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HEADACHE (R.B. HALKER SINGH, SECTION EDITOR)

# Updates in the Diagnosis and Management of Giant Cell Arteritis

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## Abstract

**Purpose of Review** Giant cell arteritis is a systemic large vessel vasculitis that affects the older population and can cause progressive and at times, devastating complications including vision loss. While this has been commonly diagnosed and treated among vasculitides, the treatment options are limited and can have long-term adverse effects. The purpose of our review on GCA is to identify and discuss the pathophysiology and clinical aspects of GCA as they relate to the most recent data. The review will describe any new data on the diagnosis and treatment of this systemic large vessel vasculitis.

**Recent Findings** The latest data suggests that the mainstay of treatment of GCA remains glucocorticoids but alternate agents are being identified and used in an attempt to reduce the cumulative exposure to glucocorticoids and reduce treatment-related adverse effects while managing and maintaining remission of this systemic disease.

**Summary** There is much more information to collect in terms of identification and standardization of the optimal length of time to treat with glucocorticoids as well as regarding the long-term efficacy of alternate treatments. In addition, investigation continues to identify measureable risk factors to predict outcomes of individual patients with this diagnosis.

**Keywords** Giant cell arteritis · Polymyalgia rheumatica · Chronic glucocorticoid use · Tocilizumab · Methotrexate

## Introduction

Systemic vasculitides are a complex group of rheumatologic diseases primarily involving lymphocytic infiltration of vessel walls. This subsequently leads to the loss of vascular integrity, bleeding, eventual end organ tissue ischemia, and necrotic damage. The resultant clinical manifestations are based upon the size and location of vessel involvement. Prompt diagnosis is imperative in reducing morbidity and systemic damage and in some cases, in preventing mortality.

Giant cell arteritis (GCA) is a systemic vasculitis involving the large vessels. It is a chronic disease characterized by the granulomatous inflammatory changes that occur at the level of the large vessels, namely the aorta and the branch vessels.

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## Epidemiology

Giant cell arteritis is the most common form of primary systemic vasculitis, with an overall incidence of 15–25 per 100000 per year [1]. This is seen more commonly in women and has been found to be prevalent in North America and Western Europe. It affects large and middle-sized blood vessels artery in individuals older than 50 years of age. It is highly unusual to occur before the age of 50 and the incidence appears to rise with the age of the patient [2]. Mortality does not appear to be increased in these patients except in some cases of aortitis [3].

## Pathophysiology

The definitive pathogenesis involved is still not completely understood leading to limitations in development of treatment regimens. Both innate and adaptive immune systems appear to play a role with newer evidence pointing towards a dual T

lymphocyte pathway with important roles for $T_H1$- and $T_H17$-driven inflammatory cascades [4•].

CD4 T cells along with highly activated macrophages give rise to multinucleated giant cells which tend to infiltrate the internal elastic membrane of the artery. GCA is characterized by a prominent $T_H1$-mediated immune response with vigorous expression of IFNγ and IFNγ-induced products in accordance with the granulomatous nature of vasculitic lesions. IFNγ activates macrophages which initiate and maintain inflammatory cascades and participate in vascular injury. This then induces pro-inflammatory cytokines IL-1, TNFα, and IL-6 which in turn correlate with the intensity of the systemic inflammatory response, which is typical of the disease and also differentiates it from Polymyalgia Rheumatica [5].

A driving force in this inflammatory cascade is the dendritic cell which causes the most activity at the outermost layer of the blood vessel, the adventia. This then allows for CD4 T cells and the macrophages to combine to form the granuloma to stabilize the inflammatory response. This leads to a heightened abnormal response by the blood vessel wall causing arterial occlusion, ischemia, and resultant necrosis.

At this time, there is no evidence showing a direct role of B cells in the pathogenesis of GCA. This distinguishes the large vessel vasculitis from the ANCA-associated vasculitides that are associated with the small vessels.

IL-21 has also been recently implicated as present in vasculitic lesions. This is most specifically produced by Th17, Th9, and Tfh (follicular helper cells). This has been shown to be highly responsive to glucocorticoids [6, 7]. IL-22 is also being further investigated as having some influence in initiating and maintaining inflammation in blood vessels [8].

