Annals of Internal Medicine®

In the Clinic®

Giant Cell Arteritis

Diagnosis

Treatment

Practice Improvement

Giant cell arteritis (GCA) is a chronic inflammatory disease that affects medium-sized and large arteries, most typically the aortic arch and its primary and distal branch vessels (1). GCA is the most common form of vasculitis in older adults but is rare in persons younger than 50 years. Women are affected 2 to 3 times more than men. The absence of an identifiable cause and dramatic improvement with corticosteroid therapy has led to the presumption that GCA is an autoimmune disease.

The CME quiz is available at www.annals.org. Complete the quiz to earn up to 1.5 CME credits.

Physician Writer
Gary S. Hoffman, MD, MS

doi:10.7326/AITC201611010

CME Objective: To review current evidence for diagnosis, treatment, and practice improvement of giant cell arteritis.

Funding Source: American College of Physicians.

Acknowledgment: The author thanks Drs. Maria C. Cid and José Hernández-Rodríguez for their review of this paper.

Disclosures: Dr. Hoffman, ACP Contributing Author, reports personal fees from Roche. Disclosures can also be viewed at www.acponline.org/authors /icmje/ConflictOf InterestForms.do?msNum=M16-0974.

With the assistance of additional physician writers, the editors of ***Annals of Internal Medicine*** develop **In the Clinic** using **MKSAP** and other resources of the American College of Physicians.

In the Clinic does not necessarily represent official ACP clinical policy. For ACP clinical guidelines, please go to https://www.acponline.org/clinical_information/guidelines/.

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

Pathogenesis of giant cell arteritis (GCA) involves activation of dendritic cells in the vessel adventitia–media border that recruit T cells and monocytes into the vessel wall. Macrophages coalesce in the media, forming multinucleated giant cells secreting metalloproteinases and reactive oxygen species that compromise the vessel's structural integrity. Simultaneously, intimal proliferation can reduce blood flow and induce partial or complete ischemia of the affected tissue bed.

Common clinical features of GCA include headache, scalp and temporal artery tenderness, and symptoms of polymyalgia rheumatica (PMR). Masticatory muscle ischemia accounts for symptoms of "jaw claudication" with chewing. Although large vessel symptoms are present in a few patients, evidence of large vessel involvement is nearly universal on autopsy and common on vascular imaging studies. Thus, the older terms "temporal arteritis" and "cranial arteritis" have fallen into disfavor because they understate involvement of other vessels that may significantly affect diagnosis and prognosis. Vision symptoms, including monocular or binocular blindness, and aortic aneurysm rupture or dissection are the most feared complications of GCA. Diagnosis is based on a characteristic pattern of symptoms, physical examination findings, elevated acute-phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), biopsy findings, and vascular imaging. High-dose corticosteroid therapy typically leads to dramatic improvement within 5 days and reduces the risk for vision loss.

The incidence of GCA increases with age. The mean age of affected individuals is 74–76 years. A recent study from Sweden of 840 biopsy-positive GCA patients (626 female [75%]) showed that for each additional decade beyond 50 years, the per 100 000 persons/year incidence increased from 2.0 (age 50–60 y) to 11.8 (age 61–70) to 31.3 (age 71–80) (2). Women are affected more often than men (2–3:1), and GCA is more common among whites, persons of Nordic or Northern European ancestry (incidence, 27–56 per 100 000 persons/y), and others residing in northern latitudes (17–23 per 100 000 persons/y). GCA is uncommon in persons of African, Asian, Hispanic, and Arab descent (3). It has polygenic influences—certain genetic markers, such as HLA-DRB1*04 (both alleles 04:01, 04:04) and non-HLA gene polymorphisms (e.g., PTPN22), seem to play important roles in pathogenesis (3–5). However, these associations are not so precise that genetic screening for diagnostic purposes is recommended.

Exogenous factors that increase the risk for GCA include history of or current smoking (6, 7). In 1 large study, smoking was found to be a risk factor for GCA in women but not men. Given that only about 14% of patients in this study were ever smokers vs. about 3% of controls ($P = 0.00006$, odds ratio [OR], 5.48 [95% CI, 2.12–14.19]), it was suggested that smoking might be an important cofactor for GCA pathogenesis in only a few patients (6).

Recent reports indicate a possible association of GCA with varicella zoster virus (VZV) (8, 9). Although these provocative data may have etiologic and therapeutic implications, it would be premature to use anti-VZV therapies in GCA until the findings are confirmed and data from clinical treatment trials become available.

1. MKSAP 17: Giant cell arteritis. In: MKSAP 17. Medical Knowledge Self-Assessment Program, 17th ed. Philadelphia: American College of Physicians; 2015.
2. Mohammad AJ, Nilsson JA, Jacobsson LT, et al. Incidence and mortality rates of biopsy-proven giant cell arteritis in southern Sweden. Ann Rheum Dis 2015; 74:993–997. [PMID: 24442881]
3. Borchers AT, Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmunity Rev. 2012; 11:544-54. [PMID: 22285588]
4. Mackie SL, Taylor JC, Haroon-Rashid L, Martin S, Dasgupta B, Gough A, et al; UK GCA Consortium. Association of HLA-DRB1 amino acid residues with giant cell arteritis: genetic association study, meta-analysis and geo-epidemiological investigation. Arthritis Res Ther. 2015;17:195. [PMID: 26223536]
5. Carmona FD, Mackie SL, Martín JE, Taylor JC, Vaglio A, Eyre S, et al; Spanish GCA Group. A large-scale genetic analysis reveals a strong contribution of the HLA class II region to giant cell arteritis susceptibility. Am J Hum Genet. 2015;96: 565-80. [PMID: 25817017]
6. Duhaut P, Pinede L, Demolombe-Rague S, Loire R, Seydoux D, Ninet J, et al. Giant cell arteritis and cardiovascular risk factors: a multicenter, prospective case-control study. Groupe de Recherche sur l'Artérite à Cellules Géantes. Arthritis Rheum. 1998;41:1960-5. [PMID: 9811050]
7. Larsson K, Mellstrom D, Nordborg C, et al. Early menopause, low body mass index, and smoking are independent risk factors for developing giant cell arteritis. Ann Rheum Dis. 2006; 65: 529-32. [PMID: 16126796]
8. Gilden D, White T, Khmeleva N, Heintzman A, Choe A, Boyer PJ, et al. Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis. Neurology. 2015; 84:1948-55. [PMID: 25695965]
9. Nagel MA, White T, Khmeleva N, Rempel A, Boyer PJ, Bennett JL, et al. Analysis of Varicella-Zoster Virus in Temporal Arteries Biopsy Positive and Negative for Giant Cell Arteritis. JAMA Neurol. 2015;72: 1281-7. [PMID: 26349037]

What are the characteristic clinical features of GCA?

