



EDUCATIONAL OBJECTIVE: Readers will suspect giant cell arteritis in older patients who present with temporal headache, visual changes, and other pertinent symptoms

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Giant cell arteritis: Suspect it, treat it promptly

ABSTRACT

Giant cell arteritis is the most common form of vasculitis affecting older people, and the diagnosis should be considered in older patients who present with the new onset of headache, visual dysfunction, polymyalgia rheumatica, or systemic inflammatory symptoms. Physicians should be familiar with its variety of clinical presentations and the abnormal laboratory findings associated with it.

KEY POINTS

Giant cell arteritis is often associated with an intense acute-phase response and cranial symptoms.

Large-vessel involvement is commonly present and may result in serious complications such as visual loss, stroke, limb claudication, and aortic aneurysm.

The diagnosis is usually confirmed by an abnormal temporal artery biopsy.

Symptoms of giant cell arteritis usually respond rapidly and completely to glucocorticoid therapy, still the mainstay of treatment. Most patients need prolonged therapy.

Several studies have evaluated alternative drugs in an attempt to avoid toxicity from long-term use of glucocorticoids. Results have been mixed, and further study is needed.

GIANT CELL ARTERITIS is the most common primary systemic vasculitis. The disease occurs almost exclusively in people over age 50, with an annual incidence of 15 to 25 per 100,000.¹ Incidence rates vary significantly depending on ethnicity. The highest rates are in whites, particularly those of North European descent.² Incidence rates progressively increase after age 50. The disease is more prevalent in women. Its cause is unknown; both genetic and environmental factors are thought to play a role.

INFLAMED ARTERIES

Giant cell arteritis is characterized by a granulomatous inflammatory infiltrate affecting large and medium-size arteries. Not all vessels are equally affected: the most susceptible are the cranial arteries, the aorta, and the aorta's primary branches, particularly those in the upper extremities.

The disease is usually associated with an intense acute-phase response. Vessel wall inflammation results in intimal hyperplasia, luminal occlusion, and tissue ischemia. Typical histologic features include a mononuclear inflammatory infiltrate primarily composed of CD4+ T cells and activated macrophages. Multinucleated giant cells are seen in only about 50% of positive biopsies; therefore, their presence is not essential for the diagnosis.³

FOUR MAIN PHENOTYPES

Some of the possible symptoms of giant cell arteritis readily point to the correct diagnosis, eg, those due to cranial artery involvement, such as temporal headache, claudication of masti-

catory muscles, and visual changes. However, the clinical presentation can be quite varied.

There are four predominant clinical phenotypes, which may be present at the onset of disease or appear later as the disease progresses. Although they will be described separately in this review, these clinical presentations often overlap.

Cranial arteritis

Cranial arteritis is the clinical presentation most readily associated with giant cell arteritis. Clinical features result from involvement of branches of the external or internal carotid artery.

Headache, the most frequent symptom, is typically but not exclusively localized to the temporal areas.

Visual loss is due to involvement of the branches of the ophthalmic or posterior ciliary arteries, resulting in ischemia of the optic nerve or its tracts. It occurs in up to 20% of patients.^{4,5}

Other symptoms and complications from cranial arteritis include tenderness of the scalp and temporal areas, claudication of the tongue or jaw muscles, stroke, and more rarely, tongue infarction.

Polymyalgia rheumatica

Polymyalgia rheumatica is a clinical syndrome that can occur by itself or in conjunction with giant cell arteritis. It may occur independently of giant cell arteritis, but also occurs in about 40% of patients with giant cell arteritis. It may precede, develop simultaneously with, or develop later during the course of the giant cell arteritis.^{6,7} It is a common clinical manifestation in relapses of giant cell arteritis, even in those who did not have symptoms of polymyalgia rheumatica at the time giant cell arteritis was diagnosed.

Polymyalgia rheumatica is characterized by aching of the shoulder and hip girdle, with morning stiffness. Fatigue and malaise are often present and may be severe. Some patients with polymyalgia rheumatica may also present with peripheral joint synovitis, which may be mistakenly diagnosed as rheumatoid arthritis.⁸ Muscle weakness and elevated muscle enzymes are *not* associated with polymyalgia rheumatica.

