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The Treatment of Giant Cell Arteritis

J. Alexander Fraser, MD[*], **Cornelia M. Weyand, MD, PhD**[†], **Nancy J. Newman, MD**[‡,§,¶], and **Valérie Biousse, MD**[‡,§]

[*] Department of Clinical Neurological Sciences, University of Western Ontario School of Medicine, London, Ontario, Canada

[†] Department of Medicine, Lowance Center for Human Immunology, Emory University School of Medicine, Atlanta, GA

[‡] Department of Ophthalmology, Emory University School of Medicine, Atlanta, GA

[§] Department of Neurology, Emory University School of Medicine, Atlanta, GA

[¶] Department of Neurological Surgery, Emory University School of Medicine, Atlanta, GA

Abstract

Although giant cell arteritis (GCA) is a well-known vasculitis sensitive to corticosteroid-mediated immunosuppression, numerous issues of 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. This article systematically reviews the treatment options for patients with neuro-ophthalmic and neurological complications of GCA, as well as the evidence for possible adjuvant therapies for patients with GCA. Although there is no randomized controlled clinical trial specifically evaluating GCA patients with ocular and neurological complications, we recommend that GCA patients with acute visual loss or brain ischemia be admitted to the hospital for high-dose intravenous methyl-prednisolone, close monitoring, and prevention of steroid-induced complications. Aspirin may also be helpful in these cases. The evidence supporting the use of steroid-sparing immunomodulatory agents such as methotrexate for long-term management remains debated.

Keywords

Arteritic ischemic optic neuropathy; Giant cell arteritis; Steroids; Stroke; Temporal arteritis

Giant cell arteritis (GCA) is a vasculitis affecting medium and large vessels, with a predilection for the aorta and its branches. The term *giant cell arteritis* is often used interchangeably with *temporal arteritis* and *cranial arteritis*, but these terms are misleading. Although GCA usually involves the superficial temporal artery and other extracranial branches of the carotid, the disease also frequently affects the aorta and its large branches, and is by no means confined to the head.[1]

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,[2] but increases with age, and reaches its peak in the eighth decade of life.[3] The prevalence of GCA is highest in northern latitudes and in individuals of Northern European descent[4]; women are 2 to 6 times more commonly affected than men.[1,5,6]

Headache is the most common symptom of GCA, present in two-thirds of patients.[4] Jaw claudication, scalp tenderness, and visual loss are less frequent, but provide important clues

toward making the correct diagnosis; 40% 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.7 Visual loss is the most dreaded complication of GCA and, before the era of corticosteroid treatment, was noted in 30% to 60% of patients.8 Despite the widespread use of corticosteroids in the modern era, devastating visual loss may still occur in 14% to 20% of patients with GCA.4,8 Cerebral infarction, which has a strong predilection for the vertebrobasilar territory in GCA, is rare (occurring in only 1% of patients).[9,10]

Visual loss typically occurs on the basis of arteritic anterior ischemic optic neuropathy (AION)—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.11 If left untreated, GCA is associated with visual loss in the fellow eye within days to weeks in up to 50% of individuals.7,12 Permanent visual loss is preceded by episodes of transient visual loss in 44% of patients.8 A substantial proportion (21.2%) of patients with GCA present with visual loss alone,[13] 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.[14] 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. Intimal proliferation and marked disruption of the internal elastic lamina are characteristic findings, and multinucleated giant cells are present in a subset of patients.1,4,15

TAB 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.[16]

Treatment of GCA

GCA encompasses a broad spectrum of clinical subtypes, including cranial arteritis with severe ischemic complications (eg, 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.[7]

Few studies evaluate treatment protocols by individual GCA subtype. Instead, studies examining treatment protocols for GCA are influenced by the patient populations from which they draw, 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 those of rheumatologists and researchers performing population-based studies.11,17 Rheumatologists, for example, may use low-dose oral prednisone to treat "isolated" PMR, whereas neuro-ophthalmologists often use high-dose

intravenous (IV) methylprednisolone to treat patients with abrupt visual loss or brain ischemia.

