Treatment of giant-cell arteritis: where we have been and why we must move on

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In 1890, Hutchinson[1] provided an original description of painful inflammation of the temporal vessels. Following this case report, medical insights about temporal arteritis were slow to follow. It was not until 1932 that Horton, Magath, and Brown,[2] at the Mayo Clinic, noted in 2 patients that temporal arteritis was a component of a systemic disease. Biopsy proof of inflammation was presented and distinguished from "periarteritis nodosum."[2,3] The impact of blindness was first realized in 1946,[4] and the first observations regarding efficacy of corticosteroid (CS) therapy were noted in 1950 at the Mayo Clinic by Shick et al.[5] These investigators were the first to demonstrate decrease in blindness in the CS era and even reversal of visual abnormalities in some patients treated shortly after onset of symptoms.[6] How far have we come since those reports?

Since these seminal events, descriptive studies have made physicians keenly aware of classical and even unusual manifestations of giant-cell arteritis (GCA). Descriptions of illness in the elderly emphasize the implications of new-onset atypical or severe headaches, regional jaw and oral pain, or visual symptoms, especially if such symptoms are associated with proximal aching or constitutional abnormalities **(Table 1)**.

When combinations of these features are due to GCA, the Westergren erythrocyte sedimentation rate is elevated in over 90-95% of patients,[7-9] and temporal-artery biopsies reveal a lymphomonocytic or granulomatous infiltrate in at least 50% of temporal-artery biopsies.

Some presentations and disease profiles are very unusual. For example, the histopathologic finding of apparently sterile granulomatous vasculitis with giant cells in a resected aneurysm of the aortic root often leads surgeons to consult medical colleagues. In at least 75% of patients with such a presentation, there is no concurrent evidence of a systemic illness, headaches, or other clues that would support the diagnosis of classical GCA. In fact, such patients may not be elderly. Some have required surgical intervention for severe aortic regurgitation during the fourth decade of life.[10] Do these patients represent "outliers" for classical GCA? We recognize that this type of aortic abnormality may complicate the course of classical GCA in at least 15-20% of patients. However, is it possible that some of these patients have a distinctly different disease from GCA if they are not systemically ill, do not have headaches, visual symptoms, and other classical features of that illness? Should they be treated with CS medications? The answers to these questions are not always clear. However, it is recognized that within this group exist individuals who never received CS or other immunosuppressive therapies, and who have not subsequently developed additional similar vascular events or overt GCA during follow-up periods as long as 12 years.[10] Similar cases of aortitis, with or without giant cells, have been identified in <1-10% of postmortem series. In almost all cases, retrospective review of medical records failed to identify features of GCA or other systemic rheumatologic illnesses.[11,12] Because there is considerable doubt about the value of classifying such patients together with those having typical GCA, they will not be included in subsequent discussion of treatment strategies and outcomes for that disorder.

MEDICAL THERAPY OF GCA OF THE ELDERLY

Authorities agree that once a convincing diagnosis of GCA is assumed, treatment with CS should begin immediately. This sense of urgency is conveyed because of the knowledge that in the pre-CS era, GCA could be complicated by blindness in up to 30 to 60% of cases.[6] In fact, irreversible loss of vision may be a presenting feature in as many as 18% of cases in more current large series.[9,13-17] Risk of blindness increases further among patients with a recent history of amaurosis, unilateral blindness, or stroke.[9]

Prednisone is the most popular form of CS therapy employed. How much prednisone should be used initially? How long should the initial dose be maintained before it is tapered? How long should one expect to treat a patient with GCA? The answers to such questions are as numerous as authorities who have studied GCA. **Table 2** provides a summary of some recommendations. Comparative studies have not been performed that would clearly recommend any one approach above others.