Polymyalgia rheumatica is a clinical diagnosis. Approximately 80% of patients with polymyalgia rheumatica have an elevated

erythrocyte sedimentation rate or an elevated C-reactive protein level.⁹ When it occurs in the absence of giant cell arteritis, it is treated differently, with less intense doses of corticosteroids. All patients with polymyalgia rheumatica should be routinely questioned regarding symptoms of giant cell arteritis.

Nonspecific systemic inflammatory disease

Some patients with giant cell arteritis may present with a nonspecific systemic inflammatory disease characterized by some combination of fever, night sweats, fatigue, malaise, and weight loss. In these patients, the diagnosis may be delayed by the lack of localizing symptoms.

Laboratory tests typically show anemia, leukocytosis, and thrombocytosis. The erythrocyte sedimentation rate and the C-reactive protein level are usually very high.

Giant cell arteritis should be in the differential diagnosis when these signs and symptoms are found in patients over age 50.

Large-vessel vasculitis

Although thoracic aortic aneurysm and dissection have been described as late complications of giant cell arteritis, large-vessel vasculitis may precede or occur concomitantly with cranial arteritis early in the disease.^{10,11}

Population-based surveys have shown that large-vessel vasculitis is extremely frequent in patients with giant cell arteritis. In a post-mortem study of 11 patients with giant cell arteritis, all of them had evidence of arteritis involving the subclavian artery, the carotid artery, and the aorta.¹²

Patients may have no symptoms or may present with symptoms or signs of tissue ischemia such as claudication of the extremities, carotid artery tenderness, decreased or absent pulses, and large-vessel bruits on physical examination.

■ CONSIDER THE DIAGNOSIS IN OLDER PATIENTS

Giant cell arteritis should always be considered in patients over age 50 who have any of the clinical features described above. It is therefore very important to be familiar with its symptoms and signs.

Giant cells are not necessary for the diagnosis of giant cell arteritis

A complete and detailed history and a detailed but focused physical examination that includes a comprehensive vascular examination are the first and most important steps in establishing the diagnosis. The vascular examination includes measuring the blood pressure in all four extremities, palpating the peripheral pulses, listening for bruits, and palpating the temporal arteries.

Temporal artery biopsy: The gold standard

Confirming the diagnosis of giant cell arteritis requires histologic findings of inflammation in the temporal artery. Superficial temporal artery biopsy is recommended for diagnostic confirmation in patients who have cranial symptoms and other signs suggesting the disease.

The biopsy should be performed on the same side as the symptoms or abnormal findings on examination. Performing a biopsy in both temporal arteries may increase the diagnostic yield but may not need to be done routinely.¹³

Although some experts recommend temporal artery biopsy in all patients in whom giant cell arteritis is suspected, biopsy has a lower diagnostic yield in patients who have no cranial symptoms. Interestingly, 5% to 15% of temporal artery biopsies performed in patients who had isolated polymyalgia rheumatica were found to be positive.^{14,15} Patients with polymyalgia rheumatica and no clinical symptoms to suggest giant cell arteritis generally are *not* biopsied.

The segmental nature of the inflammation involving the temporal artery in giant cell arteritis may result in negative biopsy results in patients with giant cell arteritis. A temporal artery biopsy length of 5 mm or less has a very low (8%) rate of positive results, whereas a length longer than 20 mm exceeds a 50% rate of positive results. Although the optimal length of a temporal artery specimen is still debated, a longer biopsy specimen should be obtained to increase the chance of arterial specimens showing inflammatory changes.^{16,17}

Typical findings in an inflamed temporal artery (FIGURE 1) include a lymphocytic infiltrate with activated macrophages and multinucleated giant cells (in 50% of cases). Typical panarteritis is not always seen, and infiltrates limited to the adventitia may be the only histologic finding in some patients.¹⁸

