neuropathy, and choroid infarction can all be seen [23]. Sometimes, visual loss is preceded by transient monocular (rarely binocular) visual loss also known as amaurosis fugax. Diplopia occurs in 5% of patients with GCA [18], which also increases the probability of a positive biopsy [22]. Diplopia may herald impending visual loss and should prompt immediate initiation and/or escalation of corticosteroids.

Neurologic Complications

Both the central and peripheral nervous system can be involved in GCA. Described neurological phenomenon includes transient ischemic attacks, ischemic strokes, dementia, mononeuropathies, and polyneuropathies [1]. Stroke within 4 weeks of the diagnosis of GCA is seen in 3% of patients usually in the vertebrobasilar distribution [24]. Extradural arteritis is most prevalent, with the vertebral arteries being affected much more often than the carotid system [25]. Strokes have been reported after steroid treatment or while tapering the dose. Since GCA occurs in the elderly population who usually also have traditional vascular risk factors of stroke, it is difficult to determine if stroke is the direct result of GCA. Nonetheless, a recent meta-analysis calculated an overall risk ratio of 1.40 (95% CI, 1.27 to 1.56) of cerebrovascular accidents in GCA versus non-GCA controls [26].

Neuropsychiatric symptoms are reported in 3% of GCA patients which include dementia, mood disorders, and psychotic symptoms, with corticosteroid toxicity being an important differential [18]. GCA is a treatable cause of dementia, where steroids improve or stabilize symptoms [27].

Peripheral mononeuropathies (including mononeuritis multiplex) and polyneuropathies occur in 7% of GCA patients [18]. The most commonly involved peripheral nerve is median nerve, as well as a predilection for the C5-C6 roots. Peripheral neuropathy may respond to steroids in the majority of cases.

Cranial neuropathy aside from optic neuropathy have also been reported including involvement of olfactory [28], oculomotor [29], abducens [30, 31], facial [32], and vestibulocochlear nerves (most common symptom is hearing loss, while vertigo and tinnitus are also noted) [18].

Systemic and Other Complications

GCA can present with constitutional symptoms such as fever, fatigue, and weight loss which can be observed in 40% of cases [33]. Fever is generally low-grade, but temperature greater than 39 °C (102.2 °F) can be seen in a minority of patients [34]. Large vessel complications of aneurysms and dissections are also feared complications of GCA, particularly involving the thoracic and abdominal aorta. Aortic aneurysms are recognized in 10–20% of cases, while dissection is observed in 1–6% of cases [35–37]. Dilation of thoracic aorta was noted at the time of presentation in 15% of patients [38]. There is no reliable feature to predict which patients will develop large vessel vasculitis, but involvement of thoracic aorta (61%), abdominal aorta (42%), and both axillary (39–44%) and subclavian (39–61%) are not uncommon [39]. Associated ischemic complications have been reported in all these vascular distributions.

PMR is observed in 40–50% of patients with GCA. Symptoms of PMR usually begin sub-acutely (less than 2 weeks) and include aching and morning stiffness of the shoulder, hip girdle, neck, and torso which generally last for at least 30 min. In patients who present with isolated symptoms of PMR, temporal artery inflammatory changes are only observed in 4.4% of cases [40].

Physical Examination

Frequently the physical exam is unremarkable in patients with GCA, apart from a patient that may appear systematically ill. A normal examination does not exclude the diagnosis of GCA. On the other hand, scalp tenderness alone is not a significant predictor of positive biopsy [22]. The clinical examination should include an appraisal of the patient's general appearance and vital signs, including temperature. Abnormalities of temporal artery including tenderness, reduced pulsation, erythema, and induration should be assessed by palpation and compared to the contralateral side. It is important to palpate peripheral limb pulsations and listen for bruits over thoracic and abdominal aorta [41]. Aortic regurgitation may be encountered in the setting of ascending aortic dilation. The scalp and tongue should be inspected for necrotic or ischemic changes [42, 43]. Fundoscopy may be normal or may demonstrate swollen pale disc concerning for anterior ischemic optic neuropathy. Lastly, active range of motion of shoulders, neck, and hips should be observed to help identify PMR.