Corticosteroids

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.[4,9,11,17] 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.[11]

Oral prednisone is first-line acute therapy for GCA. The initial starting dose used to control GCA varies widely in the literature—from 20 mg/d in a mixed population of patients with either GCA or PMR but with strictly constitutional signs and symptoms,18 to more than 100 mg/d in a high-risk neuro-ophthalmic population with recent or impending visual loss.[11] Selection bias during enrollment influences the conclusions of these studies; rheumatological reports often combine GCA with PMR (a much milder condition that 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 1 mg/kg/d, or between 40 and 60 mg/d.[4,15] Higher doses of 80 to 100 mg/d are suggested for patients with visual or neurological symptoms of GCA.[9,11]

IV pulse methylprednisolone has been proposed as an induction therapy, particularly in cases where vision is at risk. Four studies have examined IV steroid therapy in GCA, 2 of which were prospective randomized controlled trials (Table 1). The study by Chevalet and colleagues19 showed no benefit for a single low induction dose of IV methylprednisolone, 250 mg, in reducing cumulative steroid dose at 1 year; however, the recent study by Mazlumzadeh and coworkers[20] found that a 3-day course of induction IV methylprednisolone at a much higher dose of 15 mg/kg/d (about 1000 mg/d) 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 1 study, by Chan and associates,[21] evaluated IV 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 treated with induction IV steroids compared with oral steroids alone. We recommend treating GCA with a 3-day induction dose of IV methylprednisolone, 15 mg/kg/d, followed by oral prednisone maintenance therapy at an initial dose of 1 mg/kg/d.

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.[4] Improvement of visual loss from arteritic AION is much less striking, and occurs in only 4% to 34% of patients in the largest series (Table 2). Visual improvement, when it occurs, is mild, with persistent and often severe visual field defects.[22-24] When treatment is initiated within 24 hours of visual symptoms, 58% of patients have visual improvement, compared with the 6% of patients who improve after a delay in treatment, illustrating the urgency of corticosteroid treatment.[1]

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.[25,26]

However, when deterioration occurs in this setting, it does so early—typically within the first 5 days of treatment.[8,27]

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.[4,9,11] 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.[4] Indeed, a 1- to 2-year course is typically required. The daily oral dose can be tapered by 10 mg every month at first, followed by 5 mg every month, and then by as little as 1 mg every month once the dose reaches 10 to 15 mg/d.[28] A prospective study by Hunder and colleagues[29] demonstrated decreased efficacy and increased risk of relapse with alternate-day dosing; therefore, corticosteroids should be given daily rather than on alternate days. Close follow-up is indicated during the tapering process, with follow-up visits every 2 to 3 weeks until the dose of prednisone reaches 40 mg/d, followed by regular visits every 4 to 6 weeks thereafter until the dose of prednisone reaches a low maintenance dose, at which point the patients may be followed approximately every 3 months.[9]

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.[11,28] 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.28 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 need to be followed carefully with repeat ESR and CRP a few days later to confirm relapse prior to increasing steroids. 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.4

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 “smoldering” disease.[11,30] Persistent elevation of interleukin (IL)-6 levels, even when CRP and ESR are within normal limits, supports the concept of ongoing subclinical disease activity.[30] Even after steroids have been successfully tapered and discontinued, it is prudent to follow patients for at least 1 year to monitor for further relapses.31

We recommend tapering prednisone only after disease control has been achieved, that is, after the ESR and CRP have normalized and when systemic symptoms of GCA are no longer apparent. We suggest tapering the prednisone dose every month, if possible, as guided by ESR, CRP, and patient symptoms. Any recurrence of symptoms or increase in laboratory parameters should prompt an increase in the prednisone back to the last effective dose. Tapering must be done slowly, as described above. We suggest follow-up visits every 2 to 3 weeks while the patient is on more than 40 mg per day of prednisone, every 4 to 6 weeks until the patient has reached a low maintenance dose, and then every 3 months thereafter. When maintenance corticosteroids are discontinued, we recommend a further 1 year of outpatient follow-up to guard against further relapses of GCA.