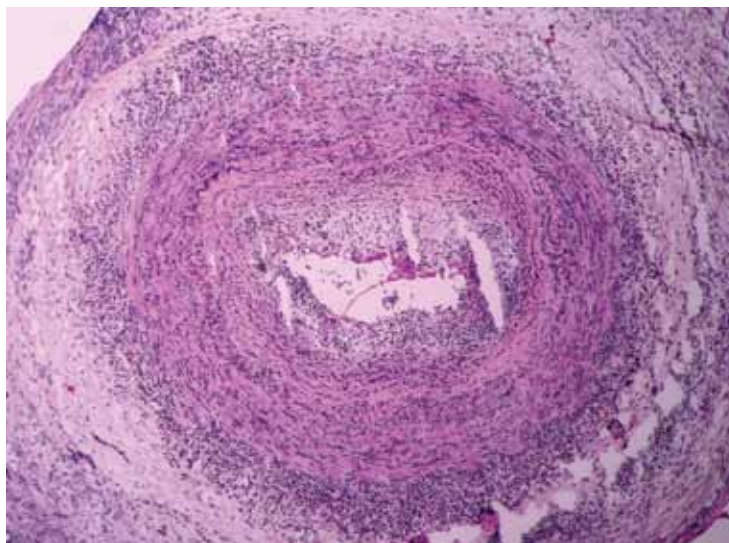


FIGURE 1. Temporal arteritis with intense inflammatory infiltrate within the arterial wall causing intimal thickening with nearly complete occlusion of the arterial lumen (hematoxylin and eosin, $\times 90$).

Laboratory studies:

Acute-phase reactants may be elevated

High levels of acute-phase reactants should increase one's suspicion of giant cell arteritis. Elevations in the erythrocyte sedimentation rate and C-reactive protein and interleukin 6 levels reflect the inflammatory process in this disease.¹⁹ However, not all patients with giant cell arteritis have a high sedimentation rate, and as many as 20% of patients with biopsy-proven giant cell arteritis have a normal sedimentation rate before therapy.²⁰ Therefore, a normal sedimentation rate does not exclude the diagnosis of giant cell arteritis and should not delay its diagnosis and treatment.

As a result of systemic inflammation, the patient may also present with normochromic normocytic anemia, leukocytosis, and thrombocytosis.

Imaging studies are controversial

Imaging studies are potentially useful diagnostic tools in large-vessel vasculitis but are still the subject of significant controversy.

Ultrasonography of the temporal artery has been a controversial subject in many studies.^{21,22} Color duplex ultrasonography of the temporal artery has been reported to be helpful in the diagnosis of giant cell arteritis (showing a “halo” around the arterial lumen),

A normal sedimentation rate does not exclude the diagnosis of giant cell arteritis

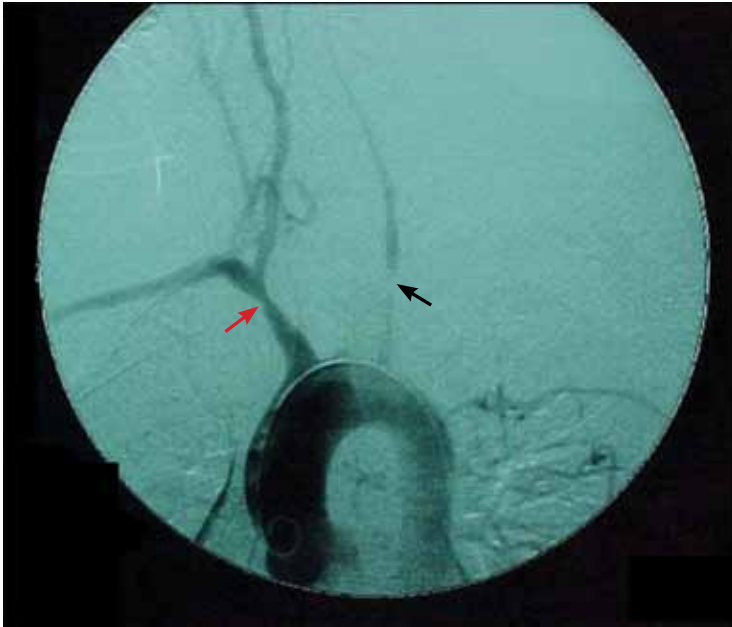


FIGURE 2. Digital subtraction angiography shows occlusion of the left subclavian artery and the left common carotid artery (black arrow), brachiocephalic dilatation, and post-dilatation stenosis (red arrow).

Ultrasonography is neither a substitute for biopsy nor a screening test for this disease

but further studies are needed to establish its clinical utility.

At this time, temporal artery biopsy remains the gold standard diagnostic test for giant cell arteritis, and ultrasonography is neither a substitute for biopsy nor a screening test for this disease.²³ Some have suggested, however, that ultrasonography may help to identify the best site for biopsy of the temporal artery in some patients.