Approximately 20%–50% of GCA patients have constitutional symptoms, such as fever (usually low-grade but can be as high as 40 °C), malaise, anorexia, and weight loss (**Table 1**) (10). Thus, GCA should be considered in the differential diagnosis of fever of unknown origin in patients older than 50 years (11). Most patients report headache, either diffuse or localized in the temporal or occipital regions. Approximately 40%–70% of patients have scalp or temporal artery pain, and they may note scalp or temporal tenderness when combing their hair or wearing a hat or eyeglasses. Vision symptoms, such as amaurosis fugax, blurred vision, diplopia, and blindness (monocular and binocular) occur in 12%–40% of patients. Binocular blindness most often occurs sequentially over days to a week; concurrent bilateral vision loss is less common. Occlusion of the ophthalmic or posterior ciliary arteries can result in anterior ischemic optic neuropathy and sudden vision loss that is often painless but irreversible (10). Blindness infrequently occurs as a result of central retinal artery occlusion or occipital infarction. Masticatory muscle ischemia accounts for symptoms of fatigue or jaw claudication in 30%–70% of patients. Some patients report muscle aches and stiffness in a distribution characteristic of PMR (e.g., symptoms affecting the neck, shoulder, and pelvic girdle).

Although GCA often affects tributaries of the external carotid arteries, any primary branch of the aorta can be involved. Large vessel vasculitis (LVV) symptoms and signs occur in approximately 25% of patients (12–14) but the disorder is usually subclinical (15, 16). Large vessel involvement may also occur in patients who do not have the typical features of cranial involvement (i.e., headache, temporal artery pain, jaw claudication) (10). Approximately 50% of patients with GCA of the subclavian or axillary arteries have negative results on temporal artery biopsy (10, 17). Thus, GCA should be considered in elderly patients

Table 1. **Spectrum of Clinical Features of Giant Cell Arteritis***

Feature Manifestation	*Characteristics*
Vascular injury	
Common features (30%–80% of patients)	
Headache	No particular pattern; severe, sometimes throbbing; often localized
Scalp tenderness	Often temporal; elicited by touching, grooming, or wearing glasses; temporal artery can be thickened, tender, or nodular
Jaw claudication	Elicited by prolonged talking or chewing
Less common features (<20% of patients)	
Ocular symptoms	Partial or complete vision loss, amaurosis fugax, or diplopia
Blindness	Unilateral or bilateral; usually permanent
Painful dysphagia	Sore throat
Respiratory symptoms	Dry, nonproductive cough
Limb claudication	Elicited by use of arms; combined with paresthesias
Absent or asymmetrical pulses	
Asymmetrical blood pressure readings	
Infrequent features (<5% of patients)	
Ischemia of the central nervous system	Typically vertebrobasilar insufficiency, imbalance, cortical blindness, confusion
Tongue claudication	
Aortic regurgitation	Dilatation of the proximal aorta
Myocardial infarction	
Peripheral neuropathy	
Deafness	
Tissue gangrene	Scalp, tongue, or extremities
Systemic inflammation	
Common features (40%–100% of patients)	
Intense acute-phase response	Elevated erythrocyte sedimentation rate, C-reactive protein level, interleukin-6 level, levels of other acute-phase proteins; elevated liver function test results; thrombocytosis
Anemia	Normocytic, normochromic
Polymyalgia rheumatica	Pain and morning stiffness, particularly affecting neck, shoulders, and pelvic girdle muscles
Wasting syndrome	Fever, anorexia or weight loss, malaise, night sweats, depression

* *Table modified and reprinted with permission from reference 10.*

10. Weyand CM, Goronzy JJ. Giant-cell arteritis and polymyalgia rheumatica. Ann Intern Med. 2003; 139:505-15. [PMID: 13679329]
11. MKSAP 16: Giant cell arteritis. In: MKSAP 16. Medical Knowledge Self-Assessment Program, 16th ed. Philadelphia; American College of Physicians; 2013.

Table 2. **Differential Diagnosis of Giant Cell Arteritis**

Disease	*Distinguishing Features*
Common or migraine headache	Normal eryrthrocyte sedimentation rate and C-reactive protein levels Absence of temporal artery or large vessel abnormalities Absence of polymyalgia rheumatica symptoms
Atherosclerosis of large vessels	Claudication most common in legs Transient ischemic attack or stroke occurs in the absence of inflammatory signs and symptoms
Takayasu arteritis	Affects young women predominately (mean age of onset 26 y)
Headache and temporal artery involvement due to other forms of vasculitis*	Characteristic features of vasculitis will be present

* *Granulomatosis with polyangiitis (Wegener granulomatosis), eosinophilic angiitis with granulomatosis (Churg-Strauss syndrome), polyarteritis nodosa, hepatitis-associated vasculitis.*

with large and medium-sized vessel symptoms. Involvement of the subclavian vessels may result in arm claudication or subclavian steal syndrome (11). Aortic valve regurgitation may occur with GCA involvement of the proximal ascending aorta. Aortic aneurysm and dissection are other potential complications.

What should the physical examination include?

The clinician should carefully examine the head and neck. Physical findings may include erythema, tenderness, nodularity and thickening of the temporal artery, and decreased pulse (compared with the unaffected temporal artery). The eyes should be examined to assess visual acuity and visual fields and to evaluate the optic disc and retinal vessels. Pulse and blood pressure should be assessed in all 4 limbs to determine whether asymmetry is present. Subclavian artery lesions may be associated with differences in pulse and blood pressure in the involved versus the uninvolved arm. Clinicians should listen for bruits over the thoracic and abdominal aorta and for aortic regurgitation. Involvement of the carotid or subclavian vessels may manifest as audible bruits in the neck or supraclavicular fossa, respectively.

What other diagnoses should clinicians consider?

The differential diagnosis of GCA includes common or migraine headache and atherosclerotic disease (**Table 2**). The finding of a thoracic aortic aneurysm in the absence of compelling clinical features of GCA should prompt consideration of other diagnoses, such as noninflammatory aortic diseases, infection, or other forms of vasculitis and systemic autoimmune conditions. Because GCA affects elderly patients, diagnostic confusion is likely, especially in patients with multiple comorbid conditions. For example, diagnostic uncertainty may occur in the setting of claudication, stroke, or vision loss (i.e., whether these symptoms are due to atherosclerosis, embolic events, or GCA), joint pain (e.g., osteoarthritis, microcrystalline disease), carpal tunnel syndrome, bursitis and tendinitis, or hand edema. While it may be tempting to ascribe such findings to GCA, it is important to consider that contemporaneous events may not indicate disease relationships. For example, inflammatory small joint disease (e.g., hands, wrists), bursitis, and tendinitis have been reported in a few patients with GCA, and a meta-analysis of 21 studies found that the presence of synovitis on examination significantly reduced the likelihood of positive results on a temporal artery biopsy (18).