Adverse effects of corticosteroids—Corticosteroids have well-recognized adverse effects (Table 3) 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 a 15-year study of patients with GCA, 58% of patients had at least 1 serious steroid-related adverse effect during their course of treatment.[32] Even cases of sudden death from high-dose IV corticosteroids have been reported,[9,33] possibly a result of coronary artery thrombosis and myocardial infarction.[34] 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 3 mechanisms.[35,36] 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 IV corticosteroid therapy. Additionally, introduction of antiplatelet agents should be considered.[37,38]

Some adverse effects from corticosteroids can be mitigated through simple measures (Table 4). 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 (1200 mg/d) and vitamin D (800 IU/d), as well as a bisphosphonate if osteoporosis is seen on baseline bone mineral densitometry. Vitamin D levels can now be measured in the blood, enhancing detection of insufficient substitution therapy. Weight-bearing exercises, smoking cessation, and reduction of alcohol intake are also advised for bone protection.[39,40] 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 radiographs followed by MRI.

Because adverse effects of corticosteroids are common and a source of serious morbidity in elderly populations, treating clinicians are often under pressure from patients and their primary care physicians to taper corticosteroids and discontinue treatment, with subsequent risk of rebound GCA and visual loss. A positive TAB result becomes essential in such cases to justify prolonged corticosteroid treatment, underscoring the importance of obtaining pathological proof of the disease at the time of symptom onset.

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 with corticosteroids in a prospective double-blinded fashion. They can, however, be used adjunctively with corticosteroids and compared with corticosteroid treatment alone. Of the many immunosuppressive drugs used as steroid-sparing agents, methotrexate is the best studied (Table 5).

Three randomized placebo controlled trials have compared methotrexate with placebo as adjunctive therapy in the treatment of GCA with corticosteroids, with contradictory results (Table 5). Studies by Spiera and colleagues[41] and Hoffman and coworkers[42] reported no significant decrease in cumulative steroid dose or in relapse rate at 1 year among patients treated with corticosteroids and methotrexate compared with those treated with corticosteroids and placebo. The study by Jover and associates,[43] however, reported a significant decrease in cumulative steroid dose and relapse rate at 2 years among patients

treated with adjuvant methotrexate compared with placebo. The methodologies of these 3 trials differ, and each has been subject to criticism.

A recent meta-analysis of the methotrexate studies[44] reanalyzed the pooled data and revealed a benefit for oral methotrexate 7.5 to 15 mg/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 2 groups. A benefit of methotrexate over placebo in preventing GCA relapses began late in the disease course, between weeks 24 and 36, and strengthened as the follow-up period increased. In a prespecified subgroup analysis, a statistically significant benefit was seen in women, but not in men. 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 methotrexate (Table 6). Immunohistochemical examination of the damaged vessel walls of GCA-positive TAB specimens has suggested an abundance of the cytokine tumor necrosis factor-α (TNF-α) within giant cells, macrophages, and T cells.[45] Case reports of successful treatment of corticosteroid-resistant GCA with the monoclonal anti-TNF-α antibody infliximab have been published,[46,47] and success with this agent has been seen in several other inflammatory diseases, such as rheumatoid arthritis and psoriasis.

Based on this groundwork, Hoffman and colleagues[48] studied the utility of infliximab 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.[49]

Another recent trial50 examined the use of infliximab in the related condition of PMR, with a study design similar to that of the study by Hoffman and coworkers.[48] This trial was also negative, showing no effect of infliximab. As a consequence of these 2 randomized controlled trials, research attention has now turned away from TNF-α blockade, and toward the blockade of other cytokines implicated in the pathogenesis of GCA, particularly IL-1, IL-6, interferon-α, and chemokine ligand 2 (CCL2).[51]

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.[52] 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 1 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.[53]

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 12 months."[54] 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[55-57] and cyclophosphamide[58] in the treatment of GCA; however, dapsone can have serious hematologic side effects, including hemolysis and granulocytopenia, whereas 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.