Arteriography is an accurate technique for evaluating the vessel lumen and allows for measuring central blood pressure and performing vascular interventions. However, because of potential complications, it has been largely replaced by noninvasive angiographic imaging to delineate vascular anatomy.

Magnetic resonance angiography and computed angiography. These two noninvasive imaging tests have been used in the diagnosis and serial monitoring of patients with large-vessel involvement from giant cell arteritis (FIGURE 2). In addition to measuring lumen dimensions, magnetic resonance angiography (edema-weighted images) may also give information on vessel-wall signal intensity that may reflect inflammation. This information may be helpful in serial monitoring of patients with established

large-vessel involvement, but it should be interpreted with great caution as it does not always correlate with active inflammation or with new structural changes in the vessel.^{24,25}

■ TREATMENT

Glucocorticoid therapy remains the standard of care

Once the diagnosis of giant cell arteritis is established, glucocorticoid treatment should be started. Glucocorticoids are the standard therapy, and they usually bring about a prompt clinical response. Although never evaluated in placebo-controlled trials, these drugs have been shown to prevent progression of visual loss in a retrospective study.²⁶

In patients with visual symptoms or imminent visual loss, therapy should be started promptly once suspicion of giant cell arteritis is raised; ie, one should not wait until the diagnosis is confirmed by biopsy.

Ideally, a glucocorticoid should be started after a temporal artery biopsy is done, but treatment should not be delayed, as it rapidly suppresses the inflammatory response and may prevent complications from tissue ischemia, such as blindness. Visual loss is usually irreversible.

There is still a role for obtaining a temporal artery biopsy up to several weeks after glucocorticoid therapy is started, as the pathological abnormalities of arteritis do not rapidly resolve.²⁷

Glucocorticoid therapy is highly effective in inducing disease remission in patients with giant cell arteritis. Nearly all patients respond to 1 mg/kg (40–60 mg) per day of prednisone or its equivalent.

The initial dosing is usually maintained for 4 weeks and then decreased slowly. The duration of therapy varies; most patients remain on therapy for at least 1 year, and some cannot stop it completely without recurrence of symptoms.

If a patient is about to lose his or her vision or has lost all or some vision in one eye, a higher initial dose of a glucocorticoid is usually used (ie, a pulse of 500 or 1,000 mg of intravenous methylprednisolone) and may be beneficial.²⁸

Although a rapid clinical response to therapy is usually seen within 48 hours, some patients may have a more delayed clinical improvement.

Alternate-day therapy was compared with

daily therapy and was found to be less effective, and as a result it is not recommended.²⁹

Glucocorticoid therapy can cause significant toxicity in patients with giant cell arteritis, as they commonly must take these drugs for long periods. The rate of relapse in those who discontinue therapy is quite high—as high as 77% within 12 months.³⁰

Given the concern about glucocorticoid toxicity, several studies have evaluated alternative strategies and other immunosuppressive drugs. However, no study has concluded that other medications are effective in the treatment of giant cell arteritis.

Mazlumzadeh et al³¹ evaluated the initial use of intravenous pulse methylprednisolone therapy (15 mg/kg ideal body weight on 3 consecutive days) in an attempt to decrease the glucocorticoid requirement. Although the group receiving this therapy had a lower relapse rate than in the placebo group, and their cumulative dose of glucocorticoid was lower (all patients also received oral prednisone), there was no reduction in the rate of glucocorticoid-associated toxicity.³¹ Care must be taken to prevent and monitor for corticosteroid complications such as osteoporosis, glaucoma, diabetes mellitus, and hypertension.

Methotrexate: Mixed results in clinical trials

Methotrexate has been evaluated in three prospective randomized trials,^{30,32,33} with mixed results.

Spiera et al³² enrolled 21 patients in a double-blind placebo-controlled trial: 12 patients received low-dose methotrexate (7.5 mg/week) and 9 received placebo. In addition, all 21 received a glucocorticoid. There was no significant difference between the methotrexate- and placebo-treated patients in the cumulative dose of glucocorticoid, duration of glucocorticoid therapy, time to taper off the glucocorticoid to less than 10 mg of prednisone per day, or glucocorticoid-related adverse effects.

