Neuro-ophthalmic Complications in Giant Cell Arteritis

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Giant cell arteritis (GCA) is a medical emergency characterized by systemic inflammation and critical ischemia. Neuro-ophthalmic complications occur early, with permanent vision loss in up to one fifth of patients. This mainly results from failure of prompt recognition and treatment. Diagnosis of GCA is often preceded by unrecognized symptoms, including constitutional upset and jaw claudication. Features predictive of permanent visual loss include jaw claudication and temporal artery abnormalities on physical examination. These patients often do not mount high inflammatory responses. Modern imaging techniques show diagnostic promise, and have led to an increased recognition of major artery involvement in GCA. However, temporal artery biopsy remains the gold standard for investigation. Intimal hyperplasia on histologic examination is associated with neuro-ophthalmic complications. The mainstay of therapy remains corticosteroids. Experience using conventional disease-modifying drugs has been mixed, and biologic therapies require further evaluation for their steroid-sparing potential.

Introduction

Giant cell arteritis (GCA) is the most common systemic vasculitis in Western countries. It involves large and medium arteries, with a predilection for the cranial arteries. Its clinical features are manifold, and include symptoms of systemic inflammation and ischemic complications in territories supplied by affected arteries.

A disease of the elderly, GCA is 20 times more common in the ninth compared with the sixth decade. Unlike other vasculitides, there is a two- to fourfold female predominance. Incidence of GCA varies geographically and is higher in people of Northern European descent (2.9/10,000 in Norway compared with 1.0/10,000 in Spain). This is irrespective of place of birth or residence, because a similarly high frequency is seen in Olmstead County, MN, USA, where Nordic heritage is common. GCA is uncommon in non-Caucasian populations [1]. The incidence in the United Kingdom is 2.2/10,000 person-years [2]. The HLA genotype DRB1*4 is associated with GCA (48.8% in affected subjects, 19.8% in controls) [3]. It appears to confer an increased risk of ischemic visual complications and corticosteroid-resistant disease [4,5••].

We review the neuro-ophthalmic complications seen in GCA, risk factors for their development, available diagnostic modalities (including imaging techniques), and evidence for different treatment strategies. Figure 1 outlines the recommended management pathway for GCA.

Neuro-ophthalmic Complications in GCA

Permanent visual loss is the best known and most feared complication of GCA. A retrospective Spanish study of 161 patients with biopsy-proven GCA found that 42 patients (26%) had visual manifestations of their disease, of whom 24 patients (14.9%) developed permanent visual loss (9.9% unilateral, 5% bilateral) [6]. Moreover, 7.5% patients experienced amaurosis fugax before developing permanent loss of vision; 5.6% had diplopia. Permanent visual loss was caused by anterior ischemic optic neuritis in 91.7% and central retinal artery occlusion in 8.3%; one patient had a vertebro-basilar stroke causing cortical visual loss.

An Italian study reported visual symptoms in 30.1% of their subjects, with partial or total visual loss in 19.1% [5••]. Of the 26 cases with visual loss, 92.3% were due to anterior ischemic optic neuritis and 7.7% had central retinal artery occlusion. Visual loss was unilateral in 73.1% patients and bilateral in 26.9%. Furthermore, 25 of the 26 patients developed visual loss before corticosteroid therapy was started. Similar numbers were reported in a British study and in an Israeli cohort [6,7].

Table 1. Key messages for management of patients with GCA

GCA is a medical emergency. Irreversible visual loss occurs rapidly. Early disease recognition and immediate initiation of high-dose steroid therapy saves sight. The recommended pathway is outlined in Figure 1.
GCA does not always present classically. Pitfalls for the unwary include the following:
GCA does not always present with headache.
Jaw claudication is a cardinal red flag warning of imminent visual loss, and should always be inquired about.
Patients at highest risk of visual loss often do not have high erythrocyte sedimentation rate or C-reactive protein values.
Temporal artery biopsy is indicated in all patients with suspected GCA. It can remain positive for several days after initiation of steroids. Treatment should not be delayed while awaiting biopsy results.
A negative biopsy does not exclude diagnosis of GCA.

