LEARNING OBJECTIVES
1. The attendee will be able to know the most recent literature on the acute treatment of giant cell arteritis.
2. The attendee will be able to recognize that different studies use different populations of patients with giant cell arteritis and that all results may not be applicable to those patients with visual loss.
3. The attendee will be able to practically manage a giant cell arteritis patient with visual loss.

CME QUESTIONS
Indicate whether the following statements are true or false:
1. The acute treatment of the patient with giant cell arteritis should be slightly delayed in order to first obtain a temporal artery biopsy.
2. The acute treatment of the patient with giant cell arteritis and visual loss should be identical to the treatment of those patients with giant cell arteritis and no visual loss.
3. High-dose intravenous corticosteroids administered initially reduces the long-term cumulative doses of steroids necessary to control giant cell arteritis at one year.

KEY WORDS
1. giant cell arteritis
2. corticosteroids
3. visual loss
4. treatment

ABSTRACT
Although giant cell arteritis (GCA) is a well-known vasculitis sensitive to corticosteroid-mediated immunosuppression, numerous issues of short-term and long-term therapeutic management remain unresolved. Because GCA encompasses a broad spectrum of clinical subtypes, ranging from devastating visual loss and neurological deficits to isolated systemic symptoms, the treatment of GCA must be adjusted to each case, and recommendations vary widely in the literature. Although there is no randomized controlled clinical trial specifically evaluating GCA patients with ocular and neurological complications, it is this author’s recommendation that GCA patients with acute visual loss or brain ischemia be admitted to the hospital for high-dose intravenous methylprednisolone, close monitoring, and prevention of steroid-induced complications. Aspirin may also be helpful in these cases.

1. INTRODUCTION
Giant cell arteritis (GCA) is a vasculitis affecting medium and large vessels, with a predilection for the aorta and its branches. GCA is the most common primary vasculitis in adults, affecting individuals over 50 years of age almost exclusively. Disease incidence in people over 50 is about 18 per 100,000 per year, but increases with age, and reaches its peak in the eighth decade of life. The prevalence of GCA is highest in northern latitudes and in individuals of Northern European descent; women are two to six times more commonly affected than men.

Headache is the most common symptom of GCA, present in two thirds of patients. Jaw claudication, scalp tenderness, and visual loss are less frequent, but provide important clues towards making the diagnosis. Forty percent of patients have polymyalgia rheumatica (PMR), a syndrome of proximal myalgias and stiffness. About one-third of patients present with a syndrome of wasting characterized by fever, sweats, malaise, anorexia and weight loss. Visual loss is the most dreaded complication of GCA and, before the era of corticosteroid treatment, was noted in 30–60% of patients with GCA. Despite the widespread use of corticosteroids in the modern era, devastating visual loss may still occur in 14–20% of patients with GCA. Cerebral infarction, which has a strong predilection for the vertebrobasilar territory in GCA, is rare, occurring in only 1% of patients.

Visual loss typically occurs on the basis of arteritic anterior ischemic optic neuropathy (AAION) – an occlusion of the short posterior ciliary arteries causing ischemia of the optic nerve head; however, it may also result from vasculitic ischemia of the choroid, the posterior optic nerve, or, less commonly, the retina. Visual loss can be partial or complete but is typically devastating and permanent, with initial visual acuities of count fingers or worse in 54% of affected eyes. If left untreated, GCA is associated with visual loss in the fellow eye within days to weeks in up to 50% of individuals. Permanent visual loss is preceded by episodes of transient visual loss in 44% of patients. A substantial proportion (21.2%) of
patients with GCA present with visual loss alone, without any systemic complaints. Making the diagnosis in such patients with “occult GCA” therefore requires a high index of suspicion.

The treatable nature of GCA and the devastating visual consequences of a delayed diagnosis make the identification and treatment of GCA a true medical emergency. Suspicion for GCA arises from the clinical history, review of systems, and physical examination, and is supported by abnormal serological tests of inflammation, such as elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and thrombocytosis. Retinal fluorescein angiogram is helpful in selected cases. The gold standard for definitive diagnosis of GCA, however, is the temporal artery biopsy (TAB), which typically shows focal or segmental inflammatory infiltrates.

Temporal artery biopsy is mandatory in suspected cases of GCA and must be done shortly after initiating steroid treatment to establish a definitive diagnosis. Because visual loss can occur rapidly and irreversibly in GCA, treatment must not be delayed while the biopsy is being arranged. Evidence suggests that immediate treatment with corticosteroids does not usually confound the biopsy, as characteristic histological changes may be seen for up to a few weeks after initiation of treatment.