Jover et al,³³ in another double-blind placebo-controlled trial, studied 42 patients with giant cell arteritis, half of whom were randomized to receive methotrexate 10 mg/week, while the other half received placebo. All patients received prednisone. Patients in the

methotrexate group had fewer relapses and a 25% lower cumulative dose of prednisone during follow-up. However, the incidence of adverse events was similar in both groups. Methotrexate was discontinued in 3 patients who developed drug-related adverse events.

Hoffman et al³⁰ randomized 98 patients to receive either methotrexate (up to 15 mg/week) or placebo in a double-blind fashion. All patients also received prednisone at an initial dose of 1 mg/kg/day (up to 60 mg/day). At completion of the study, no differences between the groups were noted in the rates of relapse or treatment-related morbidity or in the cumulative dose of glucocorticoid. However, treatment with methotrexate appeared to lower the rate of recurrence of isolated polymyalgia rheumatica in a small number of patients.³⁰

Comment. Differences in the results of these trials may be attributed to several factors, including different definitions of relapses and different glucocorticoid doses and tapering regimens.

A meta-analysis of these three trials³⁴ showed a reduction in the risk of relapse: 4 patients would have to be treated to prevent one first relapse, 5 would have to be treated to prevent one second relapse, and 11 would need to be treated to prevent one first relapse of cranial symptoms in the first 48 weeks. However, the main goal of methotrexate therapy is to decrease the frequency of adverse events from glucocorticoids, and this meta-analysis found no difference in rates of glucocorticoid-related adverse events in patients treated with methotrexate.

The study raises the question of whether methotrexate should be further evaluated in in different patient populations and at higher doses.³⁴

Infliximab is not recommended

In a prospective study, patients with giant cell arteritis were randomly assigned to receive either infliximab (Remicade) 5 mg/kg every 8 weeks or placebo, in addition to standard glucocorticoid therapy. The study showed no significant difference in the relapse rate and a higher rate of infection in the infliximab group (71%) than in the placebo group (56%). Given the lack of any benefit observed in this study, infliximab is not recommended in the treatment of patients with giant cell arteritis.³⁵

In suspected cases of giant cell arteritis with visual changes, start a glucocorticoid without delay

Aspirin is recommended

Daily low-dose aspirin therapy has been shown in several studies to be effective in preventing ischemic complications of giant cell arteritis,

including stroke and visual loss. It is currently recommended that all patients with giant cell arteritis without a major contraindication take aspirin 81 mg daily.³⁶⁻³⁸