Tan and associates[59] reported the successful use of etanercept, a TNF-α receptor fusion protein, in a patient described as having corticosteroid-resistant GCA. The patient described in their report, however, had diffuse aching in the shoulders, arms, and legs, and a negative TAB result, and may actually have had PMR instead of GCA.[17,60] No further case reports of success with etanercept in GCA have emerged. In fact, a contradictory case report has been published describing the development of GCA in a patient taking etanercept for rheumatoid arthritis.61 A single case report supports the use of adalimumab, a fully human recombinant anti-TNF-α monoclonal antibody, in GCA62 but is counterbalanced by a recent case report of a patient with rheumatoid arthritis who developed biopsyproven GCA after 2 years of treatment with adalimumab.[63] A phase III randomized, double-blind, placebo-controlled trial (the Humira to Spare Steroids in Giant Cell Arteritis [HECTHOR] trial), is now underway and will study the efficacy and safety of adalimumab as an adjunct to corticosteroids in GCA.

Rituximab is an anti-CD20 monoclonal antibody that depletes B cells and is often used in the treatment of non-Hodgkin's lymphoma and B-cell leukemias. Bhatia and colleagues[64] described a patient with PMR and GCA who was treated with "B cell depletion therapy" (IV methylprednisolone, cyclophosphamide, and rituximab). The patient developed respiratory failure 4 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.[20,21]

Antithrombotic 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[65] 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 antiplatelet agent in the prevention of myocardial infarctions and brain ischemia for decades.[66,67] Weyand and coworkers[68] have demonstrated additional potent anti-inflammatory effects of aspirin in the mouse chimera model of GCA, primarily through aspirin's inhibition of interferon-α synthesis, a complementary mechanism of action to the suppression of NF-kB–dependent monokines by corticosteroids.

The clinical effectiveness of aspirin in GCA has been studied in 2 retrospective reviews (Table 7). One study by Nesher and colleagues37 found significantly fewer GCA-related

cranial ischemic complications, both at the time of GCA diagnosis and during the follow-up of patients who were taking aspirin at the time of diagnosis, compared with those not taking aspirin. This protective effect of aspirin was seen in spite of the significantly increased prevalence of cerebrovascular risk factors in the aspirin-treated group. The other study, by Lee and colleagues,[38] had a similar design but compared patients taking any antithrombotic agent (aspirin, clopidogrel, or warfarin) with those not taking such agents. The authors' multivariate analysis revealed a protective effect against ischemic events in patients taking an antithrombotic agent, and did not demonstrate an increase in bleeding complications. The authors recommended the use of low-dose aspirin in the treatment of GCA, but did not comment on a role for anticoagulation. All patients in both trials were treated with prednisone after the diagnosis of GCA was made.

It is important to emphasize that despite emerging evidence for the use of aspirin acutely in GCA, some surgeons are reluctant to perform TABs on patients treated with an antiplatelet agent because of the risk of bleeding. At some centers, this may limit the acute use of aspirin in GCA patients.

Although anticoagulation has sometimes been used in treating GCA,[69] no published prospective trials have verified its utility. Buono and coworkers[70] reported 1 case of arteritic AION that progressed, despite high-dose IV corticosteroid administration. Five days after initiating corticosteroid treatment, the authors added IV heparin, and saw improvement over the next 2 days in the patient's visual acuity, static perimetry, and short posterior ciliary artery blood flow on color Doppler imaging. The authors proposed that the improvement was related to the institution of heparin therapy, rather than a coincidental improvement due to high-dose corticosteroids. We recommend the use of aspirin as an adjunct to corticosteroids in the treatment of GCA, unless contraindicated. Aspirin may be delayed until after the TAB if necessary.