In synthesizing a treatment plan from this literature,

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TABLE 1
GIANT-CELL ARTERITIS: CLINICAL FEATURES (FREQUENCY %)

Author (#cases)	Hunder (94)	Liozan (147)	González-Gay (239)	Chevalet (164)	*Hoffman (98)
Headache	77	NS	83	67	93
Abnormal temporal artery	53	55	72	21	NS
Jaw claudication/pain	51	38	39	16	60
Constitutional symptoms	48	65	70	NS	NS
Polymyalgia rheumatica	34	27	47	49	55
Fever	27	NS	11	46	5
Diplopia	12	NS	7	NS	NS
Amaurosis	5	NS	17	NS	NS
Blindness	13	13	14	NS	18
Stroke	NS	NS	3.5	NS	0
Mean age (yrs)	75	75	73	73	74
Percent female	74	63	56	71	71

* At presentation in this cohort. NS = Not stated.

one may be guided by comorbidities and other risk factors that influence an individual's prognosis or risk of toxicity. For example, in the setting of only headache, polymyalgia rheumatica, and constitutional symptoms, it would appear reasonable to use lower starting doses (eg, 30-40 mg/day) of prednisone, especially if the patient has diabetes, severe atherosclerosis, osteoporosis, or congestive heart failure. However, even if these comorbidities exist, in the setting of threatened or recent (24 to 48 hours) visual loss, higher doses of CS should be employed. Delay in initiation of CS therapy after onset of premonitory visual symptoms has been associated with poor visual outcomes.[15] Treatment may be effective in reversing or halting further visual loss if it is provided in the acute setting.[9,14,15] González-Gay et al[14] noted visual improvement in 7/12 patients who were treated for new-onset ocular symptoms within 24 hours, compared to in 1/17 in whom treatment was delayed more than 24 hours. No patient had improvement if treatment was provided >2 days after visual loss. Patients with visual loss also had an increased risk of stroke.

There is general agreement that once CS therapy has been started, the likelihood of subsequent visual loss is dramatically reduced.[6,13,14] However, one recent study that utilized an aggressive CS tapering protocol noted a prevalence of visual loss in 18% of patients at study enrollment and in an additional 13.8% at 1-year follow-up.[17]

How long to treat?

Whereas some early reports of GCA suggested that treatment may only be necessary for 6 to 12 months, in 1973 Beevers et al[18] recognized the chronic nature of this illness and noted that in many cases CS therapy may be required for several years. Indeed, this is now a widely accepted perception **(Table 2)**. Relapse rates in the course of CS tapering have been reportedly ~30->80% over 1 to 4 years of follow-up.[16-23] No doubt this broad range reflects differences between treatment protocols, definitions of relapse, and possibly even ethnic differences in study cohorts. Regardless of such differences, it is apparent that GCA is not readily controlled in many patients once CS are reduced to low or moderate doses (ie, prednisone 5-15 mg/day). Even after 2 to 3 years of therapy, about 50% of patients remain CS-dependent, a situation that has led to substantial morbidity in an already fragile elderly population. The risk of fractures and cataracts are 5 and 3 times greater, respectively, in patients with GCA compared to age-matched controls not treated with CS.[24] Nesher et al[25] found that among 43 patients followed for a mean period of 3 years, 35% had fractures and 21% had severe infections, which in two-thirds led to death. An important role for CS could be implicated in 37% of all deaths.

Whether mortality rates among patients with GCA are different than that of age- and sex-matched controls remains controversial. Definitive conclusions may not be possible because of the limited ability of published studies to detect differences among subsets of the very elderly, who have high mortality. Nonetheless, it is difficult to argue that when a patient with GCA is found to have died because of granulomatous inflammation, contributing to aortic dissection or rupture, that the illness did not play a role in premature death. These events are not rare. Among 100 cases of GCA followed at the Mayo Clinic, 16 patients had acute aortic dissection, which was fatal in 50%.[26,27] Others have also noted that GCA may contribute to death by stroke, myocardial infarction, or aortic aneurysm rupture. Most recognized disease-related deaths have been early in the course of illness. It has been sug-

