Management guidelines and outcome measures in giant cell arteritis (GCA)

K.J. Warrington, E.L. Matteson

Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA.

Kenneth J. Warrington, MD; Eric L. Matteson, MD, MPH.

Please address correspondence to: Kenneth J. Warrington MD, Mayo Clinic, Rheumatology E15, 200 First St. SW, Rochester, MN 55905, USA.
E-mail: Warrington.Kenneth@mayo.edu

Received and accepted on September 7, 2007.

Clin Exp Rheumatol 2007; 25 (Suppl. 47): S137-S141.

Key words: Vasculitis, giant cell arteritis, polymyalgia rheumatica, headache, corticosteroids, aneursym.

Conflict of interest: Dr. Matteson has been a paid consultant for and has received grant support fron Centocor Inc; Dr. Warrington has declared no competing interests.

ABSTRACT

Giant cell arteritis (GCA) is a common form of vasculitis that predominantly affects the elderly. Cranial symptoms and elevated inflammatory markers are suggestive of the condition and the diagnosis is usually established by temporal artery biopsy. Corticosteroids are the mainstay of treatment for GCA and prolonged therapy is often necessary. Disease relapses and steroid-related adverse effects, however, are common. Serious complications of the disease may include visual loss, stroke, and aortic involvement with aneurysm formation.

Introduction

Giant cell arteritis (GCA), also referred to as temporal arteritis, is a type of vasculitis characterized by granulomatous inflammation in the wall of medium-size and large arteries. The extra-cranial branches of the carotid artery are preferentially involved, although the aorta and its major branches may be targeted as well.

GCA is the most common form of systemic vasculitis in adults and affects predominantly older individuals of Northern European descent with an average annual incidence of 18.8 cases per 100,000 persons over 50 years of age. The incidence rises steadily after age 50 and is highest between 70 and 80 years of age. GCA is two to four times more common in women compared to men (1, 2). Besides cranial and constitutional symptoms, patients with GCA often experience concomitant symptoms of polymyalgia rheumatica (PMR).

The cause of GCA remains unknown. Genetic and environmental factors are thought to contribute to its development, possibly triggered by an environmental cause and/or endogenous triggers in a genetically predisposed individual, whereby age-related altered immune function may be a further factor (3). GCA should be treated promptly with an appropriate dose of corticosteroids to reduce disease complications. The most common serious consequence of GCA is irreversible visual loss due to optic nerve ischemia (4).

The proposed guidelines in the following article are based on expert clinical experience and available evidence from the medical literature.

Diagnosis of GCA

The diagnosis of GCA should be considered in a patient over the age of 50 years who presents with new onset of headache, visual disturbances or jaw claudication. Approximately one-third of patients will have symptoms of polymyalgia rheumatica (PMR) (4).

The American College of Rheumatology 1990 criteria for the classification of GCA are listed below. For the diagnosis of GCA, at least 3 of the following 5 criteria must be present. The presence of any 3 or more criteria yields a sensitivity of 93.5% and a specificity of 91.2% for distinguishing GCA from other forms of vasculitis (5).

1. *Age at disease onset ≥ 50 years*
   Development of symptoms or findings beginning at age 50 or older.
2. *New headache*
   New onset of or new type of localized pain in the head.
3. *Temporal artery abnormality*
   Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of the cervical arteries.
4. *Elevated erythrocyte sedimentation rate (ESR)*
   Erythrocyte sedimentation rate ≥ 50 mm/hour by the Westergren method.
5. *Abnormal artery biopsy*
   Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multi-nucleated giant cells.

Clinical assessment

A detailed history should be performed which should specifically include information regarding the presence or absence of:

- Headache/scalp tenderness (including location, duration)
- Visual symptoms: visual loss, amaurosis fugax and diplopia
- Jaw claudication, carotidynia
- PMR symptoms: aching and stiffness in the neck, shoulders, hips and proximal extremities
- Systemic symptoms: low-grade fever, malaise, fatigue and weight loss
- Extremity claudication

A detailed, focused physical examination should be performed and should include careful clinical assessment of the following:

- Temporal artery pulses and evaluation for thickening, tenderness, or nodularity. Other scalp arteries including the occipital arteries may be affected and should be examined.
- Carotid, brachial and radial pulses.
- Auscultation over the carotid, subclavian and brachial arteries for bruits.
- Bilateral brachial artery blood pressure measurements.