There have been discussions that if these pathways are truly involved in causation, we need to find a treatment approach targeting both pathways preferably with the same agent. This led to various trials being conducted to determine the efficacy of biologics which have the potential to target both limbs of this model. Developments in this vein continue to emerge, and preliminary efficacy of a few biologics, especially tocilizumab, has been noted.

There has been some questionable correlation seen between GCA and infectious diseases like VZV and parvovirus. VZV is the only human virus that has been shown to replicate in arteries and cause disease, and it has been described that the vascular disease caused is not limited to the intracranial circulation but can also affect TAs and lead to GCA. The distribution of VZV in the temporal arteries and the presence of VZV in skip areas was found to parallel the pathology in GCA [9•, 10]. However, more recent studies have failed to formally suggest a causal association with VZV and the pathogenesis of GCA. This has led to the question of whether antiretroviral agents need to be added to the treatment regimen; however no clear guidelines about which agent or the duration of empirical treatment currently exist.

## Clinical Features

Giant cell arteritis is a heterogenous disease with several clinical presentations (Table 1). As with all vasculitides, the phenotype can be variable based upon the arterial vessels involved.

The two most common presentations of GCA are the classic cranial GCA and large-vessel GCA, where often the cranial arteries are spared. In general, symptoms of GCA are often subacute in onset, though they may be also associated with the more acute presentation of polymyalgia rheumatica (PMR) which routinely will involve hip and shoulder girdle pain and stiffness which may occur in roughly 40–50% of patients with GCA [11].

Many of the clinical features are nonspecific, i.e., constitutional symptoms of fever and weight loss, headache, and diffuse musculoskeletal complaints. Other symptoms may also include scalp tenderness, tongue claudication, decreased temporal artery pulsations, nodular temporal arteries with swelling or erythema, and sore throat [15]. Others are strongly suggestive of a robust inflammatory response and carry a high likelihood ratio of the diagnosis and a positive temporal artery biopsy. The symptoms with the highest likelihood ratio for a positive biopsy are jaw claudication and diplopia [16].

Ultimately, aneurysmal disease resulting from vascular inflammation is the most common cause of morbidity and mortality with thoracic aortic aneurysms most commonly implicated, occurring in 18% of patients. Aortic dissection occurs in 5% of patients and is also associated with a significantly reduced median survival of 1.6 years [17]. Due to the intense myo-intimal proliferation and vessel occlusion, which in up to 20% of the cases may lead to potentially permanent blindness, GCA can be considered a medical emergency.

## Large-Vessel GCA

A variant of GCA is large-vessel GCA when the great vessels are involved, namely the subclavian, brachial, and axillary arteries [17]. This variant has a predilection for the thoracic aorta over the abdominal aorta. This presentation rarely involves temporal arteries, making a temporal artery biopsy less significant or meaningful in making the diagnosis. Monitoring the patient for aneurysm or ischemic limb symptoms is also very important as imaging studies have shown evidence for aortitis in up to 65% patients with GCA [18]. These patients are often evaluated and monitored with attention paid to development of worsened chest pain or ischemic limb symptoms, which can be rare. Often medical management can help improve or stabilize these manifestations.

Acute phase reactants can be helpful in assessing disease activity and can be just as useful as it is in cranial GCA.

**Table 1** Clinical manifestations of giant cell arteritis

| | |
|---|---|
| Constitutional symptoms | Low grade fever, fatigue, weight loss, anorexia. May be the only early manifestation so should evaluate if these occur with no alternate cause |
| Headache | New onset for the patient |
| | Temporal but can be occipital or frontal |
| | Scalp tenderness may be associated |
| | Often nonspecific and need to rule out other causes |
| Jaw claudication | Can present as trismus or severe pain and fatigue on increased use of the jaw that occurs immediately on movement |
| Transient visual loss | Amaurosis fugax-this is an abrupt, early partial field defect or monocular loss |
| | Can foreshadow permanent visual loss |
| Permanent visual loss | Most concerning and devastating complication of GCA. |
| | Sudden onset and painless |
| | Can be unilateral or bilateral |
| | Despite treatment, blindness can be in 15–20% of patients and is most commonly irreversible. |
| | If untreated, loss of vision in the unaffected eye is 25–50% |
| | Proposed risk factors of visual loss: **prior transient visual loss is strongest predictor, age, HTN, thrombocytosis [11, 12], diplopia, and visual hallucinations |
| Causes of vision loss in GCA | Anterior ischemic optic neuropathy (80% of GCA patients with vision loss) |
| | Central retinal artery occusion (10%) |
| | Posterior ischemic optic neuropathy (< 5%) |
| | Cerebral ischemia secondary to occipital lobe infarct due to interruption in the vertebrobasilar circulation [13, 14] |
| Musculoskeletal | Peripheral synovitis |
| | Distal extremity swelling with pitting edema (Remitting seronegative symmetrical synovitis with pitting edema) Rs3pe |
| Upper respiratory symptoms | In about 10% GCA |
| | Nonproductive cough |