GCA—giant cell arteritis.

Although visual loss in GCA typically progresses over only a few days, slowly progressive visual loss is also possible [8]. Other reported neuro-ophthalmic presentations of GCA include vertebro-basilar stroke, isolated choroidal ischemia, and orbital infiltration with proptosis [4,9,10].

Risk Factors for Neuro-ophthalmic Complications

Patients with visual loss at presentation are unlikely to recover vision [11]. This tends to occur early, before or within the first week of treatment with steroids [5••,11,12]. However, unrecognized symptoms, such as headache, jaw claudication, and constitutional upset, often precede the diagnosis (Table 1). Therefore, it is important to identify factors that can predict neuro-ophthalmic complications, which are nearly always associated with positive findings on temporal artery biopsy (Fig. 1) [13].

A meta-analysis performed in 2002 identified the clinical features most predictive of biopsy-positive GCA [14]. Overall, the prevalence of temporal artery biopsy positivity when GCA was clinically suspected was 39%. The only symptoms with significant positive predictive value were jaw claudication and diplopia, with likelihood ratios (LR) of 4.2 and 3.4, respectively. Predictive examination features were temporal artery abnormalities, with enlargement, prominence, beading (LR > 4), and tenderness (LR 2.6). Absent temporal artery pulse (LR 2.7) was not statistically significant. Features that made biopsy-positive GCA less likely were the absence of any temporal artery abnormality on examination (LR 0.53) and a normal erythrocyte sedimentation rate (ESR) (LR 0.2). Several features commonly held to be suggestive of GCA—temporal headache, fever, scalp tenderness, and ESR—did not confer a significantly increased probability of biopsy-positive GCA.

Other features reported to be associated with permanent visual loss include older age, optic disc swelling, hypertension, jaw claudication, and other ischemic complications (eg, amaurosis fugax and cerebrovascular accidents) [4,5••,6,7]. There is also a strong association between HLA-DRB1*4 and ischemic visual complications [4]. A negative correlation is often reported between ischemic visual complications and markers of a high inflammatory response (eg, constitutional symptoms, fever, anemia, and acute phase proteins) [4,5••,7].

Large Artery Involvement in GCA

GCA is not solely a disease of the cranial arteries. Patients can have ischemic complications in vascular territories elsewhere in the body, or can present with nonspecific system features. A retrospective study of the Olmstead County cohort identified that 27% of patients had experienced a large artery complication of GCA, with an incidence of 30.5/1000 person-years at risk [15]. In this cohort, 18% had aortic aneurysm or dissection, and 13% had large artery stenosis. This was negatively associated with cranial symptoms (HR 0.1) and high ESR (HR 0.8). Modern imaging techniques have improved our recognition of major artery involvement in GCA.

Pathogenesis of Ischemia

Visual damage in GCA is due to ischemic injury to end organs (eg, optic nerve). This is caused by arterial occlusion due to intimal hyperplasia and thrombus formation. Histologic examination of temporal artery biopsies shows inflammation through all layers of the vessel wall. GCA is a T-cell–mediated disease. T lymphocytes and macrophages predominate with characteristic granulomata and multinucleated giant cells. B lymphocytes are rare. The T-cell cytokine products, interleukin (IL)-2, interferon (IFN)-γ, and the macrophage products, IL-1β, IL-6, and transforming growth factor (TGF)-β are seen in high levels [16].