Approximately 30%–50% of patients with GCA also have PMR, and these disorders share demographic features. Overall, PMR is 2–3 times more common than GCA. PMR is characterized by morning stiffness in the neck, shoulder girdle, and proximal upper extremities, with or without pain, that lasts at least 30 minutes. Although similar symptoms occur less often in the pelvic girdle, including the hips and thighs, these

12. 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;48:3522-31. [PMID: 14674004]
13. Gonzalez-Gay MA, Garcia-Porrua C, Pineiro A, et al. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from Northwestern Spain. A population based study. Medicine. 2004;83: 335-41. [PMID: 15525845].
14. Kermani TA, Warrington KJ, Crowson CS, Ytterberg SR, Hunder GG, Gabriel SE, et al. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. Ann Rheum Dis. 2013; 72:1989-94. [PMID: 23253927]
15. Prieto-González S, Arguis P, García-Martínez A, Espígol-Frigolé G, Tavera-Bahillo I, Butjosa M, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. Ann Rheum Dis. 2012;71:1170-6. [PMID: 22267328]
16. Ostberg G. Morphological changes in the large arteries in polymyalgia arteritica. Acta Med Scand Suppl. 1972; 533:135-59. [PMID: 4508179]

features may dominate in some patients. Onset of PMR symptoms is often subacute, occurring over a period of less than 2 weeks. Duration of symptoms for more than 4 weeks increases the likelihood of diagnosis. Low-grade fever, fatigue, depression, anorexia, and weight loss occur in a few patients. The ESR is usually elevated (>40 mm/h). Because PMR is not associated with a specific diagnostic clinical or laboratory finding, it is essential to rule out possible mimics, such as infection or inflammatory muscle, endocrine (e.g., hypothyroidism), and systemic autoimmune diseases (**Table 3**). New-onset, atypical headache, and other vascular symptoms are not features of PMR and are more suggestive of GCA. Approximately 20% of patients presenting only with PMR symptoms may develop obvious features of GCA. Considering the shared demographic features and overlapping temporal artery cytokine profiles, some investigators suggest that PMR and GCA are parts of a clinical spectrum (19, 20).

Table 3. **Differential Diagnosis of Polymyalgia Rheumatica**

Disease	*Distinguishing Features*
Elderly-onset rheumatoid arthritis	Synovitis, distal involvement more typical in rheumatoid arthritis
Polymyositis/dermatomyositis	Proximal weakness, increase in muscle enzymes, rash (dermatomyositis), electromyographic abnormalities
Fibromyalgia	Proximal and distal symptoms, normal eryrthrocyte sedimentation rate and C-reactive protein levels
Late-onset spondyloarthritis	Axial symptoms, synovitis, HLA B27 association in most patients
Crystalline arthritis	Usually acute, asymmetrical involvement, synovitis
Cancer-associated muscle pain	Unrelenting symptoms, usually unresponsive to corticosteroids
Infection-associated muscle pain	Diffuse, self-limited (viral infections), or resolution of symptoms with antibiotic treatment
Osteoarthritis	Insidious onset, brief morning stiffness, normal eryrthrocyte sedimentation rate and C-reactive protein levels
Hypothyroidism	Normal acute phase reactants, elevated thyroid-stimulating hormone

Takayasu arteritis is a rare LVV that mainly affects young women (9:1 ratio); typical age of onset is between 15 and 25 years (1, 11). The aorta and its major branches are primarily affected. Neck and extremity pulses may be diminished or absent and are often accompanied by bruits. Laboratory findings typically include elevated ESR. The imaging findings and histomorphologic features on biopsy found in Takayasu arteritis may be indistinguishable from those found when GCA affects larger vessels (10). Thus, these 2 conditions may represent a spectrum of presentation rather than distinct diseases (21, 22).

What is the role of laboratory testing?

Marked elevations in ESR and CRP are often found in untreated patients and provide circumstantial evidence for GCA if other reasons for these abnormalities are not identified (e.g., infection, cancer). In 1 study (23) that included 177 patients with biopsy-proven GCA, elevated CRP and ESR were 86.9% and 84.1% sensitive, respectively, for positive results on temporal artery biopsy. ESR and CRP were elevated in 159 (89.8%) of GCA patients, whereas 10.2% had normal ESR and CRP at the time of diagnosis. There was good concordance between ESR and CRP, as both were either elevated or normal in 92% of patients; about 8% of patients had discordant results between CRP and ESR (23). Several studies with smaller sample sizes are more guarded about the utility of ESR and CRP. In 1 study of 25 patients, 24% with biopsy-proven GCA before treatment had a normal ESR (24). Thus, while usually valuable at initial presentation, ESR and CRP are imperfect markers of GCA. A normal ESR or CRP does not exclude GCA, and a diagnostic evaluation with biopsy or imaging should be done when GCA is suspected.

Many patients with GCA have hypochromic or normochromic or

17. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. Arthritis Rheum. 1999;42:311-7. [PMID: 10025926]
18. Smetana GW, Shmerling RH. Does this patient have temporal arteritis? JAMA. 2002;287:92-101. [PMID: 11754714]
19. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet. 2008; 372:234-45. [PMID: 18640460]
20. Weyand CM, Hicok KC, Hunder GG, Goronzy JJ. Tissue cytokine patterns in patients with polymyalgia rheumatica and giant cell arteritis. Ann Intern Med. 1994; 121:484-91. [PMID: 8067646]
21. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? Medicine (Baltimore). 2009;88: 221-6. [PMID: 19593227]
22. Grayson PC, Maksimowicz-McKinnon K, Clark TM, Tomasson G, Cuthbertson D, Carette S, et al; Vasculitis Clinical Research Consortium. Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. Ann Rheum Dis. 2012;71:1329-34. [PMID: 22328740]

23. Kermani TA, Schmidt J, Crowson CS, Ytterberg SR, Hunder GG, Matteson EL, et al. Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. Semin Arthritis Rheum. 2012;41:866-71. [PMID: 22119103]
24. Weyand CM, Fulbright JW, Hunder GG, et al. Treatment of giant cell arteritis. Interleukin-6 as a Biologic Marker of Disease Activity. Arthritis Rheum. 2000; 43:1041–1048.
25. Narváez J, Bernad B, Roig-Vilaseca D, García-Gómez C, Gómez-Vaquero C, Juanola X, et al. Influence of previous corticosteroid therapy on temporal artery biopsy yield in giant cell arteritis. Semin Arthritis Rheum. 2007;37:13-9. [PMID: 17360027]
26. 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; 120:987-92. [PMID: 8185147]
27. Taylor-Gjevre R, Vo M, Shukla D, Resch L. Temporal artery biopsy for giant cell arteritis. J Rheumatol. 2005;32: 1279-82. [PMID: 15996065]
28. Breuer GS, Nesher G, Nesher R. Rate of discordant findings in bilateral temporal artery biopsy to diagnose giant cell arteritis. J Rheumatol. 2009; 36:794-6. [PMID: 19228656]
29. Bienvenu B, Ly KH, Lambert M, Agard C, André M, Benhamou Y, et al; Groupe d'Étude Français des Artérites des gros Vaisseaux, under the Aegis of the Filière des Maladies Auto-Immunes et Auto-Inflammatoires Rares. Management of giant cell arteritis: Recommendations of the French Study Group for Large Vessel Vasculitis (GEFA). Rev Med Interne. 2016;37:154-65. [PMID: 26833145]
30. Hall S, Persellin S, Lie JT, O'Brien PC, Kurland LT, Hunder GG. The therapeutic impact of temporal artery biopsy. Lancet. 1983;2:1217-20. [PMID: 6139569]
31. Rodriguez-Valverde V, Sarabia JM, González-Gay MA, Figueroa M, Armona J, Blanco R, et al. Risk factors and predictive models of giant cell arteritis in polymyalgia rheumatica. Am J Med. 1997;102: 331-6. [PMID: 9217613]

normocytic anemia, and thrombocytosis (10). Liver function test abnormalities, particularly elevated alkaline phosphatase levels, may also be found. No autoantibody tests help identify GCA.

What is the role of temporal artery biopsy in diagnosis?