In addition, fundoscopic examination for optic disc changes including pallor, edema or other findings such as cotton wool patches and hemorrhages is recommended. Referral to an ophthalmologist should be considered if clinically indicated.

Laboratory evaluation

This should include:

- The ESR is often markedly elevated in GCA. An ESR of least 50 mm/hour is one of the five criteria used for classification of GCA. However, a minority of patients may have a normal sedimentation rate.
- C-reactive protein (CRP) is typically markedly elevated and may be a more sensitive indicator of inflammation in some patients.
- Complete blood count (CBC). Most patients have a normochromic normocytic anemia related to the chronic inflammation and an elevated platelet count.
- Liver function tests. About one-third of patients may have mildly abnormal liver function tests, particularly elevation of alkaline phosphatase.
- If the diagnosis is uncertain and other rheumatologic etiologies are being considered, autoantibodies such as rheumatoid factor and antinuclear antibodies may be obtained and evaluated in the context of the clinical picture. These are usually negative in patients with GCA.
- Consider obtaining: serum protein electrophoresis

Temporal artery biopsy

The gold standard test for GCA is a temporal artery biopsy. Temporal artery biopsies should be performed on the side of abnormal clinical findings if present. Bilateral temporal artery biopsies may increase the diagnostic yield if the first side is negative.

An adequate length of temporal artery (3-5 cm) should be obtained at biopsy because inflammatory lesions may be present in a segmental fashion. Treatment should not be delayed while awaiting biopsy; however, the diagnostic yield of biopsy diminishes with the initiation of corticosteroids. When present, symptoms of jaw claudication and diplopia are powerful predictors of a positive temporal artery biopsy result (6).

Temporal artery biopsy may be normal in the subset of patients who present with only large artery (e.g., aorta) involvement.

Imaging

Currently, no imaging tests are established in the routine evaluation of patients with suspected GCA. However, several have shown some clinical utility and promise. Color duplex ultrasonography appears to be a sensitive and specific tool for the diagnosis of GCA. The most specific finding on ultrasound is the ”halo sign,” which may be due to edema of the temporal artery wall. However, the accuracy of this technique is highly operator-dependent and expertise is not widely available (7, 8). More recently, Bley *et al*. have demonstrated that post-contrast high-resolution (3-Tesla) MRI can be useful to visualize inflammatory changes in the cranial arteries of patients with GCA (9).

Involvement of larger vessels in GCA may be diagnosed by conventional angiography, magnetic resonance angiography or computed tomography scan (10). Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) appears to be a useful modality for the evaluation of disease activity and extent in extra-cranial GCA. In a study of 35 patients with GCA, Blockmans *et al*. noted vascular FDG uptake in 29 patients (83%), especially in the subclavian arteries, but also in the aorta and up to the femoral arteries. FDG uptake diminished with therapy over time (11). Further studies on the utility of PET for the diagnosis and monitoring of patients with GCA are awaited before this technique becomes widely used. Vascular imaging studies are indicated for the subset of patients suspected of having extra-cranial GCA. Otherwise, for most patients these imaging modalities are of uncertain clinical utility and require further evaluation in research settings.

Management of GCA

Principles

The goal of treatment for GCA is to improve the patients' symptoms and prevent ischemic complications such as visual loss. Corticosteroids are the standard of therapy for GCA, and patients typically respond promptly to treatment.

Initial therapy

Prednisone. Because of the concern about sequelae from ischemic events including loss of vision and stroke, glucocorticosteroid therapy should be initiated promptly after a diagnosis of GCA is suspected. The initial daily dose of prednisone should be 40-60 mg for 4 weeks. Prednisone therapy for GCA has been shown in clinical practice over decades to be very effective in the treatment of GCA. Therefore, it has not been evaluated in placebo-controlled clinical trials for obvious ethical reasons. However, in an early retrospective study comparing treated patients to a pre-corticosteroid group, it was demonstrated that cortisone significantly prevented progression of visual loss (12).

Alternate-day corticosteroid therapy has been compared with daily prednisone in a randomized, prospective study. Disease control was inadequate in patients on alternate-day therapy, and this approach is therefore not recommended (13).

More aggressive treatment is indicated for patients who present with impending or recent onset of visual loss. These patients should receive pulse dose methylprednisolone intravenously (1 gram daily for 3 days), followed by the standard oral prednisone regimen. This recommendation is based on a retrospective study which demonstrated that patients with visual loss who received intravenous steroids were more likely to improve compared to those receiving oral therapy (14).