Diagnostic Evaluation

Laboratory data can provide supplementary information in the evaluation of GCA and should be obtained. Classically, elevated levels of ESR and CRP are seen, but they are imperfect and non-specific laboratory markers [44]. ESR is elevated in majority of patients with a mean value of 85 mm/h [45]. Normal range for ESR is age dependent, with a formula of age / 2 for men and (age + 10) / 2 for women [46]. It is important to keep in mind that normal ESR and CRP do not exclude the diagnosis of GCA. A minority of biopsy-proven patients (~ 4%) will have both normal ESR and CRP at the time of diagnosis, a subgroup in which PMR symptoms may be over-

represented and constitutional symptoms are less common [44]. Normochromic anemia, thrombocytosis, and elevated hepatic enzymes are also observed with many patients [47].

Temporal artery biopsy (TAB) is the gold standard in GCA diagnosis, but must be technically adequate [48]. The biopsy itself is a brief, low-risk procedure. Whenever possible, biopsy should be performed in those suspected of GCA. Treatment should never be delayed or withheld for results of biopsy. Many studies have shown that corticosteroid treatment less than 2 weeks does not decrease the yield of a positive biopsy result [49, 50]. Pathologic subtleties that exist as structural changes in the temporal artery may also be seen in the setting of normal aging, atherosclerosis, quiescent (healed) arteritis, and inflammation limited to the adventitia. Patients with inflammation limited to the adventitia may not be at risk for GCA-like complications [51], although the clinical context of the case should be individually reviewed with the pathologist. False negatives may occur because of the segmental involvement of GCA which result in "skip areas," or the patient may have GCA without cranial arteritis [52]. The yield of a second, contralateral biopsy is thought be low (~ 5%). If the pre-test probability is sufficient, the diagnosis may be further supported by other available testing.

Adjunctive imaging such as the color Doppler ultrasonography (CDUS), computed tomography (CT) or CT with angiography (CTA), magnetic resonance imaging (MRI) or MR angiography (MRA), and positron emission tomography (PET) has a role in supporting the diagnosis of GCA. CDUS can visualize large vessels such as carotid and axillary arteries; meta-analysis of the prospective studies has demonstrated excellent specificity (91%) and good sensitivity (68%) [53]. Edema, wall thickening, and/or enhancement can be seen on MRI/MRA while CTA can demonstrate vascular stenosis and dilation [38, 54–56]. Finally, PET can be used to support GCA diagnosis as increased uptake of fluordeoxyglucose (FDG) is noted with GCA [57]. Results of these studies should be used with caution as unlike TAB, imaging results can be affected soon after steroid treatment is begun especially with MR and CDUS [54, 58].

Differentials of GCA include other neurologic disorders (stroke, migraine, optic neuropathy), other rheumatologic disorders (such as CREST, rheumatoid arthritis) [59], neoplastic disorders (such as lymphoma [60]), and other vasculitides (such as Takayasu's arteritis [39], granulomatosis with polyangiitis [61], cryoglobulin-induced vasculitis [62], and polyarteritis nodosa) [63].

Pearls and Pitfalls in GCA Treatment

The current standard of care is prompt initiation of glucocorticoid treatment if there is suspicion for GCA [64, 65]. Treatment should never be delayed for confirmation of diagnosis with biopsy, to avoid irreversible morbidity such as visual loss. Biopsy results may remain positive for 2 to 6 weeks after initiation of steroids [49, 66].

Currently, there are no randomized controlled trials comparing different dosing or administration strategies of glucocorticoids. The current practice in the setting of uncomplicated GCA (no jaw claudication or visual symptoms) is to treat with single dose of 40–60 mg of oral prednisone daily [64, 65]. If visual loss has already occurred, then prednisone 60 mg daily should be started [64, 65]. For patients with active visual and/or neurological symptoms, high-dose methylprednisolone should be initiated, although this approach has not been validated. Typically, the dose is 500–1000 mg IV daily for 3 days [64, 65]. This is then followed by oral prednisone 1 mg/kg/day (maximum 60 mg/day). High-dose prednisone is then continued for 2–4 weeks. Additionally, even if biopsy reveals no evidence of disease, but clinical suspicion is high, treatment should be continued as false negatives may occur in up to 9% of GCA cases [67]. Patients report dramatic improvement of symptoms (including complete remission of headache) within 24–48 h of steroid initiation. Additionally, ESR generally improves within a few days as well after therapy is initiated.

Prednisone taper should begin after 2–4 weeks if symptoms are well controlled. A typical taper schedule is to reduce dose by 10 mg every 2 weeks to 20 mg, then by 2.5 mg every 2–4 weeks to 10 mg, and then by 1 mg every month [64, 65]. Disease flare-ups generally occur at doses lower than 15 mg/day. In this case, an increased glucocorticoid dose will likely be necessary with a longer tapering schedule. Low-dose aspirin is recommended in patients with GCA and no contraindications to decrease the risk of visual loss, TIA, or stroke [64, 65].

Patients should have a close follow-up during the first month of treatment with serial lab measurements that includes ESR/CRP, electrolytes, blood count, and glucose. Example of follow-up schedule recommended by the British Rheumatology Society is week 0, 1, 2, and 6 and then months 3, 6, 9, and 12 in the first year and any additional visits for relapse or adverse events [64].

Recognizing relapses may be challenging. Relapses should be recognized as return of signs and symptoms of GCA, which can be supported by elevations in the ESR and CRP. In a prospective cohort study, relapses occurred in 34% of 128 patients on treatment [68••]. Treatment decisions should not be made solely based on inflammatory markers as in this study markers were normal in 21% of clinical GCA relapses [68••]. The most common symptoms during relapse included headache (42%), PMR (51%), and ischemic symptoms such as visual symptoms, tongue/jaw claudication, or limb claudication (29%). A median number of 2 (range 1–6) symptoms were present at relapse. Headache as an isolated symptom of GCA relapse was seen in only four relapses (three patients), all

Table 1 Updates in the pathophysiology, diagnosis, and treatment of giant cell arteritis

Pathophysiology	Diagnosis	Treatment
A failure in T regulatory cell function may fundamentally underlie CD4+ T cell hyperimmunity in GCA, along with insights into corresponding molecular mechanisms, including NADPH oxidase 2 (NOX2) deficiency [8••].	Patients with non-cranial presentations have significant delays in diagnosis, which may lead to significant patient morbidity [17].	Subcutaneous tocilizumab given either weekly or every other week has been convincingly demonstrated in a phase 3 clinical trial to improve the rates of 52-week glucocorticoid-free remission in patients with GCA, leading to it being the first FDA-approved treatment for the disorder [71••].
Tocilizumab, which has recently demonstrated efficacy in GCA treatment, has at least one mechanism of action through restoring T regulatory cell failure [9].	In a prospective cohort, ESR and CRP were normal in 21% of relapses, highlighting the importance of not relying on inflammatory markers for diagnosis of GCA relapse. The most common symptom at relapse was polymyalgia rheumatica [68••]. Headache was only occasionally (~ 7% of relapses) seen as an isolated symptom at relapse (T. Kermani, personal communication, September 14, 2017).	A small, randomized, double-blind trial of abatacept (CTLA-4Ig) has demonstrated higher rates of relapse-free survival at 1 year as compared to placebo (48 versus 31%), with both arms receiving identical prednisone tapers [72]. No differences in overall or serious adverse effects between arms were noted. The drug is thought to modulate T cell activation.
Novel genetic risk variants related to immunity, angiogenesis, and vascular remodeling have been identified in a large genome-wide association study for GCA [15].	Patients with temporal artery biopsies that demonstrate inflammation limited to the adventitia alone are not at risk for GCA-like adverse events [51].	Treatment trials for GCA not yet or currently recruiting include phase 2 evaluations of baricitinib (NCT03026504) and ustekinumab (NCT02955147) and phase 3 evaluations of tocilizumab (NCT03202368), sirukumab (NCT02531633), and anakinra (NCT02902731).

of whom had elevated inflammatory markers (T. Kermani, personal communication, September 14, 2017).

Lastly, symptoms of limb claudication, persistently high inflammatory markers, aortic regurgitation, and systemic symptoms should raise suspicion of aortitis [64]. Large vessel complications include aortic aneurysm or dissection and large-artery stenosis. If enlarging aortic aneurysms 3–5 cm in diameter with elevated inflammatory markers are observed, then glucocorticoids need to be re-initiated. Chest x-ray is recommended every 2 years to monitor for aortic aneurysm [64].

Glucocorticoid-related morbidity is a common treatment challenge for the majority of patients with GCA [69]. Common adverse effects with use of high doses of prednisone include weight gain, glucose intolerance, diabetes mellitus, hypertension, opportunistic infections, and osteoporosis. Close follow-up of patients and serial laboratory monitoring is recommended. Additionally, elemental calcium 1200 mg/day, vitamin D supplementation 800 IU/day, and proton pump inhibitors should be prescribed as prophylaxis. For postmenopausal women and men over age 50, bisphosphonate is recommended if prednisone treatment exceeds 3 months [70]. Additionally, bone marrow density measurement is recommended for patients at risk for osteoporosis during therapy initiation.

Although prednisone is the mainstay of treatment, both methotrexate and most recently tocilizumab [71••] and abatacept (CTLA-4Ig) [72] have been evaluated as possible glucocorticoid-sparing agents. Methotrexate is the best studied corticosteroid-sparing agent, but to date, three randomized controlled trials have shown mixed results [73]. Meta-analysis has shown that methotrexate is safe and is moderately effective albeit the effects may take months to occur [73]. Methotrexate is not recommended as a first-line medication, but can be considered in patients who frequently relapse and/or have corticosteroid-related adverse events.

Interleukin-6 and a Trial of Tocilizumab in GCA

Tocilizumab (TCZ) is a humanized monoclonal antibody against IL-6 which is a cytokine that is secreted by a variety of immune cells and levels of which are elevated among patients with GCA. IL-6 levels in GCA are strongly associated with systemic inflammation and glucocorticoid response [74]. TCZ has demonstrated efficacy in both phase 2 [75] and phase 3 [71••] clinical trials.

In the phase 2 trial [75], 30 patients with new-onset GCA were randomized (2:1) to receive either treatment with TCZ (8 mg/kg) or placebo. Both groups received prednisolone beginning at 1 mg/kg daily with a tapering protocol. At both 12 and 52 weeks, complete remission (85 versus either 40% (at 12 weeks) or 20% (at 52 weeks)) was more likely in TCZ-

treated patients, who were also more successful at tapering off prednisolone completely (80 versus 20%). Nine episodes of neutropenia and 15 episodes of leukopenia occurred in the TCZ treatment arm. A single instance of gastrointestinal perforation occurred in each treatment arm, likely highlighting the toxicity of prednisone. The results were so promising that the question was even raised in an accompanying editorial as to whether there is a potential to "cure giant cell arteritis" [76]. Along these lines, an ongoing open-label study (*NCT0324470*) will evaluate sustained remissions following discontinuation of TCZ.

In a larger phase 3 trial, 251 patients were randomized (2:1:1:1) to either TCZ 162 mg/sq weekly or every other week (combined with 26-week prednisone taper) or either 26- or 52-week prednisone tapers with placebo. The primary outcome of achieving glucocorticoid-free remission at 52 weeks was more likely in both TCZ treatment arms (56 and 53%) as compared to prednisone + placebo arms (14 and 18%). The overall rates of adverse events were similar between the trial arms, with infection being the most common adverse event noted. A single patient in the every-other-week TCZ arm developed anterior ischemic optic neuropathy, who was considered a treatment failure in the reported analysis. There is a lack of data regarding long-term safety of TCZ in GCA, and results of the 2-year open-label follow-up from this study are pending. The Food and Drug Administration (FDA) has granted approval for the use of subcutaneous TCZ to include GCA, making it the first FDA-approved therapy for this disorder.

Conclusions

While GCA continues to represent a serious medical threat to older adults, there have been important recent advances in our understanding of disease pathophysiology and treatment (Table 1). Contemporary thinking implicates a fundamental failure of T regulatory cell function in GCA pathophysiology, representing opportunity for novel therapeutic avenues. Tocilizumab has become the first FDA-approved treatment for GCA following demonstration of efficacy in a phase 3 clinical trial. Multiple, ongoing phase 2 and phase 3 trials for GCA herald further hope for advancement of our clinical care for patients with this disease.

Compliance with Ethical Standards

Conflict of Interest Swati Pradeep and Jonathan H. Smith declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Smith JH, Swanson JW. Giant cell arteritis. Headache. 2014;54(8):1273–89. https://doi.org/10.1111/head.12425.
2. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. Ann Intern Med. 1995;123(3):192–4. https://doi.org/10.7326/0003-4819-123-3-199508010-00006.
3. Aiello PD, Trautmann JC, McPhee TJ, Kunselman AR, Hunder GG. Visual prognosis in giant cell arteritis. Ophthalmology. 1993;100(4):550–5. https://doi.org/10.1016/S0161-6420(93)31608-8.
4. Hill CL, Black RJ, Nossent JC, Ruediger C, Nguyen L, Ninan JV, et al. Risk of mortality in patients with giant cell arteritis: a systematic review and meta-analysis. Semin Arthritis Rheum. 2017;46(4):513–9. https://doi.org/10.1016/j.semarthrit.2016.08.015.
5. 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;33(8):1122–8.
6. 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. J Exp Med. 2004;199(2):173–83. https://doi.org/10.1084/jem.20030850.
7. Watanabe R, Hosgur E, Zhang H, Wen Z, Berry G, Goronzy JJ, et al. Pro-inflammatory and anti-inflammatory T cells in giant cell arteritis. Joint Bone Spine. 2017;84(4):421–6. https://doi.org/10.1016/j.jbspin.2016.07.005.
8.•• Wen Z, Shimojima Y, Shirai T, Li Y, Ju J, Yang Z, et al. NADPH oxidase deficiency underlies dysfunction of aged CD8+ Tregs. J Clin Invest. 2016;126(5):1953–1967. **CD8+ T regulatory cells appear to be deficient in patients with GCA, independent of treatment, potentially allowing for observed CD4+ T cell hyperimmunity**. https://doi.org/10.1172/JCI84181.
9. Miyabe C, Miyabe Y, Strle K, Kim ND, Stone JH, Luster AD, et al. An expanded population of pathogenic regulatory T cells in giant cell arteritis is abrogated by IL-6 blockade therapy. Ann Rheum Dis. 2017;76(5):898–905. https://doi.org/10.1136/annrheumdis-2016-210070.
10. Weyand CM, Younge BR, Goronzy JJ. IFN-gamma and IL-17: the two faces of T-cell pathology in giant cell arteritis. Curr Opin Rheumatol. 2011;23(1):43–9. https://doi.org/10.1097/BOR.0b013e32833ee946.
11. 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. Autoimmun Rev. 2017;16(8):833–44. https://doi.org/10.1016/j.autrev.2017.05.014.
12. Watad A, Bragazzi NL, Adawi M, Amital H, Toubi E, Porat BS, et al. Autoimmunity in the elderly: insights from basic science and clinics—a mini-review. Gerontology. 2017;63(6):515–23. https://doi.org/10.1159/000478012.
13. Lee HY, Oh BH. Aging and arterial stiffness. Circ J. 2010;74(11):2257–62. https://doi.org/10.1253/circj.CJ-10-0910.
14. Wang M, Monticone RE, Lakatta EG. Arterial aging: a journey into subclinical arterial disease. Curr Opin Nephrol Hypertens. 2010;19(2):201–7. https://doi.org/10.1097/MNH.0b013e3283361c0b.
15. Carmona FD, Vaglio A, Mackie SL, Hernández-Rodríguez J, Monach PA, Castañeda S, et al. A genome-wide association study identifies risk alleles in plasminogen and P4HA2 associated with

giant cell arteritis. Am J Hum Genet. 2017;100(1):64–74. https://doi.org/10.1016/j.ajhg.2016.11.013.
16. Gilden D, Nagel MA. Varicella zoster virus triggers the immunopathology of giant cell arteritis. Curr Opin Rheumatol. 2016;28(4):376–82. https://doi.org/10.1097/BOR.0000000000000292.
17. 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;15(1):120. https://doi.org/10.1186/s12916-017-0871-z.
18. Caselli RJ, Hunder GG, Whisnant JP. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. Neurology. 1988;38(3):352–9. https://doi.org/10.1212/WNL.38.3.352.
19. Jimenez-Jimenez FJ, Garcia-Albea E, Zurdo M, Martinez-Onsurbe P, Ruiz de Villaespesa A. Giant cell arteritis presenting as cluster headache. Neurology. 1998;51(6):1767–8. https://doi.org/10.1212/WNL.51.6.1767.
20. Rozen TD. Brief sharp stabs of head pain and giant cell arteritis. Headache. 2010;50(9):1516–9. https://doi.org/10.1111/j.1526-4610.2010.01718.x.
21. Solomon S, Cappa KG. The headache of temporal arteritis. J Am Geriatr Soc. 1987;35(2):163–5. https://doi.org/10.1111/j.1532-5415.1987.tb01348.x.
22. Smetana GW, Shmerling RH. Does this patient have temporal arteritis? JAMA. 2002;287(1):92–101. https://doi.org/10.1001/jama.287.1.92.
23. Miller NR. Visual manifestations of temporal arteritis. Rheum Dis Clin N Am. 2001;27(4):781–797, vi. https://doi.org/10.1016/S0889-857X(05)70235-0.
24. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Gomez-Acebo I, Pego-Reigosa R, Lopez-Diaz MJ, Vazquez-Triñanes MC, et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. Medicine (Baltimore). 2009;88(4):227–35. https://doi.org/10.1097/MD.0b013e3181af4518.
25. Wilkinson IM, Russell RW. Arteries of the head and neck in giant cell arteritis. A pathological study to show the pattern of arterial involvement. Arch Neurol. 1972;27(5):378–91. https://doi.org/10.1001/archneur.1972.00490170010003.
26. Ungprasert P, Wijarnpreecha K, Koster MJ, Thongprayoon C, Warrington KJ. Cerebrovascular accident in patients with giant cell arteritis: a systematic review and meta-analysis of cohort studies. Semin Arthritis Rheum. 2016;46(3):361–6. https://doi.org/10.1016/j.semarthrit.2016.07.005.
27. Pascuzzi RM, Roos KL, Davis TE Jr. Mental status abnormalities in temporal arteritis: a treatable cause of dementia in the elderly. Arthritis Rheum. 1989;32(10):1308–11. https://doi.org/10.1002/anr.1780321017.
28. Schon F. Involvement of smell and taste in giant cell arteritis. J Neurol Neurosurg Psychiatry. 1988;51(12):1594. https://doi.org/10.1136/jnnp.51.12.1594.
29. Dimant J, Grob D, Brunner NG. Ophthalmoplegia, ptosis, and miosis in temporal arteritis. Neurology. 1980;30(10):1054–8. https://doi.org/10.1212/WNL.30.10.1054.
30. Jay WM, Nazarian SM. Bilateral sixth nerve pareses with temporal arteritis and diabetes. J Clin Neuroophthalmol. 1986;6(2):91–5.
31. Tamhankar MA, Biousse V, Ying GS, Prasad S, Subramanian PS, Lee MS, et al. Isolated third, fourth, and sixth cranial nerve palsies from presumed microvascular versus other causes: a prospective study. Ophthalmology. 2013;120(11):2264–9. https://doi.org/10.1016/j.ophtha.2013.04.009.
32. Roomet A, Allen JS. Temporal arteritis heralded by facial nerve palsy. JAMA. 1974;228(7):870–1. https://doi.org/10.1001/jama.1974.03230320040027.
33. Healey LA, Wilske KR. Presentation of occult giant cell arteritis. Arthritis Rheum. 1980;23(6):641–3. https://doi.org/10.1002/art.1780230605.
34. Calamia KT, Hunder GG. Giant cell arteritis (temporal arteritis) presenting as fever of undetermined origin. Arthritis Rheum. 1981;24(11):1414–8. https://doi.org/10.1002/art.1780241113.
35. Nuenninghoff DM, Hunder GG, Christianson TJ, McClelland RL, Matteson EL. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum. 2003;48(12):3522–31. https://doi.org/10.1002/art.11353.
36. Garcia-Martinez A, Hernandez-Rodriguez J, Arguis P, et al. Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: a cross-sectional screening of fifty-four prospectively followed patients. Arthritis Rheum. 2008;59(3):422–30. https://doi.org/10.1002/art.23315.
37. Gonzalez-Gay MA, Garcia-Porrua C, Pineiro A, Pego-Reigosa R, Llorca J, Hunder GG. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from northwestern Spain: a population-based study. Medicine (Baltimore). 2004;83(6):335–41. https://doi.org/10.1097/01.md.0000145366.40805.f8.
38. Prieto-Gonzalez S, Arguis P, Garcia-Martinez 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(7):1170–6. https://doi.org/10.1136/annrheumdis-2011-200865.
39. Grayson PC, Maksimowicz-McKinnon K, Clark TM, Tomasson G, Cuthbertson D, Carette S, et al. Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. Ann Rheum Dis. 2012;71(8):1329–34. https://doi.org/10.1136/annrheumdis-2011-200795.
40. Myklebust G, Gran JT. A prospective study of 287 patients with polymyalgia rheumatica and temporal arteritis: clinical and laboratory manifestations at onset of disease and at the time of diagnosis. Br J Rheumatol. 1996;35(11):1161–8.
41. Grayson PC, Tomasson G, Cuthbertson D, et al. Association of vascular physical examination findings and arteriographic lesions in large vessel vasculitis. J Rheumatol. 2012;39(2):303–9. https://doi.org/10.3899/jrheum.110652.
42. Tsianakas A, Ehrchen JM, Presser D, Fischer T, Kruse-Loesler B, Luger TA, et al. Scalp necrosis in giant cell arteritis: case report and review of the relevance of this cutaneous sign of large-vessel vasculitis. J Am Acad Dermatol. 2009;61(4):701–6. https://doi.org/10.1016/j.jaad.2008.11.913.
43. Husein-Elahmed H, Callejas-Rubio JL, Rios-Fernandez R, Ortego-Centeno N. Tongue infarction as first symptom of temporal arteritis. Rheumatol Int. 2012;32(3):799–800. https://doi.org/10.1007/s00296-009-1355-z.
44. Kermani TA, Schmidt J, Crowson CS, Ytterberg SR, Hunder GG, Matteson e, et al. Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. Semin Arthritis Rheum. 2012;41(6):866–71. https://doi.org/10.1016/j.semarthrit.2011.10.005.
45. Salvarani C, Hunder GG. Giant cell arteritis with low erythrocyte sedimentation rate: frequency of occurrence in a population-based study. Arthritis Rheum. 2001;45(2):140–5. https://doi.org/10.1002/1529-0131(200104)45:2<140::AID-ANR166>3.0.CO;2-2.
46. Miller A, Green M, Robinson D. Simple rule for calculating normal erythrocyte sedimentation rate. Br Med J (Clin Res Ed). 1983:286–66.
47. Gonzalez-Gay MA, Lopez-Diaz MJ, Barros S, Garcia-Porrua C, Sanchez-Andrade A, Paz-Carreira J, et al. Giant cell arteritis: laboratory tests at the time of diagnosis in a series of 240 patients. Medicine (Baltimore). 2005;84(5):277–90. https://doi.org/10.1097/01.md.0000180043.19285.54.
48. Mahr A, Saba M, Kambouchner M, Polivka M, Baudrimont M, Brochériou I, et al. Temporal artery biopsy for diagnosing giant cell

arteritis: the longer, the better? Ann Rheum Dis. 2006;65(6):826–8. https://doi.org/10.1136/ard.2005.042770.
49. Achkar AA, Lie JT, Hunder GG, O'Fallon WM, Gabriel SE. How does previous corticosteroid treatment affect the biopsy findings in giant cell (temporal) arteritis? Ann Intern Med. 1994;120(12):987–92. https://doi.org/10.7326/0003-4819-120-12-199406150-00003.
50. Narvaez J, Bernad B, Roig-Vilaseca D, et al. Influence of previous corticosteroid therapy on temporal artery biopsy yield in giant cell arteritis. Semin Arthritis Rheum. 2007;37(1):13–9. https://doi.org/10.1016/j.semarthrit.2006.12.005.
51. Jia L, Couce M, Barnholtz-Sloan JS, Cohen ML. Is all inflammation within temporal artery biopsies temporal arteritis? Hum Pathol. 2016;57:17–21. https://doi.org/10.1016/j.humpath.2016.07.004.
52. Duhaut P, Pinede L, Bornet H, Demolombe-Rague S, Dumontet C, Ninet J, et al. Biopsy proven and biopsy negative temporal arteritis: differences in clinical spectrum at the onset of the disease. Groupe de Recherche sur l'Arterite a Cellules Geantes. Ann Rheum Dis. 1999;58(6):335–41. https://doi.org/10.1136/ard.58.6.335.
53. 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;11(1):44. https://doi.org/10.1186/1471-2474-11-44.
54. Bley TA, Weiben O, Uhl M, Vaith P, Schmidt D, Warnatz K, et al. Assessment of the cranial involvement pattern of giant cell arteritis with 3T magnetic resonance imaging. Arthritis Rheum. 2005;52(8):2470–7. https://doi.org/10.1002/art.21226.
55. Bley TA, Wieben O, Uhl M, Thiel J, Schmidt D, Langer M. High-resolution MRI in giant cell arteritis: imaging of the wall of the superficial temporal artery. AJR Am J Roentgenol. 2005;184(1):283–7. https://doi.org/10.2214/ajr.184.1.01840283.
56. Geiger J, Ness T, Uhl M, Lagrèze WA, Vaith P, Langer M, et al. Involvement of the ophthalmic artery in giant cell arteritis visualized by 3T MRI. Rheumatology (Oxford). 2009;48(5):537–41. https://doi.org/10.1093/rheumatology/kep011.
57. 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. Eur J Nucl Med Mol Imaging. 2011;38(9):1764–72. https://doi.org/10.1007/s00259-011-1830-0.
58. Hauenstein C, Reinhard M, Geiger J, Markl M, Hetzel A, Treszl A, et al. Effects of early corticosteroid treatment on magnetic resonance imaging and ultrasonography findings in giant cell arteritis. Rheumatology (Oxford). 2012;51(11):1999–2003. https://doi.org/10.1093/rheumatology/kes153.
59. Chmelewski WL, McKnight KM, Agudelo CA, Wise CM. Presenting features and outcomes in patients undergoing temporal artery biopsy. A review of 98 patients. Arch Intern Med. 1992;152(8):1690–5. https://doi.org/10.1001/archinte.1992.00400200120022.
60. Roth AM, Milsow L, Keltner JL. The ultimate diagnoses of patients undergoing temporal artery biopsies. Arch Ophthalmol. 1984;102(6):901–3. https://doi.org/10.1001/archopht.1984.01040030721028.
61. Nishino H, DeRemee RA, Rubino FA, Parisi JE. Wegener's granulomatosis associated with vasculitis of the temporal artery: report of five cases. Mayo Clin Proc. 1993;68(2):115–21. https://doi.org/10.1016/S0025-6196(12)60157-8.
62. Genereau T, Martin A, Lortholary O, Noel V, Guillevin L. Temporal arteritis symptoms in a patient with hepatitis C virus associated type II cryoglobulinemia and small vessel vasculitis. J Rheumatol. 1998;25(1):183–5.
63. Haugeberg G, Bie R, Johnsen V. Vasculitic changes in the temporal artery in polyarteritis nodosa. Scand J Rheumatol. 1997;26(5):383–5. https://doi.org/10.3109/03009749709065704.
64. 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 (Oxford). 2010;49(8):1594–7. https://doi.org/10.1093/rheumatology/keq039a.
65. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009;68(3):318–23. https://doi.org/10.1136/ard.2008.088351.
66. Ray-Chaudhuri N, Kine DA, Tijani SO, et al. Effect of prior steroid treatment on temporal artery biopsy findings in giant cell arteritis. Br J Ophthalmol. 2002;86(5):530–2. https://doi.org/10.1136/bjo.86.5.530.
67. Hall S, Persellin S, Lie JT, O'Brien PC, Kurland LT, Hunder GG. The therapeutic impact of temporal artery biopsy. Lancet. 1983;2(8361):1217–20.
68.•• Kermani TA, Warrington KJ, Cuthbertson D, Carette S, Hoffman GS, Khalidi NA, et al. Disease relapses among patients with giant cell arteritis: a prospective, longitudinal cohort study. J Rheumatol. 2015;42(7):1213–1217. **Approximately 1-in-5 GCA relapses will be associated with normal serum inflammatory markers. Headache and polymyalgia rheumatica are the most common symptoms at relapse presentation, with headache only uncommonly being an isolated symptom**. https://doi.org/10.3899/jrheum.141347.
69. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum. 2003;49(5):703–8. https://doi.org/10.1002/art.11388.
70. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken). 2010;62(11):1515–26. https://doi.org/10.1002/acr.20295.
71.•• Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med. 2017;377(4):317–328. **Subcutaneous tocilizumab given either weekly or every other week has been convincingly demonstrated in a phase 3 clinical trial to improve the rates of 52-week glucocorticoid-free remission in patients with GCA, leading to it being the first FDA-approved treatment for the disorder**. https://doi.org/10.1056/NEJMoa1613849.
72. 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 Rheumatol. 2017;69(4):837–45. https://doi.org/10.1002/art.40044.
73. 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. https://doi.org/10.1002/art.22754.
74. 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(9):1286–94. https://doi.org/10.1002/art.1780360913.
75. 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. Lancet. 2016;387(10031):1921–7. https://doi.org/10.1016/S0140-6736(16)00560-2.
76. Guillevin L, Regent A. Treating giant-cell arteritis: is IL-6 the cytokine to target? Lancet. 2016;387(10031):1882–3. https://doi.org/10.1016/S0140-6736(16)30183-0.