Diagnosis of GCA is best established by the characteristic histologic lesions on temporal artery biopsy. Ideally, the biopsy should be done before treatment is instituted. Corticosteroid therapy initiated at least 15 days before biopsy does not seem to diminish positive findings (25, 26). Given the increased risk for vision loss in GCA, corticosteroid therapy should not be withheld pending biopsy.

Typical histologic features include mononuclear cell infiltrates that are most prominent in the adventitia and media. Lymphocytes, macrophages, dendritic cells, and giant cells are associated with breakdown of elastic lamina (**Figure**). Approximately 50% of biopsies compatible with GCA lack all of these features, and in some biopsies, only an isolated, periadventitial inflammatory infiltrate or vasculitis of small vessels surrounding the temporal artery is present. Because skip lesions (i.e., diseased segments alternating with normal-appearing tissue) are common, multiple sections of the artery should be examined to increase the diagnostic yield of a given temporal artery biopsy specimen. In 1 large study of 136 biopsies, specimens ≥1.0 cm were more likely to be positive than those <1.0 cm ($P = 0.037$) (27). Although the preferred length of biopsy specimen has not been determined, the diagnosis is more likely to be accurate when it is at least 1 cm long and from which multiple histologic sections are examined. Whether performed simultaneously or sequentially, bilateral biopsies may increase diagnostic yield by 3%–17% (28, 29). Given that results on temporal artery biopsy are positive in 49%–85% of patients with unequivocal GCA (29), negative results may be misleading and discourage less-experienced practitioners to treat a patient with convincing clinical evidence of GCA. Many investigators consider PMR part of the same clinical spectrum as GCA and note that patients with PMR symptoms might later present with GCA (19, 20).

In a classic study of 134 patients from Olmsted County, Minnesota, who had temporal artery biopsy for suspected GCA, 46 patients (34%) had positive results and 88 had negative results. Follow-up of the negative results revealed a wide range of diagnoses, including 8 patients who were ultimately diagnosed with GCA and 31 who were diagnosed with PMR. Thus, 44% (39 of 88) of biopsy-negative patients had an ultimate diagnosis in the PMR–GCA spectrum (30).

These data highlight the necessity of carefully following patients with negative results on temporal artery biopsies, especially those with symptoms of PMR, for emerging features of GCA. A study of 227 patients (137 with PMR only; 90 with PMR and biopsy-proven GCA) provides complementary findings (31). Patients who were aged ≥70 years at the time of disease onset and had recent headache, jaw claudication, and an abnormal temporal artery on examination were found to have a high risk for arteritis. This subset represented approximately one fourth of the group with PMR and biopsy-proven GCA. On the other hand, patients who were aged <70 years at the time of disease onset who had no new headache and a normal temporal artery examination were found to have very low risk for GCA that was further reduced by the presence of synovitis (31). One of the major limitations of this study was that not all patients in the PMR-only group had temporal artery biopsy and, thus, it is possible that some may have had subclinical GCA.

A meta-analysis of 21 studies found that 2 historical features, jaw claudication and diplopia, increased the likelihood of positive results on temporal artery biopsy by a factor of 4.2 and 3.4, respectively. An abnormal temporal artery (e.g., beading, tenderness, and swelling) on physical examination also increased positive biopsy yield, whereas a normal ESR markedly reduced the likelihood of positive results (likelihood ratio, 0.2) (18).

The risk–benefit ratio of a "no-biopsy strategy" in patients with compelling high-probability clinical diagnosis of GCA should be assessed in prospective studies with long-term follow-up to determine how often such patients are later diagnosed with illnesses other than GCA (32).

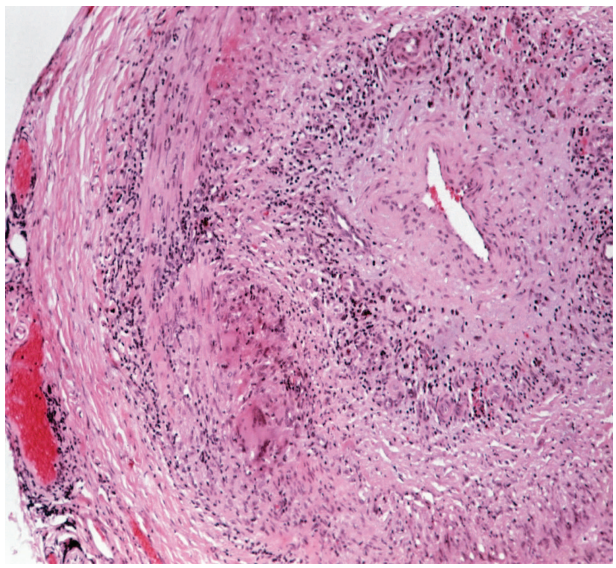
What is the value of imaging studies?

Vascular imaging studies may be performed as part of the initial evaluation of patients with suspected GCA or to detect complications of the disease during follow-up. In experienced hands, traditional ultrasonography and color duplex ultrasonography (CDUS) of the temporal artery has approximately 40%–75% sensitivity and 79%–83% specificity for diagnosis of GCA. Hypoechoic edematous wall swelling (halo sign) is most suggestive of GCA. CDUS of the carotid and axillary arteries may further increase diagnostic accuracy. Further advantages of CDUS include safety and low cost. A multicenter study is under way to compare the diagnostic performance of CDUS and temporal artery biopsy (Clinicaltrials.gov: NCT00974883). Standardization and validation of imaging techniques are needed to achieve reproducible and observer-independent results (33, 34). CDUS is not practical for the study of the entire aorta and all of its primary branches.

Magnetic resonance imaging (MRI) of the temporal artery has also been evaluated in patients with suspected GCA. Temporal artery thickening and enhancement are MRI features of GCA. In a study of 185 patients with suspected GCA, MRI had a sensitivity of 78.4% and specificity of 90.4% in detecting temporal artery involvement in patients with a clinical diagnosis of GCA. In a substudy, which used biopsy-proven disease as the gold-standard, MRI had a sensitivity of 88.7% and specificity of 75%. It was most accurate in untreated patients and those who had received steroid therapy for ≤5 days (35). As with CDUS, MRI proponents hope that this technique will identify biopsy-negative GCA patients or ultimately replace biopsy. However, greater standardization of technique and experience is required before they can be recommended in routine practice.

While once the standard modality for large vessel imaging, catheter-directed invasive angiography with contrast is less commonly used. Invasive angiography provides excellent large and medium-sized vessel resolution but does not specifically evaluate characteristics of the vessel wall. It requires iodinated contrast, involves radiation exposure, and is relatively contra-

Figure. **Temporal artery biopsy findings in giant cell arteritis include inflammatory infiltrates comprising lymphocytes, dendritic cells, macrophages, and multinucleated giant cells.**



The adventitia and media are the most intense sites of inflammation.