After 4 weeks of treatment, the daily prednisone dose should be tapered gradually by about 10% every 2 to 4 weeks. A typical tapering sequence employed by the authors is 60 mg, 50 mg, 40 mg, 30 mg, 25 mg, 20 mg, 17.5 mg, 15 mg, 12.5 mg, 10 mg followed by further reduction of 1 mg at a time over about 36 weeks, provided there is no relapse. Since the average duration of treatment is about 3 years, with a wide range of about 1 to 9 years, physicians and patients should understand that this treatment will be protracted, ultimately using the lowest dose of prednisone that controls the disease.

Therapy should never be delayed when the suspicion of GCA is high. Treatment with corticosteroids should be started immediately while awaiting confirmation of the diagnosis. There is a substantial window of several weeks during which a temporal artery biopsy may still yield a diagnosis of arteritis (15, 16).

Low-dose aspirin. Recent retrospective studies as well as experimental models indicate that prevention of platelet aggregation with low-dose aspirin is potentially effective in preventing ischemic complications of GCA. The risk of visual loss and cerebrovascular accidents was lower in patients receiving aspirin and the risk of bleeding complications was not increased (17, 18). Unless major contraindications are present, low dose aspirin (81 mg) should be recommended to patients with GCA

Measures to reduce steroid toxicity

The treatment of GCA is associated with significant toxicity in the majority of patients (19). Complications such as steroid-related diabetes and hypertension should be sought and treated appropriately. Steroid-induced bone loss should be prevented or managed with calcium, vitamin D and bisphosphonates. Periodic assessment of bone mineral density is indicated to guide therapy. Appropriate immunizations should be administered, including influenza and pneumococcal vaccines. While patients are taking doses of prednisone greater than 20 mg daily, they should receive prophylaxis for *Pneumocystis jiroveci* pneumonia with trimethoprim-sulfamethoxazole, 1 single-strength tablet daily (20). For patients with sulfa allergy, alternatives include dapsone or atovaquone.

Disease monitoring and follow-up

Patients with GCA usually require a treatment course of at least 1 to 3 years with corticosteroids, with some patients requiring low-dose prednisone for several years, or even indefinitely. Throughout the treatment course, patients should be evaluated regularly by clinical examination and laboratory studies, including inflammatory markers.

Symptoms and clinical variables to monitor

- Headache, jaw claudication, visual disturbances
- Pain and stiffness of the proximal extremities
- Upper or lower extremity claudication
- Peripheral pulses
- Vascular bruits
- Bilateral brachial artery blood pressure
- Adverse effects related to therapy: weight, diabetes, osteoporosis, blood pressure, lipid profile

Laboratory monitoring

Complete blood count, ESR/CRP, renal function, glucose, vitamin D.

Bone density

BMD every 2 years.

Frequency of follow-up

Weeks 0, 1, 4, and 8; months 3, 6, 9, and 12 and every 3-6 months thereafter (with extra visits for relapses or adverse events).

Monitoring for aneurysms

- Patients with GCA have a 17-fold increased risk of thoracic aneurysms and a 2.4-fold increased risk of abdominal aneurysms (21). More importantly, the development of aortic aneurysms may limit patient survival (22). Nuenninghoff *et al*. found that GCA patients with hyperlipidemia and coronary artery disease appeared to be at the greatest risk of aortic aneurysm and/or dissection (23). Other potential risk factors that have been identified include hypertension, aortic insufficiency murmur, and symptoms of polymyalgia rheumatica (10).
- Long-term monitoring for aortic aneurysms is therefore recommended, especially in high risk individuals, although the optimal frequency and imaging modality have not yet been studied. A screening strategy for thoracic aneurysms may include annual trans-thoracic echocardiogram (most thoracic aneurysms develop in the ascending aorta) and two-view chest radiograph for aortic enlargement. Yearly abdominal ultrasound screening for abdominal aneurysms is recommended. In patients with risk factors for large-vessel disease, CT or MR imaging might be more appropriate. If aneurysmal dilatation is detected, monitoring with CT scanning every 6 months is recommended (10).