Statins

HMG-CoA reductase inhibitors (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[71] and immunomodulatory[72,73] 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 and associates,[74] statins were not found to have any corticosteroid-sparing effect and did not improve disease outcome. The authors compared 2 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 1 year. The authors found that the 2 groups were similar in the time it took to reach a prednisone maintenance dose less than 10 mg/d, 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.

Patient Education

Patients must be informed of the risks and benefits of 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 1 to 3 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.

Conclusions and Recommendations

Table 8 presents a practical guide to the management of GCA. Even after more than 50 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 IV methylprednisolone. Methotrexate may have moderate effects as a steroid-sparing agent, but it is not clear at present whether its adverse effects outweigh the adverse effects of prolonged corticosteroid use. There is no proven role for any other cytotoxic or immunomodulatory medications in GCA at present. Aspirin appears beneficial in retrospective trials in preventing ischemic complications of GCA, but no prospective trials have been done.

Main Points

- Two-thirds of patients with giant cell arteritis (GCA) complain of headache. Other symptoms, such as jaw claudication, scalp tenderness, and visual loss, are less frequent but provide important clues toward making the correct diagnosis. 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. Widespread use of corticosteroid treatment has decreased the frequency of devastating, permanent visual loss to 14%-20% of patients with GCA.
- 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.
- After GCA is considered to be controlled, 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.
- 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, carries serious risks. 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 3 mechanisms; introduction of antiplatelet agents should be considered.
- Because of the significant morbidity associated with long-term corticosteroid use, efforts have been made to investigate steroid-sparing agents in the treatment of GCA. Of the many immunosuppressive drugs used as steroid-sparing agents, methotrexate is the best studied, although the search for safe and effective

steroid-sparing agents in GCA has broadened to include a number of other cytotoxic and immunomodulatory agents.

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Table 1

Therapeutic Trials of Intravenous Methylprednisolone for Giant Cell Arteritis

Study	Design	N	Population	Intervention	Primary Endpoint	Outcome
Chevalet et al.[19]	3-armed RCT	164	GCA without ocular or cerebrovascular involvement	**1** 1 pulse of 240 mg IV methylprednisolone followed by 0.7 mg/kg oral prednisone **2** 1 pulse of 240 mg IV methylprednisolone followed by 0.5 mg/kg oral prednisone **3** Oral prednisone, 0.7 mg/kg	Cumulative steroid dose at 1 year	No benefit with IV vs oral steroids
Chan et al.[21]	Retrospective	73	Vision loss from biopsy-proven GCA	**1** High-dose IV methylprednisolone (~ 1000 mg/d for 3 days), followed by oral, prednisolone at 75 mg/d **2** Oral prednisolone, 75 mg/d	Significant improvement in visual acuity on Snellen chart	Benefit for IV vs oral steroids (40% vs 13%; $P = .01$)
Hayreh and Zimmerman[11]	Longitudinal observational	145	Biopsy-proven GCA	**1** "Megadose" IV dexamethasone (up to 450 mg/d for up to 3 days) followed by oral prednisone, 80-120 mg/d **2** Oral prednisone alone	Visual outcome; cumulative steroid dose	No benefit with IV vs oral steroids
Mazlumzadeh et al.[20]	2-armed RCT	27	GCA without ocular or cerebrovascular involvement	Oral prednisone 40 mg/d followed by a systematic taper at week 4, plus an "induction" dose of: **1** IV methylprednisolone 15 mg/kg/d for 3 days (~ 1000 mg/d) **2** 2. Placebo	Prednisone dose of no more than 5 mg/d at 36 weeks	Benefit for IV vs oral steroids (71% vs 15%; $P = .003$)

GCA, giant cell arteritis; IV, intravenous; RCT, randomized controlled trial.