2. TREATMENT OF GIANT CELL ARTERITIS

Giant cell arteritis encompasses a broad spectrum of clinical subtypes, including: cranial arteritis with severe ischemic complications such as visual loss and brain ischemia; large vessel arteritis causing subclavian and axillary stenosis; aortitis leading to aortic dissection, aneurysm, and aortic rupture; a systemic inflammatory syndrome with nonstenosing vasculitis; and “isolated” PMR with myalgias, fatigue, anorexia, and subclinical systemic vasculitis.

Few studies evaluate treatment protocols by individual GCA subtype. Instead, studies examining treatment protocols for GCA are influenced by the patient populations they draw from, and studies done by ophthalmologists and by researchers in tertiary care centers have generally recommended more aggressive treatment measures, sustained for longer periods of time, than rheumatologists and researchers performing population-based studies. Rheumatologists, for example, may use low-dose oral prednisone to treat “isolated” PMR, while neuro-ophthalmologists often use high-dose intravenous methylprednisolone to treat patients with abrupt visual loss or brain ischemia.

A. CORTICOSTEROIDS

I) DOSING AND ROUTE OF ADMINISTRATION

There is universal agreement that glucocorticosteroids are the mainstay of treatment for GCA and should be initiated immediately and aggressively, with the goal of suppressing inflammation and preventing visual loss and ischemic stroke. The initial starting dose, route of administration, and duration of therapy are still matters of debate, however, and depend largely on the patient’s potential for visual loss or stroke.

Oral prednisone is first–line acute therapy for GCA. The initial starting dose used to control GCA varies widely in the literature – from 20mg per day in a mixed population of patients with either GCA or PMR but with strictly constitutional signs and symptoms, to more than 100mg per day in a high–risk neuro–ophthalmic population with recent or impending visual loss. Selection bias during enrollment influences the conclusions of these studies; rheumatological reports often combine GCA with PMR (a much milder condition which responds to relatively low doses of prednisone), and neuro–ophthalmic reports often enroll patients with severe visual loss and occult GCA, excluding milder forms of the disease. Although no consensus exists for initial dose of prednisone, the vast majority of patients respond to a dose of 1mg/kg/day, or between 40–60mg per day. Higher doses of 80–100mg per day are suggested for patients with visual or neurological symptoms of GCA.

Intravenous pulse methylprednisolone has been proposed as an induction therapy, particularly in cases where vision is at risk. Four studies have examined intravenous steroid therapy in GCA, two of which were prospective randomized controlled trials (see Table 1, page 83). The study by Chevalet et al. showed no benefit for a single low induction dose of intravenous methylprednisolone 250mg in reducing cumulative steroid dose at one year; however, the more recent study by Mazlumzadeh et al. found that a 3–day course of induction intravenous methylprednisolone at a much higher dose of 15mg/kg (about 1000mg) per day allowed more rapid weaning from prednisone than placebo, and also reduced the cumulative steroid dose at week 78. Interestingly, the benefits of pulse steroid therapy became obvious later in the course of the disease. Only one study, by Chan et al., evaluated intravenous steroids in exclusively “high–risk” patients – those with biopsy–proven GCA and recent or impending visual loss – and found improvement of visual acuity in significantly more patients (40% vs. 13%) treated with induction intravenous steroids (1000mg/day for 3 days) compared to oral steroids alone (75mg/day). This author recommends treating GCA with a three–day induction dose of intravenous methylprednisolone 15mg/kg per day followed by oral prednisone maintenance therapy at an initial dose of 1mg/kg per day.