Treatment of relapse

- Relapse of GCA is defined as the return of signs and/or symptoms with or without changes in inflammatory markers after reduction of therapy. Disease relapses occur frequently as prednisone is tapered (4). An isolated elevation of inflammatory markers (i.e., ESR/CRP) in the absence of clinical symptoms should not routinely result in the escalation of therapy. In the event of a relapse, the dose of prednisone should be increased, depending on the current dose at the time of relapse. In

general it is the authors' practice, for example, to increase the prednisone dose by 10 mg/day if the patient is taking 15 mg daily or more, and by 5 mg/day if the patient is on less than 15 mg daily of prednisone, based on the clinical context.

– A major complication such as visual loss or large-vessel disease should be managed by re-initiating high-dose prednisone (40-60 mg prednisone or intravenous methylprednisolone).
– Further relapses: Alternative immunosuppressive agents should be considered for patients with frequent relapses (see below). GCA patients with a strong initial systemic inflammatory response (manifesting as fever, weight loss, ESR > 85 mm/hr, hemoglobin < 11.0 g/dl) tend to have higher and more prolonged corticosteroid requirements (24).

Steroid-sparing medications for GCA

Disease-modifying or 'steroid-sparing' medications have not been conclusively shown to be effective in the treatment of GCA. Two major prospective, randomized clinical trials evaluating the efficacy of methotrexate in patients with GCA yielded conflicting results (25, 26). Still, for patients with major steroid-related toxicity and recurrent relapses, a meta-analysis recently suggested that therapy with low-dose methotrexate (7.5–20 mg/week) and folate (1 mg/day) is a reasonable approach that may allow reduction in the prednisone dosage and prevent or reduce the number of relapses (27).

Azathioprine for GCA has been evaluated in a placebo-controlled trial and was found to be of limited benefit (28). Cyclosporin does not appear to have a role in the treatment of GCA (29). Use of cyclophosphamide, dapsone and hydroxychloroquine for GCA has been reported, but these agents have not been studied in randomized clinical trials (30).

Since TNF-alpha is expressed in the temporal arteries of patients with GCA, TNF antagonists were expected to be efficacious in this disease. Indeed, initial case reports and small case series suggested that infliximab and adalimumab resulted in disease remission in most patients treated on an open-label basis with these agents (31, 32). However, a recently published randomized multi-center clinical trial demonstrated that infliximab was of no benefit as maintenance therapy in patients with newly diagnosed GCA (33).

High-dose 'pulse' steroids as initial therapy may allow for the more rapid tapering of oral prednisone. Mazlumzadeh and colleagues randomized 27 patients with GCA to either intravenous methylprednisolone (1 gram daily) or saline for 3 days followed by standard oral prednisone with rapid tapering. Patients receiving pulse steroids could taper oral therapy more rapidly and had a lower median cumulative dose of oral prednisone. However, there was no significant difference in the occurrence of steroid-related toxicity between the treatment groups, and further trials evaluating this regimen appear necessary (34).

Summary

The majority of patients with GCA respond rapidly to treatment with corticosteroids. However, GCA can be associated with significant sequelae and treatment-related morbidity, and considerable variability in patient management exists. Therefore standardized therapy and monitoring guidelines may result in improved patient outcomes. The guidelines proposed above are based upon best available evidence.

