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Giant cell arteritis: An updated review of an old disease

ABSTRACT

Giant cell arteritis is a common systemic vasculitis that affects the elderly and has a variable clinical presentation. Physicians should be aware of its different clinical phenotypes so that they can recognize it early and promptly initiate glucocorticoids, the mainstay of therapy. Clinicians should also be familiar with the toxicity of glucocorticoids and how to manage adverse effects. Tocilizumab, an interleukin 6 receptor inhibitor, is emerging as a glucocorticoid-sparing treatment, though its long-term safety and efficacy are still under study.

KEY POINTS

Giant cell arteritis can present with cranial symptoms, extracranial large-vessel involvement, or polymyalgia rheumatica.

Temporal artery biopsy is the standard for diagnosis.

Adverse effects of glucocorticoid treatment, particularly bone loss, need to be managed.

In patients treated with glucocorticoids alone, the relapse rate is high when the drugs are tapered; thus, prolonged treatment is required.

GIANT CELL ARTERITIS (GCA) is a systemic vasculitis involving medium-sized and large arteries, most commonly the temporal, ophthalmic, occipital, vertebral, posterior ciliary, and proximal vertebral arteries. Moreover, involvement of the ophthalmic artery and its branches results in loss of vision. GCA can also involve the aorta and its proximal branches, especially in the upper extremities.

GCA is the most common systemic vasculitis in adults. It occurs almost exclusively in patients over age 50 and affects women more than men. It is most frequent in populations of northern European ancestry, especially Scandinavian. In a retrospective cohort study in Norway, the average annual cumulative incidence rate of GCA was 16.7 per 100,000 people over age 50.¹ Risk factors include older age, history of smoking, current smoking, early menopause, and, possibly, stress-related disorders.²

■ PATHOGENESIS IS NOT COMPLETELY UNDERSTOOD

The pathogenesis of GCA is not completely understood, but there is evidence of immune activation in the arterial wall leading to activation of macrophages and formation of multinucleated giant cells (which may not always be present in biopsies).

The most relevant cytokines in the ongoing pathogenesis are still being defined, but the presence of interferon gamma and interleukin 6 (IL-6) seem to be critical for the expression of the disease. The primary immunogenic triggers for the elaboration of these cytokines and the arteritis remain elusive.

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■ A SPECTRUM OF PRESENTATIONS

The initial symptoms of GCA may be vague, such as malaise, fever, and night sweats, and are likely due to systemic inflammation. Features of vascular involvement include headache, scalp tenderness, and jaw claudication (cramping pain in the jaw while chewing).

A less common but serious feature associated with GCA is partial or complete vision loss affecting 1 or both eyes.³ Some patients suddenly go completely blind without any visual prodrome.

Overlapping GCA phenotypes exist, with a spectrum of presentations that include classic cranial arteritis, extracranial GCA (also called large-vessel GCA), and polymyalgia rheumatica.²

Cranial GCA, the best-characterized clinical presentation, causes symptoms such as headache or signs such as tenderness of the temporal artery. On examination, the temporal arteries may be tender or nodular, and the pulses may be felt above the zygomatic arch, above and in front of the tragus of the ear. About two-thirds of patients with cranial GCA present with new-onset headache, most often in the temporal area, but possibly anywhere throughout the head.

Visual disturbance, jaw claudication, and tongue pain are less common but, if present, increase the likelihood of this diagnosis.²

Large-vessel involvement in GCA is common and refers to involvement of the aorta and its proximal branches. Imaging methods used in diagnosing large-vessel GCA include color Doppler ultrasonography, computed tomography with angiography, magnetic resonance imaging with angiography, and positron emission tomography. In some centers, such imaging is performed in all patients diagnosed with GCA to survey for large-vessel involvement.

Depending on the imaging study, large-vessel involvement has been found in 30% to 80% of cases of GCA.^{4,5} It is often associated with nonspecific symptoms such as fever, weight loss, chills, and malaise, but it can also cause more specific symptoms such as unilateral extremity claudication. In contrast to patients with cranial GCA, patients with large-vessel GCA were younger at onset, less likely

to have headaches, and more likely to have arm claudication at presentation.⁶ Aortitis of the ascending aorta can occur with a histopathologic pattern of GCA but without the clinical stigmata of GCA.

The finding of aortitis should prompt the clinician to question the patient about other symptoms of GCA and to order imaging of the whole vascular tree. Ultrasonography and biopsy of the temporal arteries can be considered. Whether idiopathic aortitis is part of the GCA spectrum remains to be seen.