II) EFFECTS OF CORTICOSTEROIDS

Following the initiation of corticosteroid treatment, systemic symptoms of GCA disappear rapidly and dramatically over hours to days in nearly all patients. Improvement of visual loss from arteritic AION is less striking, and occurs in 4–34% of patients in the largest series/reviews (Table 2, page 83). Visual improvement, when it occurs, is usually mild, with
TABLE 1 – THERAPEUTIC TRIALS OF INTRAVENOUS METHYPREDNISOLONE FOR GIANT CELL ARTERITIS (GCA)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>N</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chevalet et al.</td>
<td>3-armed RCT</td>
<td>164</td>
<td>GCA without ocular or cerebrovascular</td>
<td>1. 1 pulse of 240mg IV methylprednisolone followed by 0.7mg/kg oral prednisone</td>
<td>Cumulative steroid dose at one year</td>
<td>No benefit with IV versus oral steroids</td>
</tr>
<tr>
<td>et al. (2000)</td>
<td></td>
<td></td>
<td>involvement</td>
<td>2. 1 pulse of 240mg IV methylprednisolone followed by 0.5mg/kg oral prednisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Oral prednisone 0.7mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al.</td>
<td>Retrospective</td>
<td>73</td>
<td>Vision loss from biopsy-proven GCA</td>
<td>1. High-dose IV methylprednisolone (~1000mg per day for 3 days), followed by oral prednisolone at 75mg/d</td>
<td>Significant improvement in visual acuity on Snellen chart</td>
<td>Benefit for IV versus oral steroids (40% vs. 13%, p=0.01)</td>
</tr>
<tr>
<td>et al. (2001)</td>
<td></td>
<td></td>
<td></td>
<td>2. Oral prednisolone alone at 75mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayreh et al.</td>
<td>Longitudinal</td>
<td>145</td>
<td>Biopsy-proven GCA</td>
<td>1. &quot;Megadose&quot; IV dexamethasone (up to 450mg per day for up to 3 days) followed by oral prednisolone at 80-120mg/d</td>
<td>Visual outcome; cumulative steroid dose</td>
<td>No benefit with IV versus oral steroids</td>
</tr>
<tr>
<td>et al. (2003)</td>
<td>observational</td>
<td></td>
<td></td>
<td>2. Oral prednisone alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazlumzadeh et al.</td>
<td>2-armed RCT</td>
<td>27</td>
<td>GCA without ocular or cerebrovascular</td>
<td>Oral prednisone 40mg per day followed by a systematic taper at week 4, plus an &quot;induction&quot; dose of:</td>
<td>Prednisone dose of no more than 5mg per day at 36 weeks</td>
<td>Benefit for IV versus oral steroids (71% vs. 15%, P=0.003)</td>
</tr>
<tr>
<td>et al. (2006)</td>
<td></td>
<td></td>
<td>involvement</td>
<td>1. IV methylprednisolone 15mg/kg per day for 3 days (about 1000mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IV: intravenous; RCT: randomized controlled trial

TABLE 2 – RECENT STUDIES OF VISUAL RECOVERY WITH CORTICOSTEROID TREATMENT OF GCA

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Design</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al.</td>
<td>1994</td>
<td>Retrospective</td>
<td>41</td>
<td>34% of patients with visual loss had visual improvement with IV or PO corticosteroids. More benefit was seen in the patients who received IV treatment.</td>
</tr>
<tr>
<td>Gonzales-Gay et al.</td>
<td>1998</td>
<td>Retrospective</td>
<td>34</td>
<td>Early treatment (within 24 hours) was the only predictor of recovery of VA. No significant difference between IV and PO treatment.</td>
</tr>
<tr>
<td>Kupersmith et al.</td>
<td>1999</td>
<td>Prospective</td>
<td>22</td>
<td>4 of 9 (44%) eyes had improved VA within one month of starting treatment with oral prednisone.</td>
</tr>
<tr>
<td>Hayreh SS et al.</td>
<td>2002</td>
<td>Retrospective</td>
<td>114</td>
<td>4% of patients had improvement of both VA and central VF on treatment. A trend towards improvement was seen with immediate treatment.</td>
</tr>
<tr>
<td>Foroozan R et al.</td>
<td>2003</td>
<td>Retrospective</td>
<td>32</td>
<td>13% of patients had improvement of VA with treatment (time from onset of symptoms not specified), but none showed significant improvement in VF.</td>
</tr>
<tr>
<td>Danesh-Meyer et al.</td>
<td>2005</td>
<td>Prospective</td>
<td>34</td>
<td>Patients received treatment within 10 days after onset of visual loss (mean 2 days). 15% of patients had improvement of VA of two or more lines. No significant improvement was seen of VF or color vision.</td>
</tr>
</tbody>
</table>

IV: intravenous; PO: per os; VA: visual acuity; VF: visual field
persistent and often severe visual field defects. When treatment is initiated within 24 hours of visual symptoms, 58% of patients have visual improvement, compared to the 6% of patients who improve after a delay in treatment, illustrating the urgency of corticosteroid treatment.

Although substantial improvement of visual acuity may rarely be seen following immediate institution of corticosteroid therapy for GCA-related vision loss, the real aim of treatment is preservation of vision in the fellow eye. Despite treatment with high-dose corticosteroids, bilateral vision loss or worsening of unilateral vision loss may sometimes occur. However, when deterioration occurs in this setting, it does so early, typically within the first five days of treatment.