IFN-γ released by T cells recruits macrophages that produce proinflammatory cytokines, matrix metalloprotease, and reactive oxygen intermediaries, which cause smooth muscle cell injury. They form multinucleated giant cells that release platelet-derived growth factor and vascular endothelial growth factor, which promote angiogenesis with myofibroblast migration and proliferation in the intima,

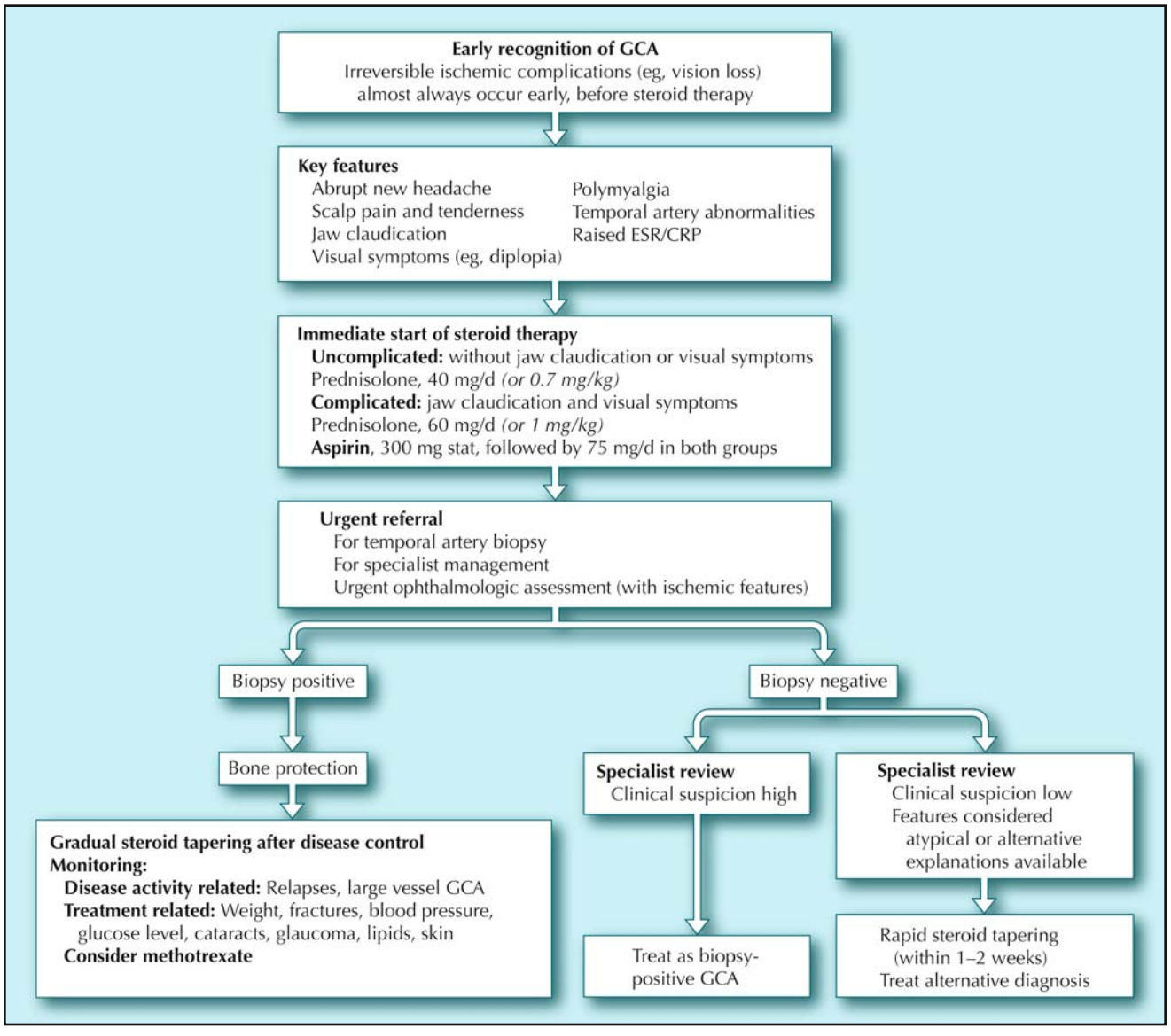

Figure 1. Southend University Hospital pathway for the management of giant cell arteritis (GCA). CRP—C-reactive protein; ESR—erythrocyte sedimentation rate.

causing stenosis and occlusion. IL-6 plays a dominant role in mediating systemic constitutional features.