## Diagnosis

GCA is suspected in patients with sudden onset of a severe headache and/or visual loss. ESR and CRP are typically elevated with ESR usually above 50. A temporal artery biopsy is the gold standard for diagnosis and should be completed within 2 weeks of starting steroids or any alternative therapy. The biopsy is a low-risk procedure and a unilateral segment measuring 1–2 cm can often increase the sensitivity of the procedure. However, as this disease is characterized by skip lesions, false negatives can occur in up to 30% of patients with GCA [19]. There also continues to be debate as to whether a contralateral biopsy improves sensitivity of acquiring a diagnostically accurate result. As it stands, there is a wide range of discordance rates reported [20, 21]. At our institution, the practice is to biopsy the contralateral artery if there is a high index of suspicion for GCA and an adequate initial sample is negative.

There also has been concern regarding the effect of glucocorticoids on the temporal artery biopsy if started prior to the biopsy. It has been documented that resolution of the inflammatory lesion in GCA occurs slowly and that findings of a "healed arteritis" can be present for up to a month after initiation of treatment [22•]. Because of the significant complications that can occur if treatment is delayed, we initiate glucocorticoid therapy at presentation if we strongly suspect the disease and then proceed with biopsy as soon as possible.

Imaging studies like MRI, ultrasound, CT, and PET scans may also be used for diagnosis; however, they each come with their benefits and limitations. US with Doppler has been used as a surrogate for biopsy especially in patients in whom a biopsy is unattainable. It is noninvasive but is often operator-dependent. The modality is used to detect a "halo sign" which is essentially an area thought to represent mural edema. Bilateral halo signs have been found to be highly specific for GCA [23]. Given its increased specificity and sensitivity in many studies recently, US with Doppler has emerged as a good alternative to a biopsy. High-resolution MRI has been evaluated with MRA to visualize the temporal artery to demonstrate mural edema [24]. This has also been used in patients with large vessel variant of GCA to identify stenosis and aneurysms [24]. PET, CT, and CTA lack the spatial resolution to adequately visualize the temporal artery, and often

FDG PET scan interpretation is limited by the brain uptake of the tracer [25].

Of note, it is still unclear if we should screen all patients with cranial GCA for large vessel involvement and development of aortic aneurysm. In one study of 164 patients with biopsy-proven GCA, 24 (15%) were found to have large vessel involvement, mainly at the thoracic aorta [26]. A retrospective multicenter study in 2016 described the clinical presentation and disease course of patients with typical cranial symptoms of GCA compared to those without cranial symptoms. Patients were enrolled based upon American College of Rheumatology criteria for GCA as well as imaging. This cohort of 143 patients revealed 31 (22%) patients were without cranial symptoms. Ultimately, the diagnosis was based upon biopsies of arterial sites but only 1/3 of those patients presented with extracranial symptoms instead. This may underscore the ongoing question as to whether we should screen all patients with and without cranial symptoms of GCA for large vessel involvement [27]. In our practice, we will do so when the patient is having symptoms of large vessel involvement such as chest pain or upper extremity claudication, rather than screen all comers. More data will need to be collected to consider changing our clinical paradigm at this time.