32. Hoffman GS. Giant cell arteritis: Commentary on recommendations of the French Study Group for Large Vessel Vasculitis (GEFA) [Editorial]. Rev Med Interne. 2016;37:151-2. [PMID: 26781693]
33. Salvarani C, Silingardi M, Ghirarduzzi A, Lo Scocco G, Macchioni P, Bajocchi G, et al. Is duplex ultrasonography useful for the diagnosis of giant-cell arteritis? Ann Intern Med. 2002;137:232-8. [PMID: 12186513]
34. Prieto-González S, Arguis P, Cid MC. Imaging in systemic vasculitis. Curr Opin Rheumatol. 2015;27:53-62. [PMID: 25405825]
35. Klink T, Geiger J, Both M, Ness T, Heinzelmann S, Reinhard M, et al. Giant cell arteritis: diagnostic accuracy of MR imaging of superficial cranial arteries in initial diagnosis-results from a multicenter trial. Radiology. 2014;273:844-52. [PMID: 25102371]

indicated in patients with renal impairment and iodine allergy. The risk for catheter-insertion site hematomas and cholesterol emboli is another concern, especially in frail elderly persons and patients receiving anticoagulant therapies. Nonetheless, angiography is preferred for placing intravascular stents for aortic aneurysms and recording intravascular pressures in patients in whom peripheral cuff pressure measurements are unreliable (e.g., innominate artery or bilateral subclavian artery stenoses or occlusions) (34).

18 F-fluorodeoxyglucose-positron emission tomography (FDG-PET) has been used as a tool for initial diagnosis and longitudinal assessment of disease activity in patients with GCA involvement of large vessels. Anatomical resolution is improved by combining FDG-PET with computed tomography angiography (CTA), which may detect concentric mural thickening not apparent with PET. However, the combination of CTA and PET adds concerns about radiation exposure, iodinated-contrast allergies, and expense (34).

In a recent meta-analysis of patients with GCA, FDG-PET had high sensitivity (90% [CI, 79%–93%]) and specificity (98% [CI, 94%–99%]) for the diagnosis of large vessel inflammation compared with controls (36).

PET can be helpful when the initial diagnosis is uncertain and for making judgments about disease activity and treatment strategies. MRI does not engender risks for radiation exposure and provides excellent anatomical renderings of large vessel anatomy; however, it may be less reliable in measuring disease activity (e.g., enhancement) (37). MRI with gadolinium contrast is contraindicated in patients with advanced renal impairment.

When should the clinician consider consulting a rheumatologist or other specialist?

Rheumatology consultation may be most useful in patients with atypical symptoms, when diagnosis of GCA is uncertain (i.e., negative biopsy results), to help determine the need for biopsy, and in patients with possible large vessel involvement (e.g., critical organ ischemia or aortic aneurysm). Urgent ophthalmology consultation is advised for patients with symptoms of vision loss or to determine whether a visual aberration is due to GCA or another condition. Cardiology consultation should be considered for evaluation of aortic murmurs, aortic aneurysms, and cardiac ischemia. The complexity of patients with large vessel involvement may require consultation from several specialties, including cardiothoracic and vascular surgery for management of aortic aneurysms or critical organ ischemia. Finally, surgical consult is necessary for obtaining a temporal artery biopsy. Different surgical specialists, including ophthalmologists, plastic surgeons, and general surgeons, can perform temporal artery biopsies.

36. Soussan M, Nicolas P, Schramm C, Katsahian S, Pop G, Fain O, et al. Management of large-vessel vasculitis with FDG-PET: a systematic literature review and meta-analysis. Medicine (Baltimore). 2015;94: e622. [PMID: 25860208]
37. Tso E, Flamm SD, White RD, Schvartzman PR, Mascha E, Hoffman GS. Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. Arthritis Rheum. 2002;46:1634-42. [PMID: 12115196]

Diagnosis... The diagnosis of GCA should be considered in patients older than 50 years who present with new-onset, localized, unilateral headache; ischemic symptoms in the cervicocranial and upper vascular territories (e.g., jaw claudication, vision aberration or loss); and muscle stiffness of the neck, shoulder, or pelvic girdle. Typical physical examination findings include tenderness, swelling, and erythema over the temporal artery and flow abnormalities of large vessels (e.g., bruits, asymmetrical pulse or blood pressure). Most patients have markedly elevated ESR or CRP. GCA involvement of large vessels is common and subclinical in most patients. Temporal artery biopsy is considered the gold standard for diagnosis.

CLINICAL BOTTOM LINE

What is the overall approach to treatment of GCA?

Treatment of suspected GCA should never be deferred pending biopsy because treatment is rapidly effective and usually prevents vision loss, and biopsy specimens remain interpretable for at least 2 weeks after treatment initiation (1). In virtually all instances, patients with GCA should receive high-dose oral prednisone, or in the case of vision loss, intravenous pulse corticosteroids. The absence of dramatic improvement within 5 days, even in patients with a positive temporal artery biopsy, should raise questions about the accuracy of diagnosis or the presence of comorbid conditions. High-dose prednisone is generally administered for approximately a month (or until signs and symptoms resolve) with a subsequent gradual taper. Patients should be closely monitored for relapse, which is common, and for steroid-related complications. Co-administration of low-dose aspirin may help reduce the risk for blindness. For patients who repeatedly have flares during prednisone tapering, such immunosuppressive drugs as methotrexate (MTX) have been used as corticosteroid-sparing agents, although evidence of effectiveness is limited and controversial (discussed below).

What is the role of steroids in management?

Although randomized, controlled trials to identify the best use of corticosteroid therapy in GCA do not exist, most patients usually receive oral prednisone (40-60 mg/d [or 1 mg/kg]) immediately after diagnosis or if GCA is strongly suspected (**Table 4**). Intravenous pulse corticosteroids (typically methylprednisolone, 1000 mg/d for 3 d) have been advocated for patients with transient, partial, or complete vision loss, but no controlled trials have compared this approach with high-dose oral prednisone. The patient may have partial and rarely complete recovery if treatment is initiated within 24 hours of vision loss (38). Patients who receive high-dose IV corticosteroids should be hospitalized for close monitoring of vision changes and treatment-related side effects.

Oral high-dose prednisone should initially be administered for approximately 2–4 weeks. If all symptoms of active disease have resolved and acute-phase reactants are normal, subsequent dose reduction should begin at a rate of about 10% every 1–2 weeks. Once 10 mg is reached, the dose should be reduced more gradually (i.e., about 1 mg/mo). Attempts to withdraw corticosteroids within 6 months of starting treatment have resulted in relapse rates as high as 90% (39). Slower tapering is less likely to result in relapse. Treatment often lasts about 24 months—some patients may require years of treatment. The ability to withdraw corticosteroids in asymptomatic patients with normal acute-phase reactants does not equate to histologic absence of disease (16). Thus, monitoring for disease progression (i.e., large vessel involvement) remains important in all patients.

What are the rationale and role of aspirin in management?

Whether patients with GCA have increased risks for cardiovascular disease remains controversial (40).