Different clinical manifestations correlate with different cytokine patterns produced in affected temporal arteries [17]. Patients with predominantly ischemic symptoms and neuro-ophthalmic complications express higher levels of IFN-γ and IL-1β. Consistent with this, high IFN-γ correlates with marked intimal hyperplasia and tissue ischemia. Fever is associated with low levels of IFN-γ. Conversely, IL-6 levels correlate positively with a strong systemic inflammatory response, but are associated with a lower incidence of ischemic events in GCA [18,19]. These findings may explain the clinical observation that patients with neuro-ophthalmic complications tend not to have high inflammatory responses.

Diagnostic Techniques

Temporal artery biopsy

Temporal artery biopsy remains the gold standard for diagnosis of GCA. It is recommended in all cases, given the prospect of prolonged corticosteroid therapy and resultant risk of steroid-related complications. The debate continues regarding the optimal technical processes to minimize falsely negative biopsies.

A recent study of 1821 biopsies found that the likelihood of biopsy positivity was not proportional to sample length, provided at least 0.5 cm was taken [20]. The odds ratio of a positive biopsy for a sample of 0.5 cm was 5.5 compared with a biopsy of less than 0.5 cm. This did not improve for successive increases in biopsy length. However, the general consensus remains that sample length should be at least 1 cm and preferably 2 cm, due to the

possibility of skip lesions. Bilateral biopsy increases the diagnostic yield by only 3% over unilateral biopsy, and studies confirm little benefit from performing bilateral biopsy [21,22]. There is no increased value from examining a biopsy sample at multiple levels [23].

Although the likelihood of obtaining a positive biopsy declines with duration of corticosteroid therapy, histology may remain positive several weeks after commencing treatment. In a Mayo clinic cohort of 535 patients, temporal artery biopsy was positive in 35% of patients who had received steroids before biopsy and in 31% in those who had not been treated [24]. Temporal artery biopsy was positive in 43% in the first week after starting steroids, 30% in the second week, and 28% at more than 2 weeks. A small prospective British study found that temporal artery biopsy could remain positive in patients 4 to 6 weeks after starting high-dose corticosteroids [25]. Therefore, initiating steroid therapy should not be delayed while waiting for a biopsy to be done, and performing temporal artery biopsy still has value, even after several days of steroid treatment.

Not only does biopsy have a diagnostic role, but it also has value in predicting the likelihood of neuro-ophthalmic complications. A recent study from our center showed that the increasing degrees of intimal hyperplasia on biopsy are associated with increased rates of neuro-ophthalmic complications [14]. Biopsies were graded according to the degree of intimal hyperplasia (grade 1 < 50% luminal occlusion, grade 2 50%–75%, grade 3 > 75%, and grade 4 total occlusion). In each of grades 3 and 4, 75% of patients had neuro-ophthalmic complications compared with 0% for grade 1 and 21% for grade 2. There was no significant difference in ESR between grades. Despite this, GCA can occur without typical histologic findings and a negative biopsy does not exclude the diagnosis (Table 1).

Imaging

Temporal artery biopsy remains the gold standard for the diagnosis of GCA. However, because it is an invasive procedure, several imaging techniques have been evaluated as a possible replacement for biopsy.