III) TAPERING AND RELAPSES

When systemic and constitutional symptoms have disappeared, visual symptoms are stable, and the ESR and CRP have reached consistently low levels, then GCA is considered to be controlled. Typically, it takes several weeks of treatment with daily high-dose oral corticosteroids to achieve satisfactory suppression of the inflammatory syndrome. Subsequently, the goal of care becomes the slow tapering of steroids to achieve either a stable maintenance dose or complete withdrawal of the drug.

Because GCA may relapse during the tapering process, necessitating an increase in corticosteroid dose, the tapering process must be individualized to each patient and may take years to accomplish. Indeed, a one- to two-year course is typically required. The daily oral dose can be tapered by 10mg every month at first, followed by 5mg every month, and then by as little as 1mg every month once the dose reaches 10–15mg per day. A prospective study by Hunder et al. demonstrated decreased efficacy and increased risk of relapse with alternate-day dosing, and, therefore, corticosteroids should be given daily, and not on alternate days. Close follow-up is indicated during the tapering process, with follow-up visits every two to three weeks until the dose of prednisone reaches 40mg per day, followed by regular visits every four to six weeks thereafter until the dose of prednisone reaches a low maintenance dose, at which point the patients may be followed approximately every three months.

At each visit, decreases in corticosteroid dose should be undertaken only when symptoms of GCA remain absent and the ESR and CRP remain normal. Because irreversible blindness from AION may occur in the absence of other GCA symptoms (occult GCA), it must be emphasized that symptom monitoring alone is insufficient to guide the tapering of corticosteroids. If ESR and CRP have both risen, in the absence of an intercurrent illness, the GCA is considered to have “relapsed”, and an immediate increase in the corticosteroid dose to the last effective dose is recommended. Although a rise in laboratory parameters from normal range into the abnormal range certainly warrants an increase in corticosteroid dose, small rises within the normal range may be tolerable on an individualized patient basis, provided they are not part of a larger trend towards GCA relapse. An isolated increase in ESR without a corresponding rise in CRP may not be an indication to increase the corticosteroid dose, and careful clinical correlation is necessary.

More than half of patients with GCA have at least one relapse during their steroid taper, and for this reason GCA is now viewed as a “smouldering” disease. Persistent elevation of IL–6 levels, even when CRP and ESR are within normal limits, support the concept of ongoing subclinical disease activity. Even after steroids have been successfully tapered and discontinued, it is prudent to follow patients for at least one year to monitor for further relapses.

IV) ADVERSE EFFECTS OF CORTICOSTEROIDS

Corticosteroids have well-recognized adverse effects and must never be considered a benign treatment. Treatment with high-dose steroids, especially in an elderly population with multiple pre-existing comorbidities such as diabetes, hypertension, and osteoporosis, carries serious risks. In one 15-year study of patients with GCA, 58% of patients had at least one serious steroid-related adverse effect during their course of treatment. Even cases of sudden death from high-dose intravenous corticosteroids have been reported, possibly a result of coronary artery thrombosis and myocardial infarction. Such thrombosis may result from the procoagulant effect of corticosteroids, from arteritic involvement of the coronary vessels, from underlying atherosclerotic coronary disease, or from a combination of all three mechanisms.

Because of the risk of acute myocardial infarction, brain ischemia, hypertensive crisis, psychosis, and hyperosmolar decompensation of diabetes, elderly patients should be admitted to the hospital for monitoring during induction intravenous corticosteroid therapy. Additionally, introduction of antiplatelet agents should be considered.

Some adverse effects from corticosteroids can be mitigated through simple measures. The American College of Rheumatology suggests that all patients receiving long-term corticosteroid treatment be started on a bone protection regimen that includes calcium supplementation (1200mg per day) and vitamin D (800IU per day), as well as a bisphosphonate if osteoporosis is seen on baseline bone mineral densitometry. Weight-bearing exercises, smoking cessation, and reduction of alcohol intake are also advised for bone protection. Peptic ulcer disease and dyspepsia may be improved or prevented with H2 blockers or proton–pump inhibitors. Hypertension and diabetes may develop or worsen with corticosteroid treatment, and should be monitored and managed aggressively to prevent cerebrovascular and cardiovascular complications. Avascular necrosis of the femoral head is an idiosyncratic adverse effect of
corticosteroids that may occur at any dose and at any time during the course of treatment; onset of hip or groin pain should be promptly investigated with plain X-rays followed by MRI.