In a study involving a U.K. primary care database, outcomes were compared between 3408 patients with incident GCA and 17 027 age-

38. González-Gay MA, Blanco R, Rodríguez-Valverde V, Martínez-Taboada VM, Delgado-Rodriguez M, Figueroa M, et al. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. Arthritis Rheum. 1998;41:1497-504. [PMID: 9704651]
39. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al; International Network for the Study of Systemic Vasculitides. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 2002;46:1309-18. [PMID: 12115238]
40. Ungprasert P, Koster MJ, Warrington KJ. Coronary artery disease in giant cell arteritis: a systematic review and meta-analysis. Semin Arthritis Rheum. 2015;44:586-91. [PMID: 25434528]

41. Tomasson G, Peloquin C, Mohammad A, Love TJ, Zhang Y, Choi HK, et al. Risk for cardiovascular disease early and late after a diagnosis of giant-cell arteritis: a cohort study. Ann Intern Med. 2014;160:73-80. [PMID: 24592492]
42. Amiri N, De Vera M, Choi HK, Sayre EC, Avina-Zubieta JA. Increased risk of cardiovascular disease in giant cell arteritis: a general population-based study. Rheumatology (Oxford). 2016;55:33-40. [PMID: 26248811]
43. Nesher G, Berkun Y, Mates M, Baras M, Rubinow A, Sonnenblick M. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. Arthritis Rheum. 2004;50:1332-7. [PMID: 15077317]
44. Lee MS, Smith SD, Galor A, Hoffman GS. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. Arthritis Rheum. 2006;54:3306-9. [PMID: 17009265]
45. Spiera RF, Mitnick HJ, Kupersmith M, Richmond M, Spiera H, Peterson MG, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin Exp Rheumatol. 2001;19:495-501. [PMID: 11579707]

and sex-matched controls without baseline cardiovascular disease (myocardial infarction, cerebrovascular accident, or peripheral vascular disease). Patients with GCA had an increased hazard ratio of 1.70 for the combined outcome of these 3 events. Risks were highest in the first month after diagnosis (hazard ratio for the combined outcome, 4.92) (41). A population-based study from Canada yielded similar results for myocardial infarcation and cerbrovascular accident (42).

Whether increased risk for cardiovascular disease is directly related to inflammation or vasculitis, vasculopathy, or factors that promote thrombosis is uncertain. Regardless, this may help to understand results from studies of low-dose aspirin in GCA. Although limited by their retrospective design, these studies suggest that low-dose aspirin (≤100 mg/d) diminished risk for cerebral, ocular, and cardiovascular events in patients with GCA (43, 44). Until more conclusive studies are performed, patients with GCA should receive low-dose aspirin if there are no contraindications (**Table 4**).

When should clinicians consider other immunosuppressant medications?

Relapse is common and requires repeated courses of prednisone, placing the patient at increased risk for steroid-related complications. Numerous studies have examined immunosuppressive medications that could be used as disease-modifying or steroid-sparing agents. The French Study Group for Large Vessel Vasculitis (GEFA) investigators (29) endorse MTX for relapsing GCA while recognizing that efficacy in this context may be modest. The 3 studies that informed these recommendations included only 161 patients (39, 45, 46) and differed in regard to the doses used, steroid tapering schedules, inclusion of new-onset vs. relapsing GCA, and definitions of relapse, making it difficult to directly compare the findings. Two of 3 studies did not demonstrate MTX benefit in reducing relapse rates or cumulative steroid dose. Although no patient developed MTX-induced pneumonitis or pancytopenia, some patients were withdrawn because of leukopenia, increases in hepatic transaminase levels, and mucositis (46). Furthermore, because GCA affects an elderly population in whom reduced renal function is common and MTX clearance depends on renal excretion, potential life-threatening complications are a serious concern that must be weighed against questionable or modest benefit.

Table 4. **Medical Treatment of Giant Cell Arteritis**

Intervention	*Dose*	*Comments*
High-dose corticosteroids—oral	Prednisone or prednisolone 1 mg/kg, up to 60 mg/d	2–4 wk, followed by tapering after remission
High-dose corticosteroids—intravenous	Methylprednisolone 1000 mg/d for 3 d	Consensus endorsement for threatened or actual *acute* vision loss or critical organ ischemia
Low-dose aspirin	81 or 100 mg/d	Prevention of ischemic events, especially blindness; efficacy based on retrospective data;
Methotrexate—oral or subcutaneous injection	15–20 mg/wk	Uncertain benefit; controversial. Hazardous in patients with liver disease, renal impairment, blood dyscrasias, or moderate/heavy alcohol use.
Tocilizumab (humanized monoclonal antibody to IL-6 receptor)	8 mg/kg every 4 wk intravenously*	Phase 2 randomized, controlled trial found marked efficacy for sustained, corticosteroid-independent remissions; not yet approved for giant cell arteritis
Other monoclonal anticytokine antibodies	Variable	Have no benefit (anti-tumor necrosis factor) or have not been studied

IL=*interleukin.*
* *Studies are ongoing with self-administered subcutaneous injections.*

Some studies have examined immunosuppressive agents that block specific components of the immune system involved in the pathogenesis of GCA, such as interleukin (IL-6). Case reports and small observational cohorts of patients with relapsing GCA treated with the humanized monoclonal antibody to the IL-6 receptor tocilizumab have been encouraging and have led to several important studies.

A recent small, phase 2, double-blind, randomized, controlled trial assigned patients to receive corticosteroids plus either tocilizumab (n = 20) or placebo (n = 10). Complete remission by week 12 was achieved in 85% of patients given tocilizumab and 40% of those given placebo (risk difference, 45% [CI, 11–79]; P = 0.0301). By week 52, relapse-free survival was achieved in 85% of patients in the tocilizumab group and 20% in the placebo group (risk difference, 65% [CI, 36–94]; P = 0.0010). In addition, after 52 weeks, patients receiving tocilizumab required 50% less prednisolone (cumulative dose) than those receiving placebo (47).

Ongoing large, double-blind, randomized, controlled trials are being done to attempt to reproduce these results (ClinicalTrials.gov: NCT01450137, NCT01791153). A trial of sirukumab, a fully human anti–IL-6 IgG1-kappa with a high affinity and specificity for binding human IL-6, is also under way (Clinical Trials.gov: NCT02531633).

Because TNF-α is abundant in temporal artery biopsies, some investigations examined the effect of adding TNF-α inhibitors, such as infliximab or adalimumab, to prednisone. These approaches did not increase the number of patients in remission or decrease corticosteroid requirements (48, 49). Such studies suggest that elevated inflammatory reactants may not equate to a dominant role in pathogenesis. Furthermore, although some of these treatment strategies may contribute to decreasing disease morbidity, they do not address the cause of GCA. Cure is unlikely without eliminating causal agents that may play a role in ongoing disease.

How should clinicians monitor patients being treated for GCA?

Once corticosteroid therapy is initiated, patients should be followed closely (initially at 2- to 4-week intervals) for clinical and laboratory signs of disease activity. As noted, most studies show that elevated CRP and ESR are very sensitive markers for predicting positive results on temporal artery biopsy in patients with compelling clinical features of GCA (23). However, the utility of ESR and CRP as an independent sign of relapse is less reliable. In a prospective study of 128 patients with established GCA (mean follow-up, 21 mo), ESR and CRP were both normal in 21% of relapses (50). The lack of specificity of acute-phase reactants in patients with GCA, who may still be receiving steroid therapy and have comorbid conditions, further complicates decision making. Although laboratory values alone should not dictate treatment decisions for GCA, unexplained marked increases in acute-phase reactants in asymptomatic patients should elicit closer follow-up.