## Treatment

The mainstay of management of giant cell arteritis has always been high-dose glucocorticoids, with the goal being induction and maintenance of remission, or absence of disease activity. Steroids are often given with more confidence when the patient has highly suggestive imaging and a positive temporal artery biopsy. When the diagnosis of GCA is suspected clinically, a temporal artery biopsy or other diagnostic procedure should be obtained as soon as possible but treatment should not be withheld in anticipation of the biopsy. Other steroid sparing options for the treatment of patients with a positive biopsy and clinical symptoms have been sought after given the known adverse effects of long-term corticosteroids, especially in the elderly. These include methotrexate and tocilizumab (Table 2).

The decision to initiate glucocorticoids in a patient with negative imaging or a negative biopsy is a bit less clear. The diagnosis is then based upon clinical evidence and alternative diagnoses will need to be excluded. The treatment of such patients is essentially the same as it is for those patients with positive biopsies. High-dose glucocorticoids are used and monitoring of the patient is important [36, 37•, 38].

## Systemic Glucocorticoids

There are no randomized placebo controlled trials regarding the efficacy of glucocorticoids for the treatment of GCA. However, through documentation of clinical experience, glucocorticoids have become the first-line treatment of GCA [36, 37•, 38]. They act quickly to improve and control symptoms of GCA and can also prevent the visual loss that can occur in aggressive untreated GCA. Time is of the essence when initiating treatment in these patients.

Glucocorticoids are given in a daily dosing regimen. Other schedules have been associated with new visual loss and relapse of disease. For that reason, we reserve alternative approaches for those patients who have high risk of complications to daily steroids such as diabetes mellitus or chronic infections. The optimal starting dose of glucocorticoids has not been formally established but the most common practice is to start with an equivalent of prednisone 1 mg/kg a day (maximum dose of 60 mg/day).

Initial studies established that a dose of 20–30 mg a day of steroids were effective in treating the symptoms and also prevented relapse [39, 40]. However, more recent findings have emphasized the finding that there is not one established dose of steroid to initiate but a more clinically accepted dose of 1 mg/kg may be appropriate to achieve optimal control of progressive disease [41].

At times, pulse steroids have been used. In our practice, we have used this in times of urgently impending visual loss. While most of the data has not shown a decrease in the cumulative dose of glucocorticoids or a decrease in GCA complications, there is still adequate support for the use of pulse methylprednisolone in threatened or established vision loss at presentation [36, 42]. We have used doses of 1 g of IV methylprednisolone daily for 3 days, a "pulse" regimen for impending visual loss or diplopia in patients with known or suspected GCA. Once completed, a maintenance of 1 mg/kg a day of prednisone is initiated.

As for tapering the steroids, a specific regimen has not been well established but in our clinical experience, we will start at 1 mg/kg a day of prednisone, no greater than 60 mg a day, and continue that dose until remission is achieved and there is complete resolution of clinical symptoms. This may take anywhere from 2 to 4 weeks. At that time, a common practice is to reduce the dose to 40 mg/day. We then maintain that dose for another 2–4 weeks and then decrease from there. Routinely, we recommend decreasing by 5–10 mg a day every 2 weeks until 20 mg a day is achieved without relapse of symptoms. Subsequently, we will then reduce the dose by 2.5 mg every 2 weeks until 10 mg/day is achieved. Once the patient is at that dose, we reduce by slower increments over the next several months. We do this to reduce the risk of relapse. Usually, we will decrease by 1 mg every 2 to 4 weeks until the patient has achieved the lowest, most effective dose that maintains