Laboratory tests often show anemia, leukocytosis, and thrombocytosis. Acute-phase reactants such as C-reactive protein and the erythrocyte sedimentation rate are often elevated. The sedimentation rate often exceeds 50 mm/hour and sometimes 100 mm/hour.

In 2 retrospective studies, the number of patients with GCA whose sedimentation rate was less than 50 mm/hour ranged between 5% and 11%.^{7,8} However, a small percentage of patients with GCA have normal inflammatory markers. Therefore, if the suspicion for GCA is high, treatment should be started and biopsy pursued.⁹ In patients with paraproteinemia or other causes of a spuriously elevated or low erythrocyte sedimentation rate, C-reactive protein is a more reliable test.

Polymyalgia rheumatica is another rheumatologic condition that can occur independently or in conjunction with GCA. It is characterized by stiffness and pain in the proximal joints such as the hips and shoulders, typically worse in the morning and better with activity. Although the patient may subjectively feel weak, a close neurologic examination will reveal normal muscle strength.

Polymyalgia rheumatica is observed in 40% to 60% of patients with GCA at the time of diagnosis; 16% to 21% of patients with polymyalgia rheumatica may develop GCA, especially if untreated.^{2,10}

Differential diagnosis

Other vasculitides (eg, Takayasu arteritis) can also present with unexplained fever, anemia, and constitutional symptoms.

Infection should be considered if fever is present. An infectious disease accompanied by fever, headache, and elevated inflammatory markers can mimic GCA.

Start high-dose glucocorticoids as soon as GCA is suspected

Nonarteritic anterior ischemic optic neuropathy can present with sudden vision loss, prompting concern for underlying GCA. Risk factors include hypertension and diabetes mellitus; other features of GCA, including elevated inflammatory markers, are generally absent.

■ TEMPORAL ARTERY BIOPSY: THE GOLD STANDARD FOR DIAGNOSIS

Temporal artery biopsy remains the standard to confirm the diagnosis. However, because inflammation in the temporal arteries can affect some segments but not others, biopsy results on conventional hematoxylin and eosin staining can be falsely negative in patients with GCA. In one study,¹¹ the mean sensitivity of unilateral temporal artery biopsy was 86.9%.

Typical positive histologic findings are inflammation with panarteritis, CD4-positive lymphocytes, macrophages, giant cells, and fragmentation of the internal elastic lamina.¹²

When GCA is suspected, treatment with glucocorticoids should be started immediately and biopsy performed as soon as possible. Delaying biopsy for 14 days or more may not affect the accuracy of biopsy study.¹³ Treatment should never be withheld while awaiting the results of biopsy study.

Biopsy is usually performed unilaterally, on the same side as the symptoms or abnormal findings on examination. Bilateral temporal artery biopsy is also performed and compared with unilateral biopsy; this approach increases the diagnostic yield by about 5%.¹⁴

■ IMAGING

In patients with suspected GCA, imaging is recommended early to complement the clinical criteria for the diagnosis of GCA.¹⁵ Positron emission tomography, computed tomography angiography, magnetic resonance angiography, or Doppler ultrasonography can reveal inflammation of the arteries in the proximal upper or lower limbs or the aorta.²

In patients with suspected cranial GCA, ultrasonography of the temporal and axillary arteries is recommended first. If ultrasonography is not available or is inconclusive, high-resolution magnetic resonance imaging of the

cranial arteries can be used as an alternative. Computed tomography and positron emission tomography of the cranial arteries are not recommended.

In patients with suspected large-vessel GCA, ultrasonography, positron emission tomography, computed tomography, and magnetic resonance imaging may be used to screen for vessel wall inflammation, edema, and luminal narrowing in extracranial arteries. Ultrasonography is of limited value in assessing aortitis.

Color duplex ultrasonography can be applied to assess for vascular inflammation of the temporal or large arteries. The typical finding of the “halo” sign, a hypoechoic ring around the arterial lumen, represents the inflammation-induced thickening of the arterial wall. The “compression sign,” the persistence of the “halo” during compression of the vessel lumen by the ultrasound probe, has high specificity for the diagnosis.¹⁶

Ultrasonography of suspected GCA has yielded sensitivities of 55% to 100% and specificities of 78% to 100%. However, its sensitivity depends on the user’s level of expertise, so it should be done only in medical centers with a high number of GCA cases and with highly experienced sonographers. High-resolution magnetic resonance imaging is an alternative to ultrasonography and has shown similar sensitivity and specificity.³

■ TREATMENT WITH GLUCOCORTICOIDS

Glucocorticoids remain the standard for treatment of GCA. The therapeutic effect of glucocorticoids in GCA has been established by years of clinical experience, but has never been proven in a placebo-controlled trial. When started appropriately and expeditiously, glucocorticoids produce exquisite resolution of signs and symptoms and prevent the serious complication of vision loss. Rapid resolution of symptoms is so typical of GCA that if the patient’s symptoms persist more than a few days after starting a glucocorticoid, the diagnosis of GCA should be reconsidered.