REFERENCES

- Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. *Ann Intern Med* 1995; 123:192-194.
- Baldursson O, Steinsson K, Björnsson J, Lie JT. Giant cell arteritis in Iceland. An epidemiologic and histopathologic analysis. *Arthritis Rheum* 1994; 37:1007-1012.
- Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. *N Engl J Med* 2003; 349:160-169.
- Aiello PD, Trautmann JC, McPhee TJ, Kunselman AR, Hunder GG. Visual prognosis in giant cell arteritis. *Ophthalmology* 1993; 100:550-555.
- Salvarani C, Cimino L, Macchioni P, et al. Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. *Arthritis Rheum* 2005; 53:293-297.
- Bahlas S, Ramos-Remus C, Davis P. Clinical outcome of 149 patients with polymyalgia rheumatica and giant cell arteritis. *J Rheumatol* 1998; 25:99-104.
- Gonzalez-Gay MA, Barros S, Lopez-Diaz MJ, Garcia-Porrua C, Sanchez-Andrade A, Llorca J. Giant cell arteritis: disease patterns of clinical presentation in a series of 240 patients. *Medicine (Baltimore)* 2005; 84:269-276.
- Salvarani C, Cantini F, Macchioni P, et al. Distal musculoskeletal manifestations in polymyalgia rheumatica: a prospective followup study. *Arthritis Rheum* 1998; 41:1221-1226.
- Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *N Engl J Med* 2002; 347:261-271.
- Lie JT. Aortic and extracranial large vessel giant cell arteritis: a review of 72 cases with histopathologic documentation. *Semin Arthritis Rheum* 1995; 24:422-431.
- Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. A population-based study. *Ann Intern Med* 1995; 122:502-507.
- Ostberg G. An arteritis with special reference to polymyalgia arteritica. *Acta Pathol Microbiol Scand Suppl* 1973; 237(suppl 237):1-59.
- Boyeve LR, Miller NR, Green WR. Efficacy of unilateral versus bilateral temporal artery biopsies for the diagnosis of giant cell arteritis. *Am J Ophthalmol* 1999; 128:211-215.
- González-Gay MA, García-Porrua C, Rivas MJ, Rodríguez-Ledo P, Llorca J. Epidemiology of biopsy proven giant cell arteritis in north-western Spain: trend over an 18 year period. *Ann Rheum Dis* 2001; 60:367-371.
- Rodríguez-Valverde V, Sarabia JM, González-Gay MA, et al. Risk factors and predictive models of giant cell arteritis in polymyalgia rheumatica. *Am J Med* 1997; 102:331-336.
- Mahr A, Saba M, Kambouchner M, et al. Temporal artery biopsy for diagnosing giant cell arteritis: the longer, the better? *Ann Rheum Dis* 2006; 65:826-828.
- Breuer GS, Neshet R, Neshet G. Effect of biopsy length on the rate of positive temporal artery biopsies. *Clin Exp Rheumatol* 2009; 27(1 suppl 52):S10-S13.
- Weyand CM, Goronzy JJ. Giant-cell arteritis and polymyalgia rheumatica. *Ann Intern Med* 2003; 139:505-515.
- Salvarani C, Cantini F, Boiardi L, Hunder GG. Laboratory investigations useful in giant cell arteritis and Takayasu's arteritis. *Clin Exp Rheumatol* 2003; 21(6 suppl 32):S23-S28.
- Salvarani C, Hunder GG. Giant cell arteritis with low erythrocyte sedimentation rate: frequency of occurrence in a population-based study. *Arthritis Rheum* 2001; 45:140-145.
- Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. *N Engl J Med* 1997; 337:1336-1342.
- Karassa FB, Matsagas MI, Schmidt WA, Ioannidis JP. Meta-analysis: test performance of ultrasonography for giant-cell arteritis. *Ann Intern Med* 2005; 142:359-369.
- Maldini C, Dépinay-Dhellemmes C, Tra TT, et al. Limited value of temporal artery ultrasonography examinations for diagnosis of giant cell arteritis: analysis of 77 subjects. *J Rheumatol* 2010; Epub ahead of print.
- Both M, Ahmadi-Simab K, Reuter M, et al. MRI and FDG-PET in the assessment of inflammatory aortic arch syndrome in complicated courses of giant cell arteritis. *Ann Rheum Dis* 2008; 67:1030-1033.
- Tso E, Flamm SD, White RD, Schwartzman PR, Mascha E, Hoffman GS. Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. *Arthritis Rheum* 2002; 46:1634-1642.
- Birkhead NC, Wagener HP, Shick RM. Treatment of temporal arteritis with adrenal corticosteroids; results in fifty-five cases in which lesion was proved at biopsy. *J Am Med Assoc* 1957; 163:821-827.
- Ray-Chaudhuri N, Kiné DA, Tijani SO, et al. Effect of prior steroid treatment on temporal artery biopsy findings in giant cell arteritis. *Br J Ophthalmol* 2002; 86:530-532.
- Chan CC, Paine M, O'Day J. Steroid management in giant cell arteritis. *Br J Ophthalmol* 2001; 85:1061-1064.
- Hunder GG, Sheps SG, Allen GL, Joyce JW. Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study. *Ann Intern Med* 1975; 82:613-618.
- Hoffman GS, Cid MC, Hellmann DB, 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; 46:1309-1318.
- Mazlumzadeh M, Hunder GG, Easley KA, et al. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: a double-blind, placebo-controlled, randomized prospective clinical trial. *Arthritis Rheum* 2006; 54:3310-3318.
- Spiers RF, Mitnick HJ, Kupersmith M, 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.
- 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; 134:106-114.
- Mahr AD, Jover JA, Spiers RF, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum* 2007; 56:2789-2797.
- Hoffman GS, Cid MC, Rendt-Zagar KE, et al; Infliximab-GCA Study Group. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med* 2007; 146:621-630.
- Weyand CM, Kaiser M, Yang H, Younge B, Goronzy JJ. Therapeutic effects of acetylsalicylic acid in giant cell arteritis. *Arthritis Rheum* 2002; 46:457-466.
- Neshet 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; 50:1332-1337.
- Lee MS, Smith SD, Galor A, Hoffman GS. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. *Arthritis Rheum* 2006; 54:3306-3309.

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