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TABLE 2
RECOMMENDED USE OF PREDNISONE* IN GIANT-CELL ARTERITIS

Author	Initial Dose(s)	Start Chronic Dose Reduction	Rate of Reduction**	Comments
Graham[19]	80 mg/day × 2 days	Day 10	5 mg/week to 10 mg/day 10 mg/day × 3 months and then slow taper	
Lundberg and Hedfors[20]	19-37 mg/day; if visual or neurologic symptoms present, 37-75 mg/day	NS	NS	• Visual loss proximate to presentation: recommend 1,000 mg methylprednisolone IV • Most patients able to stop CS within 2 years
Nesher[29]	40 mg/day adequate for most	NS	Taper to 10 mg/day by 6 months and 5-7.5 mg/day by 1 year	50% of patients remain on therapy at 3-year follow-up
Chevalet[30]	35-50 mg/day	4 weeks	50% after 4 weeks, then more gradual	Initial doses of methylprednisolone (240 mg IV) do not provide therapeutic advantages
Hunder and Valente[26]	40-60 mg/day	2 weeks	30 or 50 mg/day at week 2, then decrease by 10% every 1-2 weeks until dose = 20 mg/day, then decrease every 2-4 weeks until 10 mg/day. Then decrease by 1 mg/month	50% of patients able to discontinue CS at 2-year follow-up

*Where prednisolone was used, conversion to an equivalent dose of prednisone is provided. **All authors continued taper only in absence of active disease. NS = Not stated.

gested that early deaths were due to inadequate treatment with CS or because CS were administered too late to affect fixed vascular abnormalities.[19,27,28] Although this is likely to be true, GCA or its treatment may in fact contribute to death at any time in the course of illness.

The need for prolonged CS therapy to control GCA, and the goal of reducing disease- and treatment-related morbidity and mortality, has led investigators to explore the use of adjunctive agents to improve outcomes.

A possibly important, but not yet addressed, issue is whether anti-platelet therapies or anticoagulation would improve or worsen outcomes.

■ ADJUNCTIVE THERAPY TO CORTICOSTEROIDS IN GCA

Numerous studies have explored the utility of either methotrexate (MTX) or azathioprine as a means of achieving improved disease control and less dependence on CS therapy. Because many of these studies have either been preliminary, combined GCA and "pure" polymyalgia rheumatica, or used very low doses of second agents, they will not be discussed. However, two recent randomized, double-blind, placebo-controlled studies of weekly MTX have been completed. In both, the rate of CS taper was rapid, so that in the absence of relapse, CS withdrawal could be accomplished in 4 months[23] or 6 months.[17] In both studies, relapses were frequent and the first relapse occurred with equal frequency in the CS-only and CS + MTX groups. However, the frequency of more than one relapse differed between groups in one study and not the other. Jover et al[23] found that MTX diminished second relapses and cumulative CS use, while Hoffman et al[17] did not find MTX to be beneficial. The reason for these different conclusions is uncertain. Consequently, what role MTX or other adjunctive therapies may play in GCA remains unsettled.

Surgical considerations

At least 15 to 20% of patients with GCA will develop clinically significant thoracic aortic (less often abdominal) aneurysms and/or stenoses of arch vessels. Sudden aortic rupture or dissection rarely provides opportunities for effective therapeutic intervention. It is therefore important that physicians who provide care for patients with GCA realize that newly recognized bruits or aortic murmurs may not merely represent atherosclerosis or calcification of valve leaflets. All such findings should be investigated. If an aneurysm or aortic regurgitation is found, it should be evaluated by cardiology and cardiovascular surgery colleagues. The cost-effectiveness of different imaging techniques for sequential large-vessel evaluation and the utility of angioplasty (+/- vascular stents) for aortic arch branch vessel stenoses have not been studied.

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THE FUTURE

Our inability to control GCA without producing CS-related morbidity may not represent an impasse. Numerous investigators have demonstrated that the lesions of GCA are, in large measure, driven by macrophages and Th-1–type lymphocytes. Vascular lesions are rich in pro-inflammatory cytokines such as IL-1, TNF, and IFN-γ. It is possible that excessive up-regulation of these mediators is critical to vessel injury. Should that be the case, anti-cytokine therapies that target IL-1 and the Th-1 pathways may prove to be beneficial for GCA.

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