B. LONG-TERM “STEROID-SPARING” AGENTS

Because of the significant morbidity associated with long-term corticosteroid use, efforts have been made to investigate “steroid-sparing” agents in GCA. For ethical reasons, these agents, typically from other classes of immunosuppressive medications, cannot be directly compared to corticosteroids in a prospective double-blinded fashion. They can, however, be used adjunctively with corticosteroids and compared to corticosteroid treatment alone. Of the many immunosuppressive drugs used as steroid-sparing agents, methotrexate is the best studied (Table 3).

Three randomized placebo controlled trials have compared methotrexate to placebo as adjunctive therapy in the treatment of GCA with corticosteroids, with contradictory results (Table 3). Studies by Spiera et al.47 and Hoffman et al.48 reported no significant decrease in cumulative steroid dose or in relapse rate at one year among patients treated with corticosteroids and methotrexate compared to those treated with corticosteroids and placebo. The study by Jover et al.49, however, reported a significant decrease in cumulative steroid dose and relapse rate at two years among patients treated with adjuvant methotrexate compared to placebo. The methodologies of these three trials differ, and each has been subject to criticism.

A recent meta-analysis of the methotrexate studies50 reanalyzed the pooled data and revealed a benefit for oral methotrexate 7.5–15mg per week over placebo in preventing both first and second relapses of GCA and in reducing the cumulative corticosteroid dose by 48 weeks. No significant differences in adverse events were seen between the two groups. A benefit of methotrexate over placebo in preventing GCA relapses began late in the disease course, between weeks 24–36, and strengthened as the follow-up period increased. In a prespecified subgroup analysis, a statistically significant benefit was seen in females, but not in males. The authors concluded that low-dose methotrexate was an effective steroid-sparing agent for use in patients with GCA; however, the latency period of more than 6 months before methotrexate exerts its therapeutic effect remains unexplained. Potential benefits obtained by using methotrexate must be weighed against its possible adverse effects in elderly patients.

The search for safe and effective steroid-sparing agents in GCA has broadened to include a number of cytotoxic and immunomodulatory agents apart from methotrexate51-53.

### TABLE 3 – THERAPEUTIC TRIALS OF METHOTREXATE (MTX) FOR GIANT CELL ARTERITIS (GCA)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>N</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiera et al.</td>
<td>RCT</td>
<td>21</td>
<td>Diagnosis of GCA based on clinical, biopsy, and angiographic criteria</td>
<td>Oral prednisone 1mg/kg per day with a taper to 30mg per day, and then: 1. MTX 7.5mg per week 2. Placebo</td>
<td>Cumulative steroid dose at 1 year; duration of steroid taper; functional status; adverse effects</td>
<td>No benefit with MTX versus placebo</td>
</tr>
<tr>
<td>Jover et al.</td>
<td>RCT</td>
<td>42</td>
<td>Biopsy-proven GCA</td>
<td>Oral prednisone 60mg per day with a taper, and: 1. MTX 10mg per week 2. Placebo</td>
<td>Number of relapses; cumulative steroid dose at 2 years</td>
<td>Benefit with MTX versus placebo in number of relapses (45% vs. 84.2%; P=0.02) and cumulative steroid dose (4187mg vs. 5489.6mg; P=0.009)</td>
</tr>
<tr>
<td>Hoffman et al.</td>
<td>RCT</td>
<td>98</td>
<td>Diagnosis of GCA based on clinical, biopsy, or angiographic criteria</td>
<td>Oral prednisone 1mg/kg per day with a taper to q.o.d. dosing, and: 1. MTX 0.15mg/kg per week, increased to 0.25mg/kg per week 2. Placebo</td>
<td>Relapse and treatment failure rate; cumulative steroid dose at 1 year</td>
<td>No benefit with MTX versus placebo</td>
</tr>
<tr>
<td>Mahr et al.</td>
<td>Individual patient meta-analysis</td>
<td>161</td>
<td>Individual patients with GCA, from the above 3 trials</td>
<td>Oral prednisone and: 1. MTX 7.5-10mg per week 2. Placebo</td>
<td>Time to first and second relapses of GCA; cumulative steroid dose at 48 weeks</td>
<td>Benefit with MTX versus placebo in risk of first and second relapse (HR=0.65; P=0.04; and HR=0.49; P=0.02, respectively), and cumulative steroid dose at 48 weeks (842mg difference; P&lt;0.001)</td>
</tr>
</tbody>
</table>

q.o.d.: every other day; HR: hazard ratio; RCT: randomized controlled trial
TABLE 4 – THERAPEUTIC TRIALS OF OTHER CYTOTOXIC AND IMMUNOMODULATORY AGENTS FOR GIANT CELL ARTERITIS (GCA)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Authors</th>
<th>Design</th>
<th>N</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Hoffman et al. (2007)51</td>
<td>RCT</td>
<td>44</td>
<td>GCA as per ACR criteria, in steroid-induced remission for at least 1 week</td>
<td>Oral corticosteroid (prednisolone or prednisolone) with scheduled taper, plus: 1. Infliximab 5mg/kg 2. Placebo</td>
<td>Number of patients relapse free by week 22; adverse effects</td>
<td>No significant benefit or harm with infliximab; trial was stopped early</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>De Silva, Hazelman (1986)52</td>
<td>RCT</td>
<td>31</td>
<td>Either GCA or PMR by Jones/Hazelman criteria, in steroid-induced remission for at least 3 months</td>
<td>Oral prednisolone taper, with: 1. Azathioprine 150mg per day 2. Placebo</td>
<td>Prednisolone dosage at 52 weeks</td>
<td>Benefit with azathioprine versus placebo in steroid dose at 52 weeks (1.9mg vs. 4.2mg; p&lt;0.05); high dropout rate in azathioprine group</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>Schaufelberger et al. (2006)53</td>
<td>RCT, open-label</td>
<td>60</td>
<td>Biopsy-proven GCA meeting ACR criteria</td>
<td>Prednisone with scheduled taper, with: 1. Cyclosporine A 2mg/kg per day (tapered according to response and adverse effects) 2. Placebo</td>
<td>Change in steroid dose over 12 months</td>
<td>No efficacy data provided by authors; high rate of premature termination and adverse effects in cyclosporine A group</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Martinez-Taboada et al. (2008)62</td>
<td>RCT</td>
<td>17</td>
<td>Biopsy-proven GCA controlled on steroids with steroid side effects</td>
<td>Oral corticosteroids with scheduled taper, plus 1) Etanercept 25mg twice weekly 2) Placebo</td>
<td>Ability to withdraw corticosteroid therapy and control disease at 12 months</td>
<td>50% of etanercept patients and 22% of placebo patients with controlled GCA off steroids at 12 months (p=NS) Etanercept group with lower cumulative dose of prednisone (p=0.03) No difference in adverse events</td>
</tr>
</tbody>
</table>

ACR: American College of Rheumatology; PMR: polymyalgia rheumatica; RCT: randomized controlled trial

(Table 4). Immunohistochemical examination of the damaged vessel walls of GCA–positive temporal artery biopsy specimens has suggested an abundance of the cytokine TNF–α within giant cells, macrophages, and T cells.54 Case reports of successful treatment of corticosteroid–resistant GCA with the monoclonal anti–TNF–α antibody infliximab have been published,55,56 and success with this agent has been seen in several other inflammatory diseases, such as rheumatoid arthritis and psoriasis.

Based on this groundwork, Hoffman et al.51 undertook to study infliximab’s utility in GCA in a prospective, randomized, double–blinded fashion. Interim analysis at week 22 revealed no safety concerns; however, the analysis showed no therapeutic benefit with infliximab, and the study was therefore terminated prematurely. Lack of therapeutic efficacy in blocking TNF–α is in line with the observation that TNF–α is only minimally produced in the vasculitic lesions of GCA patients.57 Another recent trial examined the use of infliximab in the related condition of PMR was also negative, showing no effect of infliximab.58

Tan et al. reported the successful use of etanercept, a TNF–α receptor fusion protein, in a patient described as having corticosteroid–resistant GCA.59 The patient described in their report, however, had diffuse aching in the shoulders, arms, and legs, and a negative temporal artery biopsy, and may, in fact, have had PMR instead of GCA.22,60 A contradictory case report described the development of GCA in a patient taking etanercept for rheumatoid arthritis61. In a small recent randomized trial of biopsy–proven giant cell arteritis patients controlled on corticosteroids, but with side effects, 4 of 8 patients treated with etanercept and 2 of 9 patients on placebo had controlled GCA off all steroids at 1 year (p = nonsignificant), and the etanercept group had a lower cumulative dose of prednisone (p = 0.03).62 As the authors point out, the limited number of patients included in the study did not allow for definitive conclusions to be drawn. A single case report supports the use of adalimumab, a fully human recombinant anti–TNF–α monoclonal antibody, in GCA63 but is counterbalanced by a recent case report of a patient with rheumatoid arthritis who
developed biopsy–proven GCA after two years of treatment with adalimumab. A phase III randomized, double-blind, placebo-controlled trial, the HECTHOR trial, is now underway and will study the efficacy and safety of adalimumab as an adjunct to corticosteroids in GCA. Research has also turned toward the blockage of other cytokines implicated in the pathogenesis of GCA, particularly IL–1, IL–6, interferon–γ and CCL–2.

Evidence for other cytotoxic or immunomodulatory agents in GCA is weak, limited to small trials and case reports. The most robust of the trials studied azathioprine in a mixed population of patients with either GCA or PMR. Azathioprine was shown to have a mild steroid–sparing effect in these patients during the corticosteroid taper. This effect, however, only became statistically significant after one year of treatment, perhaps reflective of azathioprine’s slow mode of action. Because of the methodological limitations of this trial, as well as the increased incidence of hepatotoxicity and carcinogenesis with azathioprine, the drug is now largely ignored in the treatment of GCA.

An attempt was made to study cyclosporine A as an adjunct to corticosteroids, but the authors did not comment on the efficacy of cyclosporine, other than to state that “patients in both arms of the trial showed a significant reduction in corticosteroid doses over twelve months.” A high rate of premature termination of cyclosporine was seen due to adverse effects of the drug, and the authors concluded that cyclosporine did not show a significant steroid–sparing effect, primarily due to its poor tolerability.

Published reports claim efficacy for dapsone and cyclophosphamide in the treatment of GCA; however, dapsone can have serious hematologic side–effects, including hemolysis and granulocytopenia, while cyclophosphamide can cause bladder cancer and bone marrow suppression. Neither treatment has been supported by a controlled clinical trial, and reported success for both treatments is anecdotal. Both treatments have now been, for the most part, abandoned.

Rituximab is an anti–CD20 monoclonal antibody that depletes B cells and is often used in the treatment of non–Hodgkins lymphoma and B cell leukemias. Bhatia et al. described a patient with PMR and GCA who was treated with “B cell depletion therapy” – intravenous methylprednisolone, cyclophosphamide, and rituximab. The patient developed respiratory failure four days after treatment and was transferred to the intensive care unit for an unspecified period of time. Her GCA symptoms were reported to have resolved and her ESR and CRP normalized.

Although the search for a safe and effective steroid–sparing agent continues, there is very little persuasive evidence that any of these agents is really helpful, and their use remains debated. The best steroid–sparing agent, in fact, seems to be induction pulse methylprednisolone, which allows for faster tapering of oral prednisone.

C. ANTI-THROMBOTIC AGENTS

Ischemic complications of GCA, including visual loss and strokes, presumably result from local arteritic inflammation of vessel walls. However, the ultimate pathology of ischemia may differ depending on the location. Arteritic AION results from local inflammatory intimal hyperplasia with subsequent vaso–occlusion of the short posterior ciliary arteries. It is not clear whether intracranial ischemic strokes result from distal embolization of thrombi formed in inflamed large arteries or from proximal vessel occlusion. Wilkinson and Russell have discussed an increased susceptibility to GCA of arteries with well–developed elastic layers, possibly explaining the preponderance of vertebrobasilar infarctions over anterior circulation infarctions in GCA.

Aspirin has been used as an anti–platelet agent in the prevention of myocardial infarctions and brain ischemia for decades. Weyand et al. have demonstrated additional potent anti–inflammatory effects of aspirin in the mouse chimera model of GCA, primarily through aspirin’s inhibition of interferon–γ synthesis, a

<table>
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<td>Nesher et al.</td>
<td>Retrospective</td>
<td>166</td>
<td>GCA diagnosed by biopsy or ACR criteria between 1980–2000</td>
<td>1. Prednisone and aspirin (any dose)</td>
<td>Occurrence of a cranial ischemic complication</td>
<td>Fewer cranial ischemic complications with aspirin (8% vs. 29%; P=0.01)</td>
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<tr>
<td>Lee et al.</td>
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<td>143</td>
<td>GCA diagnosed by modified ACR criteria between 1989 and 2004</td>
<td>1. Prednisone and aspirin, clopidogrel, or warfarin</td>
<td>Occurrence of an ischemic event; occurrence of bleeding complications</td>
<td>Fewer ischemic events with aspirin (OR=0.18; P&lt;0.0005) or warfarin (OR=0.17; P&lt;0.04); no observed increase in bleeding complications.</td>
</tr>
</tbody>
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ACR: American College of Rheumatology; OR: odds ratio
D. STATINS

HMG-CoA reductase inhibitors, also known as “statins”, are drugs widely used in the treatment of dyslipidemia and prevention of atheromatous cardiovascular disease. In addition to their lipid-lowering effects, statins have also been discovered to have anti-inflammatory\(^78\) and immunomodulatory\(^79,80\) properties. Because long-term corticosteroid use can be associated with dyslipidemia, many patients being treated for GCA are treated concurrently with statins.