Although GCA-related symptoms and laboratory markers tend to respond quickly to corticosteroid therapy, flares are common with tapering of corticosteroids and are often manifested by constitutional symptoms and PMR symptoms. As part of routine follow-up, patients should be asked about cranial symptoms (e.g., headache, vision symptoms, jaw claudication) as well as new onset of large vessel ischemic symptoms (e.g., syncope, transient ischemic attack, claudication). Physical examination should include assessing blood pressure

46. Jover JA, Hernández-García C, Morado IC, Vargas E, Bañares A, Fernández-Gutiérrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2001;134:106-14. [PMID: 11177313]
47. 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;387:1921-7. [PMID: 26952547]
48. Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, et al; Infliximab-GCA Study Group. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Ann Intern Med. 2007;146:621-30. [PMID: 17470830]
49. Seror R, Baron G, Hachulla E, Debandt M, Larroche C, Puéchal X, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial. Ann Rheum Dis. 2014;73:2074-81. [PMID: 23897775]
50. Kermani TA, Warrington KJ, Cuthbertson D, Carette S, Hoffman GS, Khalidi NA, et al; Vasculitis Clinical Research Consortium. Disease Relapses among Patients with Giant Cell Arteritis: A Prospective, Longitudinal Cohort Study. J Rheumatol. 2015;42:1213-7. [PMID: 25877501]

in both arms, listening for bruits, and looking for other signs of clinical relapse. Follow-up should be lifelong.

The GEFA (29) recommends CT or MRI screening for complications of aortitis at diagnosis, then every 2–5 years. Repeated aorta and primary branch vessel imaging also should be performed whenever clinical symptoms or findings suggest new or progressive LVV. The comparative value of regional imaging (e.g., by ultrasonography or other methods) versus imaging of the entire aorta and branch vessels should be considered. Anatomically restricted studies have the disadvantage of not discovering new asymptomatic lesions that are indicative of active disease. Lesions only become symptomatic when flow is diminished to a critical degree and compensatory flow through collateral vessels becomes physiologically inadequate (32).

Because most patients require sustained corticosteroid therapy to achieve remission, treatment-related toxicity is common (51, 52). Patients should be monitored for corticosteroid-related adverse events, including osteoporosis, infection, diabetes, and ocular complications (e.g., cataracts, glaucoma). Treatment for osteoporosis should be provided whenever indicated by bone densitometry and risk factors. Given the risk for GCA-related vision loss and corticosteroid-related ocular complications, ophthalmology follow-up should also be part of routine care.

How should clinicians approach immunizations in patients with GCA?

In an analysis of GCA and matched controls from the U.K. Clinical Practice Research Datalink (a primary care database), herpes zoster infection was found in 1.2% of patients and 0.47% of controls (RR, 2.6 [CI, 1.57–4.15]) (51). This observation raises questions about the safety of live/attenuated vaccines that may be indicated for vulnerable adults (e.g., VZV, Bacille Calmette-Guerin, yellow fever, and typhoid fever) and especially elderly patients receiving corticosteroids. This concern also draws attention to vaccination in general and to case reports and small series of patients developing GCA or PMR within days to 3 months after receiving the influenza vaccine (53, 54). While not suggesting that the risks for vaccination outweigh benefits, these authors have speculated that viral antigen and vaccine adjuvants may rarely trigger autoimmunity.

The European League Against Rheumatism (EULAR) Recommendations for Vaccination in Patients with Autoimmune Inflammatory Rheumatic Diseases (55) advise that in the absence of proof of established immunity, patients may receive standard vaccinations, including influenza, during periods when the disease is stable. Such practice has been shown to be effective in generating protective immune responses. However, it is also recommended that live/attenuated vaccines should be avoided during periods of significant immunosuppression. Decisions about vaccination for VZV and assessment of concurrent degrees of immunosuppression should be made on a case-by-case basis. Because such decisions may involve judgment beyond the purview of a generalist or rheumatologist, it may be helpful to consult an infectious disease specialist.

What is the prognosis?

In a study of 239 patients with biopsy-proven GCA, vision symptoms (diplopia, transient or permanent vision loss) occurred in 29%, with 14% of all cases having

51. Petri H, Nevitt A, Sarsour K, Napalkov P, Collinson N. Incidence of giant cell arteritis and characteristics of patients: data-driven analysis of comorbidities. Arthritis Care Res (Hoboken). 2015; 67:390-5. [PMID: 25132663]
52. 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: 703-8. [PMID: 14558057]
53. Soriano A, Verrecchia E, Marinaro A, Giovinale M, Fonnesu C, Landolfi R, et al. Giant cell arteritis and polymyalgia rheumatica after influenza vaccination: report of 10 cases and review of the literature. Lupus. 2012; 21:153-7. [PMID: 22235046]
54. Felicetti P, Trotta F, Bonetto C, Santuccio C, Brauchli Pernus Y, Burgner D, et al; Brighton Collaboration Vasculitis Working Group. Spontaneous reports of vasculitis as an adverse event following immunization: A descriptive analysis across three international databases. Vaccine. 2015. [PMID: 26392009]
55. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2011;70: 414-22. [PMID: 21131643]

blindness. Amaurosis fugax was a strong marker of subsequent vision loss (odds ratio, 6.35). In the absence of aggressive treatment within 24 hours, the likelihood of restoring functional vision was very low. Monocular blindness was associated with increased risk for binocular blindness and cerebrovascular accident (odds ratio, 7.65) (38). GCA is associated with increased risks for myocardial infarction, stroke, and peripheral vascular disease especially within the first month after the diagnosis (41).

Although PET scanning suggests that subclinical aortic inflammation is common in GCA, development of aneurysms seems to be less common: About 18%–33% of patients with GCA develop aortic dilatation or aneurysms. Thoracic aneurysms are at least 3 times more common than abdominal aneurysms. It is unknown whether anti-inflammatory or immunosuppressive therapies modify outcome in regard to progressive dilatation, dissection, or rupture. GCA-associated thoracic aortic aneurysms have a risk for rupture or dissection, which is often fatal, of up to a 50% (12–14, 56). Aortic reconstruction or intravascular stent placement is often required to prevent these complications (57).

The greatest impact on quality of life are the benefits and adverse effects of corticosteroids. While essentially all patients respond to treatment within days and can later have a dose reduction, relapses and retreatment are common. Almost all patients have at least transient Cushingoid symptoms. In 1 study of 120 GCA patients, 86% experienced corticosteroid-related adverse events (fractures, diabetes, infection, cataracts) at more than 3-fold the rate of the general age- and sex-matched population (52). Although the likelihood of being able to discontinue steroids after 2 years is high, subclinical low-grade disease may continue and accounts for subsequent discovery of inflammatory aortic aneurysms at surgery or autopsy (16, 57). Most studies indicate that patients with GCA have a normal life expectancy, provided they do not develop complications, such as aortic aneurysms.

How should clinicians educate patients about GCA?

Because GCA risks and therapy complications may be profound and potentially life-threatening, patients should be encouraged to immediately notify their physicians when they have any symptoms of GCA, especially those related to organ or regional ischemia. Patients should be educated about risks and preventive measures for corticosteroid side effects. Although the benefits of such advice have not been formally evaluated, most authorities consider it to be the standard of care.

When should the clinician consider consultation with a rheumatologist or other specialist for treatment?

Rheumatologists can provide treatment guidance, particularly for patients with recurrent relapse and for those with large vessel involvement. They also can advise on prevention and management of chronic corticosteroid complications. Consultation with physical therapy, rehabilitation medicine, or counseling to help patients cope with GCA and treatment-related side effects may be useful, although studies have not examined whether these strategies improve outcomes. Nonetheless, they should be considered based on individual patient needs.