References

1. SALVARANI C, CROWSON CS, O'FALLON WM, HUNDER GG, GABRIEL SE: Reappraisal of the epidemiology of giant cell arteritis in Olmsted County, Minnesota, over a fifty-year period. *Arthritis Rheum* 2004; 51: 264-8.
2. SALVARANI C, GABRIEL SE, O'FALLON WM, HUNDER GG: The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. *Ann Intern Med* 1995; 123: 192-4.
3. WEYAND CM, GORONZY JJ: Giant-cell arteritis and polymyalgia rheumatica. *Ann Intern Med* 2003; 139: 505-15.
4. SALVARANI C, CANTINI F, BOIARDI L, HUNDER GG: Polymyalgia rheumatica and giant-cell arteritis. *N Engl J Med* 2002; 347: 261-71.
5. HUNDER GG, BLOCH DA, MICHEL BA *et al*.: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990; 33: 1122-8.
6. SMETANA GW, SHMERLING RH: Does this patient have temporal arteritis? *JAMA* 2002; 287: 92-101.
7. KARASSA FB, MATSAGAS MI, SCHMIDT WA, IOANNIDIS JP: Meta-analysis: Test performance of ultrasonography for giant-cell arteritis. *Ann Intern Med* 2005; 142: 359-69.
8. SCHMIDT WA, KRAFT HE, VORPAHL K, VOLKER L, GROMNICA-IHLE EJ: Color duplex ultrasonography in the diagnosis of temporal arteritis. *N Engl J Med* 1997; 337: 1336-42.
9. BLEY TA, WEIBEN O, UHL M *et al*.: Assessment of the cranial involvement pattern of giant cell arteritis with 3T magnetic resonance imaging. *Arthritis Rheum* 2005; 52: 2470-7.
10. BONGARTZ T, MATTESON EL: Large-vessel involvement in giant cell arteritis. *Curr Opin Rheumatol* 2006; 18: 10-7.
11. BLOCKMANS D, DE CEUNINCK L, VANDERSCHUEREN S, KNOCKAERT D, MORTELMANS L, BOBBAERS H: Repetitive ^{18}F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum* 2006; 55: 131-7.
12. 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: 821-7.
13. 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: 613-8.
14. CHAN CC, PAINE M, O'DAY J: Steroid management in giant cell arteritis. *Br J Ophthalmol* 2001; 85: 1061-4.
15. 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.
16. RAY-CHAUDHURI N, KINE DA, TIJANI SO *et al*.: Effect of prior steroid treatment on temporal artery biopsy findings in giant cell arteritis. *Br J Ophthalmol* 2002; 86: 530-2.
17. LEE MS, SMITH SD, GALOR A, HOFFMAN GS: Anti-platelet and anti-coagulant therapy in patients with giant cell arteritis. *Arthritis Rheum* 2006; 54: 3306-9.
18. 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.
19. KYLE V, HAZLEMAN BL: Treatment of polymyalgia rheumatica and giant cell arteritis. II. Relation between steroid dose and steroid associated side effects. *Ann Rheum Dis* 1989; 48: 662-6.
20. YALE SH, LIMPER AH: *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. *Mayo Clin Proc* 1996; 71: 5-13.
21. 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: 502-7.

22. NUENNINGHOFF DM, HUNDER GG, CHRISTIANSON TJ, MCCLELLAND RL, MATTESON EL: Mortality 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: 3532-7.
23. 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.
24. HERNANDEZ-RODRIGUEZ J, GARCIA-MARTINEZ A, CASADEMONT J *et al*.: A strong initial systemic inflammatory response is associated with higher corticosteroid requirements and longer duration of therapy in patients with giant-cell arteritis. *Arthritis Rheum* 2002; 47: 29-35.
25. JOVER JA, HERNANDEZ-GARCIA C, MORADO IC, VARGAS E, BANARES A, FERNANDEZ-GUTIERREZ 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.
26. HOFFMAN GS, CID MC, HELLMANN DB *et al*.: A multi-center, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002; 46: 1309-18.
27. MAHR AD, JOVER JA, SPIERA RF *et al*.: Adjunctive methotrexate to treat giant cell arteritis: An individual patient data meta-analysis. In *13th International Vasculitis & ANCA Workshop*, *2007*, Cancun, Mexico.
28. DE SILVA M, HAZLEMAN BL: Azathioprine in giant cell arteritis/polymyalgia rheumatica: A double-blind study. *Ann Rheum Dis* 1986; 45: 136-8.
29. SCHAUFELBERGER C, MOLLBY H, UDDHAMMAR A, BRATT J, NORDBORG E: No additional steroid-sparing effect of cyclosporine A in giant cell arteritis. *Scand J Rheumatol* 2006; 35: 327-9.
30. NUENNINGHOFF DM, MATTESON EL: The role of disease-modifying anti-rheumatic drugs in the treatment of giant cell arteritis. *Clin Exp Rheumatol* 2003; 21 (Suppl. 32): S29-34.
31. CANTINI F, NICCOLI L, SALVARANI C, PADULA A, OLIVIERI I: Treatment of longstanding active giant cell arteritis with infliximab: report of four cases. *Arthritis Rheum* 2001; 44: 2933-5.
32. AHMED MM, MUBASHIR E, HAYAT S, FOWLER M, BERNEY SM: Treatment of refractory temporal arteritis with adalimumab. *Clin Rheumatol* 2007; 26: 1353-5.
33. HOFFMAN GS, CID MC, RENDT-ZAGAR KE *et al*.: Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: A randomized trial. *Ann Intern Med* 2007; 146: 621-30.
34. 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: 3310-8.