**Table 2** Alternative medications to treat GCA

| Medication | Pharmacology/utility |
|---|---|
| Abatacept | Blocks T cell costimulation |
| | Activated CD4+ T cells found in the infiltrate of the temporal artery |
| | Phase 2 dB study of IV Abatacept and prednisone at weeks 1, 15, 29, and 56. (prednisone tapered to off) |
| | Rate of sustained remission of borderline significance |
| | No difference in adverse effects between two groups [28•] |
| Ustekinumab | Blocks IL-12 and IL-23, which promote Th1 and Th17 respectively. Both may play a role in pathogenesis of GCA. |
| | Open-label study of 14 patients, decrease in prednisolone use observed and 4 patients discontinued GC completely [29] |
| Azathioprine | Single Center DBRPCT of AZA 150 mg/day vs. placebo |
| | Small but statistically significant decrease in mean prednisolone dose at 1 year—20 people completed study [30] |
| Cyclophosphamide | Small uncontrolled studies |
| | May be useful in GCA patients when risk of GC-related adverse effects in non responders to other immunosuppresants is high |
| | Systematic review of 103 cases revealed 86%reported patients responded/22% relapsed despite maintenance immunosuppression. Adverse effects in 1/3 patients and 12.5% discontinued treatment due to infections and cytopenias [31] |
| Leflunomide | An open-label study observed cumulative steroid dose and number of relapses and showed it may be a good alternative [32] |
| Anti-TNF therapy | RPCT of infliximab for maintenance of remission with prednisone taper. At week 22, showed that infliximab did not reduce the proportion of patients with relapse BUT did not increase the proportion of patients who could taper prednisone to 10 mg/day without relapse. Trial stopped early [33–35]. |

remission. Once treatment has been initiated and we have been able to reduce the steroids down to a low effective dose, we have to monitor for any relapses of disease and complications of treatment. In a recent abstract, a retrospective review of 53 patients over 14 years was performed. It observed that over half of the patients had a relapse of their GCA and only one in every three patients could discontinue their treatment. There was not statistically significant difference in the characteristics of those who could discontinue treatment and those who could not [43]. Hence, we attempt to monitor these patients closely and intervene when relapse is impending or evident.

Ideally, the erythrocyte sedimentation rate (ESR) and C-reactive protein(CRP) accurately reflect the current disease activity, whether it is ongoing inflammation or a period of remission. This is then helpful to follow as we reduce the dose of glucocorticoids. Unfortunately, there are also times when the acute phase reactants do not reflect disease activity and elevations are not accompanied by symptoms of active GCA. When this is the case, we caution against the adjustment of steroids based upon the acute phase reactants, which can result in an increase of the cumulative dose of glucocorticoids and subsequent long-term side effects of treatment. Therefore, we recommend that the change of glucocorticoid does be based upon clinical symptoms rather than lab work. In addition, the ESR can be nonspecific and can increase as a result of abnormal paraproteins or age. CRP may be a more useful test as it is a surrogate marker of IL-6 which is one of the main cytokines associated with the activity of GCA. Finally, persistent elevation of the acute phase reactants may also suggest the possibility of large vessel involvement.

## Glucocorticoid-Sparing Medications

Long-term glucocorticoid use can result in several treatment-related complications including diabetes mellitus, hypertension, osteonecrosis, subcapsular cataracts, osteoporosis and fractures, and infections. Minimizing the exposure of prednisone in the elderly population can help reduce treatment-related morbidity. It is for these reasons that in cases where it is difficult to taper the glucocorticoids to the lowest most effective dose, or in cases where adverse effects have already happened, it is prudent to consider initiation of a steroid-sparing agent. In addition, if recurrence of symptoms is frequent and attributable to GCA, we also consider such agents.

Methotrexate has been the first-line medication to be evaluated as a potential alternative to GCs. Also, with greater understanding of the potential pathways involved in the pathogenesis of GCA, we have seen more biologics being studied as potential therapy options. Of late, an increasing number of studies are being conducted on abatacept, rituximab,

ustekinimab, anakinra, and tocilizumab. Of note, we do not use an adjunct medication if symptoms are mild or related to polymyalgia rheumatica. It is only when recurrence of symptoms is attributable to giant cell arteritis that we consider an alternative agent.

## Methotrexate

Methotrexate was the initial agent studied for use of an adjunctive treatment for patients who could not decrease their glucocorticoid dose. Three main randomized placebo controlled trials comparing methotrexate to placebo have been described [44–46].

A meta-analysis done of the three trials included 161 patients and indicated that the addition of MTX led to a statistically significant reduction in glucocorticoids over 48 weeks. There was also a higher likelihood of achieving remission without steroids. In addition, there was a decreased rate of relapse noted. However, the correlation was found to be weak and two of the studies were not found to be supportive of MTX efficacy. Of note, methotrexate appeared to be more effective over placebo after 6 to 8 months and in addition, the dose used was essentially low and only 10 to 15 mg per week. In a more recent abstract published in the Annals of Rheumatic Diseases, the observational study showed that there was no benefit from adjunct MTX in GCA either in terms of efficacy or toxicity [47•].