Although surgical therapy for GCA is infrequently needed, it may be critical in patients with large vessel involvement. Thoracic aortic aneurysms are of greatest concern because of the

56. García-Martínez A, Arguis P, Prieto-González S, Espígol-Frigolé G, Alba MA, Butjosa M, et al. Prospective long term follow-up of a cohort of patients with giant cell arteritis screened for aortic structural damage (aneurysm or dilatation). Ann Rheum Dis. 2014; 73:1826-32. [PMID: 23873881]
57. Svensson LG, Arafat A, Roselli EE, Idrees J, Clifford A, Tan C, et al. Inflammatory disease of the aorta: patterns and classification of giant cell aortitis, Takayasu arteritis, and nonsyndromic aortitis. J Thorac Cardiovasc Surg. 2015;149: S170-5. [PMID: 25218529]

increased rate of rupture or dissection and associated mortality. Surgery is the only effective treatment for a large or rapidly enlarging aortic aneurysm (57). Peripheral lesions, which may occur within any aortic primary branch vessel, are another concern. Stenoses within branches of the aortic arch are the most common vascular lesions and are rarely improved with medical therapy. However, symptoms, even in pulseless upper extremities, may improve over time with recruitment of collateral vessels. Patients with ischemic symptoms of peripheral or cerebral blood vessels should be seen immediately by a vascular surgeon.

Treatment... Corticosteroid therapy should begin immediately when clinical suspicion of GCA is high enough to warrant a temporal artery biopsy, especially if vision symptoms are present. Symptoms and acute-phase reactants typically respond promptly to effective treatment, but disease flares are common, particularly during corticosteroid tapering. Low-dose aspirin seems to decrease vision symptoms and cardiovascular ischemic events and should be provided to all patients who do not have contraindications. Patients should be followed closely for clinical signs of relapse or large vessel involvement and for development of corticosteroid-related complications. Lifelong surveillance for large vessel involvement, especially thoracic aortic aneurysms, is advised.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend regarding the diagnosis and management of GCA?

The American College of Rheumatology is developing guidelines for specific forms of vasculitis. In 2009, EULAR published recommendations for the management of GCA and Takayasu arteritis (58). The following recommendations are most relevant to GCA:

1. Temporal artery biopsy should be done whenever GCA is suspected but should not delay treatment. A contralateral biopsy is not routinely indicated.

2. Early initiation of high-dose corticosteroid therapy should be provided for induction of remission.

3. An immunosuppressive agent should be considered as adjunctive therapy (B level of evidence for GCA). (Note: Both EULAR and GEFA recognized that the evidence for the efficacy of MTX was "modest.")

4. Monitoring therapy for large vessel vasculitis should be clinical and supported by measurement of inflammatory markers.

5. Low-dose aspirin should be used in all patients with GCA who do not have contraindications.

The British Society of Rheumatology also recently endorsed guidelines for GCA management (59). The report emphasized that features predictive of ischemic neuro-ophthalmic complications include jaw claudication, diplopia, and temporal artery abnormalities. Urgent referral for specialist evaluation was suggested for all patients with GCA. Investigators recommended considering temporal artery biopsy whenever GCA is suspected. The guidelines noted that diagnostic

58. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al; European Vasculitis Study Group. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009;68:318-23. [PMID: 18413441]

imaging techniques show promise and are an important area for future research. Recommendations for corticosteroid use were as follows: uncomplicated GCA: 40–60 mg prednisolone daily; evolving vision loss or amaurosis fugax (complicated GCA): 500 mg to 1 g IV methylprednisolone for 3 days before oral corticosteroids; established vision loss: 60 mg prednisolone daily to protect the contralateral eye. Low-dose aspirin was also recommended in the absence of contraindications. The guidelines reserved large vessel imaging for patients suspected to have large vessel involvement—this recommendation is more conservative than that from the GEFA report. In the event of relapse, the Society's guidelines suggest discussing treatment with or referring to a specialist (59).

59. Dasgupta B, Borg FA, Hassan N, et al. BSR and BHPR guidelines for the management of giant cell arteritis. Rheumatology. 2010;49:1594–1597. [PMID: 20371504] doi:10.1093

In the Clinic
Tool Kit

Giant Cell Arteritis

Patient Information

www.hopkinsvasculitis.org/types-vasculitis/giant-cell-arteritis/
Patient information from Johns Hopkins University Vasculitis Center.

www.mayoclinic.org/diseases-conditions/giant-cell-arteritis/basics/definition/con-20023109
Patient information from the Mayo Clinic.

www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Giant-Cell-Arteritis
American College of Rheumatology information for the patient and caregiver.

www.rheumatology.org/Portals/0/Files/Giant%20Cell%20Arteritis%20Spanish.pdf
Patient information in Spanish by the American College of Rhematology.

https://medlineplus.gov/giantcellarteritis.html
Overview from Medline, including patient handouts.

Clinical Guidelines

www.rheumatology.org.uk/includes/documents/cm_docs/2010/m/2_management_of_giant_cell_arteritis.pdf
British Society of Rheumatology and British Health Professionals in Rheumatology guidelines.

www.ncbi.nlm.nih.gov/pubmed/18413441
The European League Against Rheumatism recommendations for management of large vessel vasculitis.

www.ncbi.nlm.nih.gov/pubmed/26833145
Recommendations of the French Study Group for large vessel vasculitis.

WHAT YOU SHOULD KNOW ABOUT GIANT CELL ARTERITIS

What Is Giant Cell Arteritis?

Giant cell arteritis (GCA) is a disease that happens when the body's defense system (immune system) wrongly attacks your arteries, causing them to become inflamed (or swollen). This inflammation causes your arteries to narrow, which affects blood flow. The cause of GCA is not known, but there are treatments available. You may be at higher risk for GCA if you are:

- Female
- Older than 50 years
- White

What Are the Warning Signs?

- Headache
- Tender scalp
- Sore and stiff shoulders and thighs
- Jaw pain when chewing
- Fever
- Feeling tired
- Less appetite than usual
- Weight loss
- Loss of vision in one or both eyes, double vision, or blurred vision

How Is It Diagnosed?

- Your doctor will perform a careful examination of your head and neck. He or she may also examine your vision.
- You may have your pulse checked or blood pressure taken in your arms and legs.
- You may have a blood test to check for signs of GCA.
- Your doctor may take a small piece of tissue taken from an affected artery. This is called a biopsy.
- You may also have imaging tests, such as an MRI (magnetic resonance imaging). This can help your doctor look more closely at your arteries.

How Is It Treated?

- GCA is treated with medicines called corticosteroids. These medicines reduce the inflammation in your arteries.
- Treatment usually lasts months to years. This helps prevent GCA from coming back.
- The dose of corticosteroids has to be decreased slowly. This means when your treatment is finished, your doctor will gradually reduce the amount of medicine that you take over time.
- Your doctor may also prescribe a low dose of aspirin to reduce your risk for heart attack or stroke.

Questions For My Doctor

- When will I start to feel better?
- How long will I need to take the medicine?
- Does the medicine have any side effects?
- What should I do if my symptoms come back?
- Can I still go about my usual activities?
- Does GCA put me at risk for other health problems?

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

Medline Plus
https://medlineplus.gov/giantcellarteritis.html

American College of Rheumatology
www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Giant-Cell-Arteritis

Patient Information