In a retrospective study of 245 patients with biopsy-proven GCA treated with glucocorticoids, 34 had permanent loss of sight.¹⁷ In 32 (94%) of the 34, the vision loss occurred

If symptoms persist more than a few days after starting a glucocorticoid, reconsider the diagnosis of GCA

before glucocorticoids were started. Of the remaining 2 patients, 1 lost vision 8 days into treatment, and the other lost vision 3 years after diagnosis and 1 year after discontinuation of glucocorticoids.

In a series of 144 patients with biopsy-proven GCA, 51 had no vision loss at presentation and no vision loss after starting glucocorticoids, and 93 had vision loss at presentation. In the latter group, symptoms worsened within 5 days of starting glucocorticoids in 9 patients.¹⁸ If vision was intact at the time of presentation, prompt initiation of glucocorticoids reduced the risk of vision loss to less than 1%.

High doses, slowly tapered

The European League Against Rheumatism recommends early initiation of high-dose glucocorticoids for patients with large-vessel vasculitis,¹⁹ and it also recommends glucocorticoids for patients with polymyalgia rheumatica.²⁰ The optimal initial and tapering dosage has never been formally evaluated, but regimens have been devised on the basis of expert opinion.²¹

For patients with GCA who do not have vision loss at the time of diagnosis, the initial dose is prednisone 1 mg/kg or its equivalent daily for 2 to 4 weeks, after which it is tapered.²¹ If the initial dosage is prednisone 60 mg orally daily for 2 to 4 weeks, our practice is to taper it to 50 mg daily for 2 weeks, then 40 mg daily for 2 weeks. Then, it is decreased by 5 mg every 2 weeks until it is 20 mg daily, and then by 2.5 mg every 2 weeks until it is 10 mg orally daily. Thereafter, the dosage is decreased by 1 mg every 2 to 4 weeks.

For patients with GCA who experience transient vision loss or diplopia at the time of diagnosis, intravenous pulse glucocorticoid therapy should be initiated to reduce the risk of vision loss as rapidly as possible.²² A typical pulse regimen is methylprednisolone 1 g intravenously daily for 3 days. Though not rigorously validated in studies, such an approach is used to avoid vision impairment due to GCA, which is rarely reversible.

RELAPSE OF DISEASE

Suspect a relapse of GCA if the patient's initial symptoms recur, if inflammatory markers be-

come elevated, or if classic symptoms of GCA or polymyalgia rheumatica occur. Elevations in inflammatory markers do not definitely indicate a flare of GCA, but they should trigger close monitoring of the patient's symptoms.

Relapse is treated by increasing the glucocorticoid dosage as appropriate to the nature of the relapse. If vision is affected or the patient has symptoms of GCA, then increments of 30 to 60 mg of prednisone are warranted, whereas if the patient has symptoms of polymyalgia rheumatica, then increments of 5 to 10 mg of prednisone are usually used.

The incidence of relapses of GCA in multiple tertiary care centers has been reported to vary between 34% and 75%.^{23,24} Most relapses occur at prednisone dosages of less than 20 mg orally daily and within the first year after diagnosis. The most common symptoms are limb ischemia, jaw claudication, constitutional symptoms, headaches, and polymyalgia rheumatica. In a review of 286 patients,²⁵ 213 (74%) had at least 1 relapse. The first relapse occurred in the first year in 50%, by 2 years in 68%, and by 5 years in 79%.

ADVERSE EFFECTS OF GLUCOCORTICOIDS

In high doses, glucocorticoids have well-known adverse effects. In a population-based study of 120 patients, each patient treated with glucocorticoids experienced at least 1 adverse effect (cataract, fracture, infection, osteonecrosis, diabetes, hypertension, weight gain, capillary fragility, or hair loss).²⁶ The effects were related to aging and cumulative dosage of prednisone but not to the initial dosage.

Glucocorticoids can affect many organs and systems:

- Eyes (cataracts, increased intraocular pressure, exophthalmos)
- Heart (premature atherosclerotic disease, hypertension, fluid retention, hyperlipidemia, arrhythmias)
- Gastrointestinal system (ulcer, gastrointestinal bleeding, gastritis, visceral perforation, hepatic steatosis, acute pancreatitis)
- Bone and muscle (osteopenia, osteoporosis, osteonecrosis, myopathy)
- Brain (mood disorder, psychosis, memory

Suspect a relapse if the initial symptoms recur, if markers elevate, or if classic symptoms arise

impairment)

- Endocrine system (hyperglycemia, hypothalamic-pituitary-adrenal axis suppression)
- Immune system (immunosuppression, leading to infection and leukocytosis).

Patients receiving a glucocorticoid dose equivalent to 20 mg or more of prednisone daily for 1 month or more who also have another cause of immunocompromise need prophylaxis against *Pneumocystis jirovecii* pneumonia.²⁷ They should also receive appropriate immunizations before starting glucocorticoids. Live-virus vaccines should not be given to these patients until they have been off glucocorticoids for 1 month.

Glucocorticoids and bone loss

Glucocorticoids are associated with bone loss and fracture, which can occur within the first few months of use and with dosages as low as 2.5 to 7.5 mg orally daily.²⁸ Therefore, glucocorticoid-induced bone loss has to be treated aggressively, particularly in patients who are older and have a history of fragility fracture.

For patients with GCA who need glucocorticoids in doses greater than 5 mg orally daily for more than 3 months, the following measures are advised to decrease the risk of bone loss:

- Weight-bearing exercise
- Smoking cessation
- Moderation in alcohol intake
- Measures to prevent falls²⁹
- Supplementation with 1,200 mg of calcium and 800 IU of vitamin D.³⁰

Pharmacologic therapy should be initiated in men over age 50 who have established osteoporosis and in postmenopausal women with established osteoporosis or osteopenia. For men over age 50 with established osteopenia, risk assessment with the glucocorticoid-corrected FRAX score (www.sheffield.ac.uk/FRAX/) should be performed to identify those at high risk in whom pharmacologic therapy is warranted.³¹

Bisphosphonates are the first-line therapy for glucocorticoid-induced osteoporosis.³²

Teriparatide is the second-line therapy and is used in patients who cannot tolerate bisphosphonates or other osteoporosis therapies, and in those who have severe osteopo-

rosis, with T scores of -3.5 and below if they have not had a fracture, and -2.5 and below if they have had a fragility fracture.³³

Denosumab, a monoclonal antibody to an osteoclast differentiating factor, may be beneficial for some patients with glucocorticoid-induced osteoporosis.³⁴

To assess the efficacy of therapy, measuring bone mineral density at baseline and at 1 year of therapy is recommended. If density is stable or improved, then repeating the measurement at 2- to 3-year intervals is suggested.

■ TOCILIZUMAB: A STEROID-SPARING MEDICATION

Due to the adverse effects of long-term use of glucocorticoids and high rates of relapse, there is a pressing need for medications that are more efficacious and less toxic to treat GCA.

The European League Against Rheumatism, in its 2009 management guidelines for large-vessel vasculitis, recommend using an adjunctive immunosuppressant agent.¹⁹ In the case of GCA, they recommend using methotrexate 10 to 15 mg/week, which has shown modest evidence of reducing the relapse rate and lowering the cumulative doses of glucocorticoids needed.^{35,36}

Studies of tumor necrosis factor inhibitors and abatacept have not yielded significant reductions in the relapse rate or decreased cumulative doses of prednisone.^{37,38}

Advances in treatment for GCA have stagnated, but recent trials^{39,40} have evaluated the IL-6 receptor alpha inhibitor tocilizumab, given the central role of IL-6 in the pathogenesis of GCA. Case reports have revealed rapid induction and maintenance of remission in GCA using tocilizumab.^{41,42}

Villiger et al³⁹ performed a randomized, placebo-controlled trial to study the efficacy and safety of tocilizumab in induction and maintenance of disease remission in 30 patients with newly diagnosed GCA. The primary outcome, complete remission at 12 weeks, was achieved in 85% of patients who received tocilizumab plus tapered prednisolone, compared with 40% of patients who received placebo plus tapering prednisolone. The tocilizumab group also had favorable results in secondary outcomes including relapse-

Bisphosphonates are the first-line therapy for glucocorticoid-induced osteoporosis

free survival at 52 weeks, time to first relapse after induction of remission, and cumulative dose of prednisolone.

The GiACTA trial. Stone et al⁴⁰ studied the effect of tocilizumab on rates of relapse during glucocorticoid tapering in 251 GCA patients over the course of 52 weeks. Patients were randomized in a 2:1:1:1 ratio to 4 treatment groups:

- Tocilizumab weekly plus prednisone, with prednisone tapered over 26 weeks
- Tocilizumab every other week plus prednisone tapered over 26 weeks
- Placebo plus prednisone tapered over 26 weeks
- Placebo plus prednisone tapered over 52 weeks.

The primary outcome was the rate of sustained glucocorticoid-free remission at 52 weeks. Secondary outcomes included the remission rate, the cumulative glucocorticoid dose, and safety measures. At 52 weeks, the rates of sustained remission were:

- 56% with tocilizumab weekly
- 53% with tocilizumab every other week
- 14% with placebo plus 26-week prednisone taper
- 18% with placebo plus 52-week taper.

Differences between the active treatment groups and the placebo groups were statistically significant ($P < .001$).

The cumulative dose of prednisone in tocilizumab recipients was significantly less than in placebo recipients. Rates of adverse events were similar. Ultimately, the study showed that tocilizumab, either weekly or every other week, was more effective than prednisone alone at sustaining glucocorticoid-free remission in patients with GCA.

However, the study also raised questions about tocilizumab's toxic effect profile and its long-term efficacy, as well as who are the optimal candidates for this therapy. Data on long-term use of tocilizumab are primarily taken from its use in rheumatoid arthritis.⁴³ As of this writing, Stone et al are conducting an open-label trial to help provide long-term safety and efficacy data in patients with GCA. In the meantime, we must extrapolate data from the long-term use of tocilizumab in rheumatoid arthritis.

Tocilizumab and lower gastrointestinal tract perforation

One of the major adverse effects of long-term use of tocilizumab is lower gastrointestinal tract perforation.

Xie et al,⁴⁴ in 2016, reported that the risk of perforation in patients on tocilizumab for rheumatoid arthritis was more than 2 times higher than in patients taking a tumor necrosis factor inhibitor. However, the absolute rates of perforation were low overall, roughly 1 to 3 per 1,000 patient-years in the tocilizumab group. Risk factors for perforation included older age, history of diverticulitis or other gastrointestinal tract condition, and prednisone doses of 7.5 mg or more a day.

Does tocilizumab prevent blindness?

Another consideration is that tocilizumab may not prevent optic neuropathy. In the GiACTA trial, 1 patient in the group receiving tocilizumab every other week developed optic neuropathy.⁴⁰ Prednisone had been completely tapered off at the time, and the condition resolved when glucocorticoids were restarted. Thus, it is unknown if tocilizumab would be effective on its own without concomitant use of glucocorticoids.

Vision loss is one of the most severe complications of GCA, and it is still unclear whether tocilizumab can prevent vision loss in GCA. Also, we still have no data on the effect of tocilizumab on histopathologic findings, and whether biopsy yield diminishes over time. We hope future studies will help guide us in this regard.

No guidelines on tocilizumab yet

Clinical guidelines on the appropriate use of tocilizumab in GCA are lacking. The American College of Rheumatology and the European League Against Rheumatism have yet to publish updated guidelines with comments on use of tocilizumab. Therefore, it is unclear if tocilizumab is a first-line treatment in GCA, as its efficacy alone without glucocorticoids and its long-term safety in GCA patients have not been studied.

Treatment with tocilizumab should be individualized; it should be considered in patients who have had adverse effects from glucocorticoids, and in patients who expe-

Much work needs to be done to define the safety of tocilizumab and which patients should receive it

rience a flare or cannot have their glucocorticoid dose lowered to an appropriate range.

The optimal duration of tocilizumab therapy is also unknown. However, using the GiACTA study as a rough guide, we try to limit its use to 1 year until additional data are available.

Patients on IL-6 inhibition may have suppressed C-reactive protein regardless of disease activity.⁴³ Therefore, this laboratory value may not be reliable in determining active disease in patients on tocilizumab.

The GiACTA trial has shown an impres-

sive improvement in the relapse-free remission period in patients with GCA taking tocilizumab. However, much work needs to be done to define the safety of this medication and determine which patients should be started on it. In the meantime, we recommend starting high-dose glucocorticoid therapy as soon as the diagnosis of GCA is suspected. In patients who do not tolerate glucocorticoids or whose disease flares during glucocorticoid taper, we recommend starting treatment with tocilizumab either once a week or every other week for at least 1 year. ■

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