Table 2

Recent Studies of Visual Recovery With Corticosteroid Treatment of Giant Cell Arteritis

Study	Year	Design	N	Findings
Liu et al.[33]	1994	Retrospective	41	34% of patients with visual loss had visual improvement with IV or oral corticosteroids. More benefit was seen in the patients who received IV treatment.
Gonzales-Gay et al.[8]	1998	Retrospective	34	Early treatment (within 24 hours) was the only predictor of recovery of VA. No significant difference between IV and oral treatment.
Kupersmith et al.[75]	1999	Prospective	22	4 of 9 (44%) eyes had improved VA within 1 month of starting treatment with oral prednisone.
Hayreh et al.[22]	2002	Retrospective	114	4% of patients had improvement of both VA and central VF on treatment. A trend toward improvement was seen with immediate treatment.
Foroozan et al.[23]	2003	Retrospective	32	13% of patients had improvement of VA with treatment (time from onset of symptoms not specified), but none showed significant improvement in VF.
Danesh-Meyer et al.[24]	2005	Prospective	34	Patients received treatment within 10 days after onset of visual loss (mean 2 days). 15% of patients had improvement of VA of 2 or more lines. No significant improvement was seen of VF or color vision.

GCA, giant cell arteritis; IV, intravenous; VA, visual acuity; VF, visual field.

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Table 3

Features of Corticosteroid Excess

Sign/Symptom	Frequency (%)
Truncal obesity	96
Facial fullness	82
Diabetes or glucose intolerance	80
Gonadal dysfunction	74
Hirsutism, acne	72
Hypertension	68
Muscle weakness	64
Skin atrophy and bruising	62
Mood disorders	58
Osteoporosis	38
Edema	18
Polydipsia, polyuria	10
Fungal infections	6

Adapted with permission from Boscaro et al.[76]

Table 4

Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Patient beginning therapy with glucocorticoid (prednisone equivalent ≥ 5 mg/d) with plans for treatment of more than 3 months:
Modify lifestyle risk factors for osteoporosis
Smoking cessation or avoidance
Reduction of alcohol consumption if excessive
Instruct in weight-bearing physical exercise
Initiate calcium supplementation
Initiate supplementation with vitamin D (plain or activated form)
Prescribe bisphosphonate (use with caution in premenopausal women)
Patient receiving long-term glucocorticoid therapy (prednisone equivalent ≥ 5 mg/d):
Modify lifestyle risk factors for osteoporosis
Smoking cessation or avoidance
Reduction of alcohol consumption if excessive
Instruct in weight-bearing physical exercise
Initiate calcium supplementation
Initiate supplementation with vitamin D (plain or activated form)
Prescribe treatment to replace gonadal sex hormones if deficient or otherwise clinically indicated
Measure BMD at lumbar spine and/or hip
If BMD is not normal (T-score below −1), then:
Prescribe bisphosphonate (use with caution in premenopausal women)
Consider calcitonin as second-line agent if patient has contraindication to or does not tolerate bisphosphonate therapy
If BMD is normal, follow up and repeat BMD measurement either annually or biannually

BMD, bone mineral density.

Adapted with permission from the American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis.[39]

Table 5

Therapeutic Trials of Methotrexate for Giant Cell Arteritis

Study	Design	N	Population	Intervention	Primary Endpoint	Outcome
Spiera et al.[41]	RCT	21	Diagnosis of GCA based on clinical, biopsy, and angiographic criteria	Oral prednisone, 1 mg/kg/d with a taper to 30 mg/d, and then: **1** MTX, 7.5 mg/week **2** Placebo	Cumulative steroid dose at 1 year; duration of steroid taper; functional status; adverse effects	No benefit with MTX vs placebo
Jover et al.[43]	RCT	42	Biopsy-proven GCA	Oral prednisone, 60 mg/d with a taper, and: **1** MTX, 10 mg/week **2** Placebo	Number of relapses; cumulative steroid dose at 2 years	Benefit with MTX vs placebo in number of relapses (45% vs 84.2%; $P = .02$) and cumulative steroid dose (4187 mg vs 5489.6 mg; $P = 0.009$)
Hoffman et al.[42]	RCT	98	Diagnosis of GCA based on clinical, biopsy, or angiographic criteria	Oral prednisone, 1 mg/kg/d with a taper to eod dosing, and: **1** MTX, 0.15 mg/kg/week, increased to 0.25 mg/kg/week **2** Placebo	Relapse and treatment failure rate; cumulative steroid dose at 1 year	No benefit with MTX vs placebo
Mahr et al.[44]	Individual patient meta-analysis	161	Individual patients with GCA, from the above 3 trials	Oral prednisone and: **1** MTX, 7.5-10 mg/week **2** Placebo	Time to first and second relapses of GCA; cumulative steroid dose at 48 weeks	Benefit with MTX vs placebo in risk of first and second relapse (HR = 0.65; $P = .04$; and HR = 0.49; $P = .02$, respectively), and cumulative steroid dose at 48 weeks (842 mg difference; $P < .001$)