In a retrospective study by Garcia-Martinez et al.,\(^81\) statins were not found to have any corticosteroid-sparing effect and did not improve disease outcome. The authors compared two groups of patients with biopsy-proven GCA who underwent a standardized corticosteroid tapering protocol. One group of patients had never been on a statin, and the other group of patients had been on a statin for more than one year. The authors found that the two groups were similar in the time it took to reach a prednisone maintenance dose less than 10mg per day, and similar in the cumulative dose of prednisone received at that point. A beneficial effect of statins may have been muted, however, as only low to moderate doses of statins were used, and the corticosteroid tapering schedule was gentle. The authors concluded that statins had no corticosteroid-sparing effect in GCA in their study, but that prospective randomized trials were needed to verify this result.

E. PATIENT EDUCATION

Patients must be informed of the risks and benefits of acute and long-term corticosteroid use before commencing treatment, as well as the dangers of abrupt cessation of corticosteroids. They should be told that although a typical course of steroid treatment for GCA lasts one to three years, theirs could last longer. Also, because GCA may relapse at any dose of corticosteroids during the tapering process, and thereby threaten vision, patients must be advised to seek medical attention immediately whenever symptoms of GCA recur, particularly if they develop new visual blurring or blindness.

3. CONCLUSIONS AND RECOMMENDATIONS

Table 6 (page 89) presents a practical guide to the management of GCA. Even after more than fifty years of research and study, the mainstay of treatment of GCA remains corticosteroids. Corticosteroids are highly effective in suppressing the disease and preventing the most dreaded complications of GCA – vision loss and strokes; however, their use is accompanied by serious side-effects in more than half of patients, and research efforts have been devoted to the search for an effective steroid-sparing agent. Ironically, the most promising corticosteroid-sparing medication identified to-date seems to be induction pulse intravenous methylprednisolone. Aspirin appears beneficial in retrospective trials in preventing ischemic complications of GCA, but no prospective trials have been done.

CME ANSWERS:

1. False
2. False
3. True
### Diagnosis

1. Obtain baseline CBC, platelets, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and temporal artery biopsy as soon as possible in any patient suspected of having GCA, but do not delay the initiation of treatment while waiting for the biopsy.

### Initial Treatment

2. Begin treatment with an induction dose of intravenous methylprednisolone 15mg/kg per day for three days for its steroid-sparing effects over the long term and its possible effects on visual recovery in the short-term.
3. Subsequently begin prednisone 1 mg/kg/day.
4. For prophylactic bone protection, begin calcium supplementation (1200mg per day) and vitamin D (800IU per day) and obtain a baseline bone density scan. In osteoporotic patients, begin a bisphosphonate as well.
5. Begin daily low-dose aspirin unless contraindicated (aspirin may sometimes be delayed until after the temporal artery biopsy).

### Initial Monitoring

6. Monitor clinical symptoms and platelets, ESR and CRP. Question the diagnosis of GCA if improvement of systemic symptoms does not begin to occur within the first few days.

### Tapering and Relapses

7. When disease control has been achieved (defined as normal ESR and CRP, and no systemic symptoms of GCA), begin to taper prednisone.
8. Taper prednisone every month, if possible. The taper schedule must be individualized to each patient. Begin by decreasing large doses by 10mg per month initially, then 5mg per month, and then as little as 1mg per month once a prednisone dose of 10-15mg per day has been achieved. Do not use alternate daily dosing. Instruct the patient to seek medical attention immediately upon recurrence of symptoms, particularly visual symptoms.
9. At each follow-up visit, obtain an ESR and CRP. If both are elevated above normal, increase the prednisone dose to the last level that maintained remission until the ESR and CRP have normalized again. Similarly, increase the prednisone dose when a patient has recurrence of GCA symptoms, even in the absence of elevated ESR and CRP.

### Follow-Up

10. Schedule follow-up visits every 2-3 weeks while patient is on more than 40mg per day of prednisone, then every 4-6 weeks until the patient has reached a low maintenance dose; then follow up every 3 months.

### Discontinuing Steroids

11. When a patient has been completely tapered off prednisone, follow the patient clinically and with ESR and CRP for at least one year further to guard against relapse.

### REFERENCES


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