Ultrasound

The ultrasound appearance of a hypoechoic "halo" around affected arteries, representing vessel wall edema, was originally described in 1996 [26]. This sign disappeared after a mean of 16 days of steroid therapy. Other ultrasonographic features include arterial occlusion and stenosis. A subsequent study comparing ultrasound to the gold standard of temporal artery biopsy histology reported sensitivity of 86%, specificity of 68%, and positive predictive value of 50%, with difficulty differentiating between arteritis and arteriosclerosis [27]. Overall, in a meta-analysis of 23 studies, the halo sign was found to have a pooled sensitivity of 69% and specificity of 82% compared with biopsy. The sensitivity of arterial narrowing was 68% and specificity was 77%. The sensitivity and specificity of any of these vessel abnormalities were 88% and 78%, respectively [28••]. The implication is that ultrasound may be able to guide patient selection for temporal artery biopsy. If the pre-test probability is low, negative results on ultrasound practically exclude GCA, and biopsy can be avoided. If the pre-test probability is high, biopsy is unavoidable, regardless of ultrasound findings. Ultrasound is therefore useful in this group only if the patient declines biopsy. If pre-test probability is intermediate, and other diagnoses are possible, ultrasound is useful. If ultrasound findings are positive, the post-test probability is raised, so biopsy is justified. If negative, biopsy can be considered on an individual basis. In expert hands, ultrasonography is an accurate modality for the diagnosis of GCA. However, it requires a high level of training, and these skills are not widespread.

Fluorodeoxyglucose positron emission tomography

GCA may present with nonspecific symptoms (eg, fever, malaise, weight loss, or unexplained inflammatory response). There are numerous case reports of unexpected GCA diagnosis when large vessel arteritis is found on positron emission tomography (PET) scans performed to investigate suspected malignancy or unexplained pyrexia [29]. PET has been investigated as a specific diagnostic technique in GCA. Blockmans et al. [30•] studied 35 patients with biopsy-positive GCA. PET scans were performed at diagnosis, after 3 and 6 months of steroid therapy, and at relapse. At diagnosis, 29 patients (83%) had fluorodeoxyglucose (FDG) uptake in at least one vascular territory. Subclavian involvement was most common (74%), followed by aortic (50%) and iliac/femoral (37%). With treatment, decreased intensity of FDG uptake was evident by 3 months. However, no correlation was demonstrated between PET findings and relapse.

PET is useful for detecting GCA of major arteries or with atypical presentations. It may have utility in assessing disease activity and the extent of the arterial tree involved, and therefore may influence decisions regarding the degree of immunosuppression needed. However, PET findings do not appear to correlate with relapse. PET cannot detect inflammation in the temporal arteries, so is unsuitable for the diagnosis of cranial GCA, and cannot replace temporal artery biopsy.

Magnetic resonance imaging

Narvaez et al. [31] reported the diagnosis of aortitis in six patients with GCA or polymyalgia rheumatica (PMR) using MRI and magnetic resonance angiography (MRA). Only one patient had clinical symptoms of aortitis. In the remaining patients, suspicion arose because of persistently raised inflammatory markers despite apparent clinical remission. MRI demonstrated increased vessel wall thickness, edema, and increased mural enhancement on post-contrast T1-weighted images, and luminal stenosis was seen on MRA.

A recent German study found that MRI had a sensitivity of 80.6% and specificity of 97.0% for diagnosis of GCA by American College of Rheumatology criteria [32]. For patients who had received steroids for less than 10 days, sensitivity was 85.7% and specificity 95.5%. With steroid use of more than 10 days, sensitivity fell to 33% with specificity 100%. Using temporal artery biopsy as the gold standard, MRI sensitivity improved to 90.5%, with specificity of 72.7%. Logistic regression analysis found that MRI findings were more predictive of GCA than ESR or C-reactive protein. However, temporal artery biopsy was not included in the analysis. The same authors have demonstrated that the mural inflammatory hyperenhancement seen during active disease resolved after corticosteroid therapy [33]. This correlated well with laboratory and clinical remission.

In summary, imaging modalities show promise for diagnosing and monitoring GCA, especially if large arteries are involved. However, they cannot replace temporal artery biopsy. It remains the gold standard, not only diagnostically but because of the prognostic value of histologic examination.

Treatment of GCA

Corticosteroid therapy

Corticosteroids are the mainstay of therapy for GCA, although little systematic evidence exists for this. However, it is generally accepted that doses of 40 to 60 mg/d (at least 0.75 mg/kg) should be started as soon as possible for initial induction of remission. Therapy should not be delayed pending temporal artery biopsy. Early high-dose steroid treatment is important to prevent further visual loss and for rapid control of symptoms, but meaningful recovery from existing visual loss is poor [6,12,34]. Gradual steroid dose reduction can be considered in the absence of clinical symptoms and once laboratory inflammation markers have normalized. Most patients are able to discontinue steroids after 1 to 2 years of treatment. However, the duration of therapy needed is variable, with some patients experiencing a chronic relapsing course.

A longitudinal study in Olmstead County found that a median time to initial response was 8 days, with an average initial steroid dose of 60 mg/d [35]. It was also noted that improvement often began within hours to days after starting steroids. However, fixed visual deficits showed very little recovery. The median time to discontinuation of steroids was 21.6 months. Initial steroid dose or length of treatment did not correlate with permanent visual loss, jaw claudication, or initial ESR. In this study, 48% of patients relapsed, with median time to relapse of 7 months and median steroid dose at first relapse of 5 mg.

There are reports that high-dose intravenous methylprednisolone at commencement of treatment can reverse visual loss, and this approach is often used in clinical practice when patients present with visual loss [12]. However, the literature offers no consensus regarding dosing regimen or whether intravenous therapy is beneficial.

Treatment outcomes using intravenous and oral steroids for initial management were compared in a retrospective Australian study [36]. All patients enrolled had visual loss on presentation. Difference in visual recovery was statistically significant, with vision improving in 39.5% of patients initially treated with intravenous steroids compared with 16.6% on oral steroids alone. However, 16.3% of patients receiving intravenous therapy and 10% on oral steroids worsened. Those patients treated with intravenous steroids had worse pretreatment visual performance. A small American study found that 5/39 eyes (13%) improved with intravenous steroids [37]. In a further prospective series, despite high-dose intravenous steroids, visual deterioration occurred in 27% of eyes [11]. Other studies investigating intravenous steroids to reverse visual loss report no benefit over oral steroid regimens [34].

Initial intravenous steroid therapy has been evaluated to look for a long-term steroid-sparing effect. A large trial of a single initial methylprednisolone infusion followed by oral steroids did not demonstrate any difference to oral steroids alone in time to response, steroid-sparing effect, or rates of adverse events [38]. However, the dose of methylprednisolone used was only 240 mg. Usual practice employs up to three pulses, with a dose of 500 mg to 1 g. A more recent, smaller study using three pulses of 15 mg/kg methylprednisolone found that this permitted rapid tapering of oral steroids, with a starting oral dose of just 40 mg of prednisolone, lower cumulative steroid doses, decreased frequency of relapse, and higher likelihood of steroid-free remission [39]. Both studies excluded patients with neuro-ophthalmic complications or "complicated" GCA. If we accept that GCA is a medical emergency resulting from critical ischemia, such trials need to be conducted.

Alternate-day steroid tapering regimens have been tried, but are likely to lead to a relapse in vasculitis and are therefore not advisable.

Aspirin

Low-dose aspirin was shown to decrease rate of visual loss and cerebrovascular accidents in GCA (OR 0.22 for patients receiving aspirin, 100 mg, compared with not taking aspirin) [40]. Aspirin was shown to suppress pro-inflammatory cytokines in vascular lesions in GCA [41].

Steroid-sparing strategies

Long-term corticosteroid therapy is associated with several adverse side effects. Patients affected by GCA are older and often have several comorbidities. In the Olmstead County cohort, 86% patients had one or more steroid-related adverse event: fractures in 44.6% of patients; diabetes mellitus in 10.6%; infection in 35.9%; and gastrointestinal bleeding in 4.8% [35]. GCA can also follow a chronic relapsing course, requiring lengthy therapy. Therefore, strategies to decrease the patient's cumulative steroid dose have been tried. These

include the alternative steroid regimens detailed earlier and use of other immunosuppressive drugs.

Disease-modifying therapies

Randomized controlled trials of methotrexate as a steroid-sparing agent in GCA have shown conflicting results. A small, randomized, placebo-controlled trial comparing combined methotrexate and prednisolone therapy to prednisolone alone found that adding methotrexate, 10 mg weekly, was more effective in controlling disease activity, with lower frequency of relapse and lower cumulative dose of steroid [42]. However, two further studies did not support this [43,44]. It should be noted that in one of these, a dose of only 7.5 mg of methotrexate was used, and the study was underpowered [43]. A subsequent meta-analysis of these studies suggested a role for methotrexate as a steroid-sparing agent, with a small effect on reducing the cumulative steroid dose and a higher probability of being able to discontinue steroids [45•]. The number needed to treat to prevent the first relapse was 3.6 and was 4.7 to prevent a second relapse.

A trial of azathioprine as a steroid-sparing agent in GCA and PMR reported a statistically significant difference between steroid use in the azathioprine group and the control group, but only after a year [46]. At this point, the mean prednisolone dose in the azathioprine group was 1.9 mg/d compared with 4.2 mg/d in controls, which suggests little clinical benefit. Azathioprine was also significantly less well tolerated than steroid alone.

Although there are no published studies of leflunomide for treatment of GCA, it has shown promise in a small number of patients with corticosteroid-resistant disease in our center.

Biologics

Case reports and small series report that the anti–tumor necrosis factor-α agents have been used successfully in the treatment of steroid resistant GCA [47,48]. A further case report of infliximab in two steroid-naive patients suggested an excellent initial response, but this could only be sustained for 3 months [49]. A small randomized control trial of infliximab for maintenance therapy in newly diagnosed GCA was discontinued early due to lack of efficacy [50]. Possibly, the trial was too underpowered to detect a difference, or perhaps infliximab is effective for induction but not maintenance. However, a placebo-controlled trial of infliximab for induction of remission in PMR also failed to demonstrate benefit [51]. A recent randomized controlled trial of etanercept suggests that it may be a useful steroid-sparing agent, with more patients in the etanercept group able to discontinue steroids and fewer relapses [52]. However, this study was very small, with only eight patients in the active treatment arm.

B-cell depletion (rituximab) has been used as a steroid-sparing strategy in one patient, with evidence on PET scan at 4.5 months that the arteritis had resolved [53]. However, this patient suffered the serious adverse event of pneumonia requiring mechanical ventilation, reinforcing the fact that these therapies should not be used lightly.

Conclusions

GCA is a medical emergency, with potentially serious ischemic complications (including permanent visual loss) and major implications for quality of life and independent living. Patients with total monocular visual loss, facing the prospect of visual loss in the second eye, would trade three quarters of their remaining years for perfect vision in each eye [54]. Urgent intervention can prevent visual loss, but if treatment is delayed, recovery of visual function is poor. Despite this, delays in recognition and treatment of GCA are common, especially because those at highest risk of neuro-ophthalmic complications tend not to have textbook presentations and often do not mount high inflammatory responses. Education and training are needed in early detection and management of GCA. Features such as jaw and tongue claudication, diplopia, and amaurosis fugax should raise the suspicion of GCA and trigger urgent evaluation and treatment. If GCA is considered as a "stroke" of the eye, these features are the "transient ischemic attacks" of critical ischemia, and warrant swift medical intervention. The concept of symptom-to-thrombolysis time in myocardial infarct and stroke is well established. We believe that "symptom-to-steroid" time should be adopted as an audit standard in GCA.

Disclosures

Dr. Dasgupta has served as a consultant and has received honoraria for lecturing for MSD and Servier. He is also a recipient of a grant from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) for research on PMR and GCA.

Drs. Borg and Salter reported no potential conflicts of interest relevant to this article.

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have been highlighted as:

- • Of importance
- •• Of major importance

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