In our practice, we choose to use methotrexate when the patient is experiencing significant adverse effects to the glucocorticoids or as an additional medication in those patients in whom we are unable to reduce the prednisone dose.

## Tocilizumab

The current frontrunner in GCA therapy is tocilizumab which is the first humanized monoclonal antibody targeting the IL-6 receptor subunit alpha (IL-6Rα). It decreases the circulating levels of neutrophils, neutrophil infiltration into inflamed joints, circulation of myeloid dendritic cells, monocyte levels, serum macrophage migration inhibitory factor levels, and levels of T helper 17 (Th17) cells, while increasing regulatory T cells [48]. Tocilizumab was approved for the treatment of patients with GCA by the U.S. Food and Drug Administration (FDA) in May 2017 and by the European Commission in September 2017, making this the first drug approved for the treatment GCA beyond glucocorticoids [49]. A randomized, double-blind, placebo-controlled, multicenter, phase 3 trial (GiACTA) of TCZ in patients with GCA showed that TCZ + a 26-week prednisone taper was superior to both 26-week and 52-week prednisone tapers alone for the achievement of sustained remission from GCA [50•]. The addition of TCZ to prednisone treatment in the GiACTA trial allowed a reduction in the cumulative prednisone doses required for disease control [50•]. The ideal illness-specific posology, the optimal treatment duration, and the TCZ long-term safety and efficacy remain however to be determined and studies are ongoing.

## Alternative Agents

Other medications have also been evaluated but not widely recommended given the lack of optimal studies, small effect, and toxicities among several other reasons.

## Follow-up

Typically we will see the newly diagnosed patient every month for the first 3–6 months if possible to monitor the patient's clinical course and bloodwork. We also prefer to see the patient routinely to monitor for clinical worsening of symptoms for progression of large vessel involvement such as claudication, chest pain, new bruits on exam, or discordant blood pressure. As always, we also educate our patients regarding the telltale signs and symptoms of polymyalgia rheumatica as well as worsening of their giant cell arteritis. We also monitor for symptoms of adverse effects of long-term GC use such as infection, osteoporosis, diabetes, and cataracts.

Particular attention must be paid to prevention of osteoporosis in this population given the age and long-term exposure to GC. We also want to make sure we monitor for infections, as increased risk has been documented [51].

One question that often arises is regarding the use of prophylaxis for *P. jirovecii* pneumonia (PCP). Few long-term studies of GCA have identified patients who developed PCP but these were patients on MTX [52]. Other studies have shown no cases. In our practice, we do not place patients who are on glucocorticoid monotherapy on prophylaxis and will reserve that only for patients who are on methotrexate with high dose GC.

Finally, there is conflicting data on the use of anti-platelet therapy in patients with GCA. A few studies have shown that certain ischemic events such as vision loss and stroke for reduced in these patients who remained on antiplatelet therapy. Other studies showed no effect on the occurrence of such cranial ischemic events. The current recommendation in clinical practice is to base the use of low-dose aspirin in patients with newly diagnosed giant cell arteritis upon their cardiovascular risk factors [37].

## Conclusion

GCA is the most common large vessel vasculitis associated with severe headaches, scalp tenderness, and jaw pain seen in individuals over the age of 50. Temporal artery biopsies are the gold standard for diagnosis but treatment should be started at the time of suspicion of diagnosis. There are several other noninvasive modalities that have been studied and standardized as well such as the Doppler studies. Although glucocorticoids remain the mainstay of treatment, however, newer biologics like tocilizumab are on their way to fast becoming the adjunctive standard of care to mainly prevent or reduce the adverse effects that can occur with long-term glucocorticoids. Further studies on other biologics are required to determine efficacy and potential long-term side effects. The prognosis is relatively good once the lowest, most effective dose for the steroid has been achieved. Afterwards, the patient may remain on that for essentially the next 2–3 years to maintain the highest chance of remission and low rates of relapse.

### Compliance with Ethical Standards

**Conflict of Interest** Surabhi Uppal, Mohanad Hadi, and Sheetal Chhaya each declare no potential conflicts 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.

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