Eod, every other day; GCA, giant cell arteritis; HR, hazard ratio; MTX, methotrexate; RCT, randomized controlled trial.

Table 6

Therapeutic Trials of Other Cytotoxic and Immunomodulatory Agents for Giant Cell Arteritis

Agent	Study	Design	N	Population	Intervention	Primary Endpoint	Outcome
Infliximab	Hoffman et al.[48]	RCT	44	GCA as per ACR criteria, in steroid-induced remission for ≥ 1 week	Oral corticosteroid (prednisone or prednisolone) with scheduled taper, plus: **1** Infliximab, 5 mg/kg **2** Placebo	Number of patients relapse free by week 22; adverse effects	No significant benefit or harm with infliximab; trial was stopped early
Azathioprine	De Silva and Hazleman[52]	RCT	31	Either GCA or PMR by Jones/ Hazleman criteria, in steroid-induced remission for ≥ 3 months	Oral prednisolone taper, with: **1** Azathioprine, 150 mg/d **2** Placebo	Prednisolone dosage at 52 weeks	Benefit with azathioprine vs placebo in steroid dose at 52 weeks (1.9 mg vs 4.2 mg; $P < .05$); high dropout rate in azathioprine group
Cyclosporine A	Schaufelberger et al.[54]	RCT, open-label	60	Biopsy-proven GCA meeting ACR criteria	Prednisone with scheduled taper, with: **1** Cyclosporine A, 2 mg/kg/d (tapered according to response and adverse effects) **2** Placebo	Change in steroid dose over 12 months	No efficacy data provided by authors; high rate of premature termination and adverse effects in cyclosporine A group

ACR, American College of Rheumatology; GCA; giant cell arteritis; PMR, polymyalgia rheumatica; RCT, randomized controlled trial.

Table 7

Reports of Antithrombotic Medications for Giant Cell Arteritis

Study	Design	N	Population	Intervention		Primary Endpoint	Outcome
Nesher et al.[37]	Retrospective	166	GCA diagnosed by biopsy or ACR criteria between 1980-2000	**1** **2**	Prednisone and aspirin (any dose) Prednisone alone	Occurrence of a cranial ischemic complication	Fewer cranial ischemic complications with aspirin (8% vs 29%; $P = .01$)
Lee et al.[38]	Retrospective	143	GCA diagnosed by modified ACR criteria between 1989-2004	**1** **2**	Prednisone and aspirin, clopidogrel or warfarin Prednisone alone	Occurrence of an ischemic event; occurrence of bleeding complications	Fewer ischemic events with aspirin (OR = 0.18; $P < .0005$) or warfarin (OR = 0.17; $P < .04$); no observed increase in bleeding complications

ACR, American College of Rheumatology; GCA, giant cell arteritis; OR, odds ratio.

Table 8

Suggested Steps in the Management of Giant Cell Arteritis Complicated by Ocular or Brain Ischemia

Diagnosis

1. Obtain baseline CBC, platelets, ESR, 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, 15 mg/kg/d for 3 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 (1200 mg/d) and vitamin D (800 IU/d) 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 10 mg each month initially, then 5 mg each month, and then as little as 1 mg each month once a prednisone dose of 10-15 mg/d 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 40 mg/d 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 1 year further to guard against relapse.

CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis.