



BSR and BHPR Guidelines for the management of giant cell arteritis

Bhaskar Dasgupta¹, Frances A. Borg¹, Nada Hassan¹, Leslie Alexander¹, Kevin Barraclough², Brian Bourke³, Joan Fulcher⁴, Jane Hollywood¹, Andrew Hutchings⁵, Pat James⁴, Valerie Kyle⁶, Jennifer Nott⁷, Michael Power⁸ and Ash Samanta⁹ on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group

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Definition of GCA (TA)

- Is a chronic vasculitis of large and medium vessels.
- Leads to granulomatous inflammation histologically.
- Predominantly affects the cranial branches of arteries arising from the arch of the aorta.
- Incidence is reported as 2.2/10 000 patient-years in the UK [1] and between 7 and 29/100 000 in population age >50 years in Europe.
- Incidence rates appear higher in northern climates.

Note that as both GCA and PMR often occur together, there are suggestions that the underlying pathophysiology is the same.

Why do we need guidelines for GCA?

GCA is the commonest of all the vasculitides [1]. Together with PMR, it represents one of the commonest indications

for long-term glucocorticosteroid therapy in the community [1, 2]. It is among the common causes of acute blindness and can be truly regarded as a medical emergency. Visual loss occurs in up to one-fifth of patients [3–5]. GCA is a rheumatic disease subject to wide variations of clinical practice, since it is often managed in primary or in secondary care by general practitioners, rheumatologists, non-rheumatologists and ophthalmologists [6].

What are the objectives of these guidelines?

- To outline a prompt diagnostic, management and referral process for GCA.
- To specify a data set that should be recorded for evaluation of GCA.
- To outline a process for disease diagnosis and assessment of severity using clinical factors and temporal artery biopsy (TAB) histology.
- To provide advice on management of GCA with emphasis on prevention of vision loss with early recognition and prompt high-dose glucocorticosteroid therapy.
- To provide advice on monitoring for disease activity, management of relapses and complications of disease such as large-vessel GCA.
- To provide advice on better management of long-term glucocorticosteroid therapy, and of glucocorticosteroid and other treatment-related adverse events.

¹Department of Rheumatology, Southend University Hospital, Essex, ²Painswick Centre, Painswick, ³Department of Rheumatology, St George's Hospital, London, ⁴PMRGCA Group, Southend & Essex, ⁵Health Services Research, London School of Hygiene and Tropical Medicine, London, ⁶Department of Rheumatology, Frenchay Hospital, Bristol, ⁷East Anglia PMR and GCA Support Group, ⁸Clinical Knowledge Summaries Service, Sowerby Health Informatics, Newcastle upon Tyne and ⁹Leicester Royal Infirmary, Leicester, UK. Submitted 26 May 2009; revised version accepted 15 January 2010.

Correspondence to: Bhaskar Dasgupta, Department of Rheumatology, Southend University Hospital, Prittlewell Chase, Westcliffe-on-Sea, Essex SS0 0RY, UK. E-mail: bhaskar.dasgupta@southend.nhs.uk

- To specify audit standards for the optimal management of GCA including diagnostic accuracy, initial glucocorticosteroid dose and taper, relapses, use of bone protection and duration of treatment.
- To identify areas for future research.

Who is the target audience for these guidelines?

These guidelines are directed at the diagnosis, management and referral of GCA in primary and secondary care (including rheumatologists and non-rheumatologists).

Clinical situations covered by these guidelines

These guidelines apply to the management of a newly suspected GCA in terms of diagnosis, urgent referral treatment and treatment as well as subsequent investigations and management in secondary care.

What are the areas the present guidelines do not cover?

Other vasculitides, including TA due to other causes, other CTDs and other inflammatory muscle diseases.

How have the patients' views been incorporated in the guidelines?

Patient representatives have been present at all the guideline group meetings. Each version of the guidelines has been circulated to the representatives for comment. In particular, we suggest that a new Arthritis Research Campaign (ARC) patient education booklet on GCA is developed with their suggestions and leadership.

What is the evidence to support these guidelines?

See the literature review in appendix 1.

Methodology

In order to obtain all the relevant literature, a sensitive search with appropriate search strings (for treatment in GCA or TA, TAB, duplex ultrasonography in GCA or TA, MRI and PET scans in GCA or TA) was undertaken in the most common databases of published medical literature.

Reference lists of retrieved articles were examined and experts in the field of PMR research were contacted for additional references. Recommendations were formulated by full consensus by expert opinion from the group and lay members, and after discussions at the BSR special interest group on GCA as well as at the BSR Standards, Audit and Guidelines Working Group.

How will these guidelines be piloted?

These guidelines will be piloted by the members of the Guidelines group amongst the adjacent Rheumatology and Primary Care Community in the Midlands, South London and Essex, and all results will be incorporated into a further revision of this document in future. These draft guidelines have already been used successfully as an audit standard for an All Wales audit of GCA management.

How often will these guidelines be reviewed?

These guidelines will be reviewed every 3 years or more frequently when new evidence is published.

How will these guidelines be publicized and implemented?

These guidelines will also be published in *Rheumatology* and on the BSR website and sent to all BSR members and Primary Care Trusts. The guidelines will also be sent to the Royal College of General Practitioners and to the *British Medical Journal Clinical Evidence*. A programme of education and training will be developed for relevant primary and secondary care staff and the quick reference guide (appendix 2) will be sent to all general practitioner practices.

Cost implications and conflicts of interest

Cost implications are outside the scope of these guidelines and no funding has been associated with their development; therefore, there are no conflicts of interest to disclose. These guidelines have been developed with complete editorial independence.

The guidelines (also see quick reference guide in Appendix 2)

The recommendations for the guidelines are set out in points 1 to 9.

- (1) Early recognition and diagnosis of GCA is paramount. Whenever GCA is suspected, a thorough clinical evaluation should be performed, supported by the measurement of inflammatory markers. Particular attention should be paid to the predictive features of ischaemic neuro-ophthalmic complications. (Level of evidence 3, strength of recommendation C).

Demographics of GCA [7, 8]

- Mean onset at age 70 years.
- Rare before age 50 years.
- More common in Caucasian people than in Afro-Caribbean people.
- Three times more common in females than in males.

Symptoms

- Abrupt-onset headache (usually unilateral in the temporal area and occasionally diffuse or bilateral).
- Scalp pain (diffuse or localized), difficulty in combing hair.
- Jaw and tongue claudication.
- Visual symptoms (amaurosis fugax, blurring and diplopia).
- Systemic symptoms of fever, weight loss, loss of appetite, depression and tiredness.
- Polymyalgic symptoms.
- Limb claudication.
- Fever, weight loss and other constitutional symptoms.

Examination may reveal

- Abnormal superficial temporal artery; tender, thickened or beaded with reduced or absent pulsation.

- Scalp tenderness.
- Transient or permanent reduction in visual acuity (partial or complete).
- Visual field defect.
- Relative afferent papillary defect on the swinging flashlight test.
- Pale, swollen optic disc with haemorrhages on fundoscopy (anterior ischaemic optic neuritis).
- Unilateral or bilateral central retinal artery occlusion.
- Upper cranial nerve palsies.
- Features of large-vessel GCA: asymmetry of pulses and blood pressure and bruits (usually of the upper limb).

Diagnosis and assessment of disease in GCA

The American College of Rheumatology (ACR) classification criteria for GCA [9]:

- Age at disease onset ≥ 50 years: development of symptoms or findings beginning at the age of ≥ 50 years.
- New headache: new onset of or new type of localized pain in the head.
- Temporal artery abnormality: temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries.
- Elevated ESR: ESR ≥ 50 mm/h by the Westergren method.
- Abnormal artery biopsy: biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells.

For purposes of classification, a patient shall be said to have GCA (TA) if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%.

Predictors of neuro-ophthalmic complications

Positive TAB is associated with neuro-ophthalmic complications, such as visual loss and cerebrovascular stroke. A meta-analysis in 2002 identified the following relationships between clinical features and TAB positivity [10]:

Historical features that increase likelihood of TAB positivity:

- Jaw claudication: positive likelihood ratio (LR) of 4.2 (2.8–6.2).
- Diplopia: positive LR 3.4 (1.3–8.6).

Physical findings that increase likelihood of TAB positivity:

- TA beading: positive LR 4.6 (1.1–18.4).
- TA prominence: positive LR 4.3 (2.1–8.9).
- TA tenderness: positive LR 2.6 (1.9–3.7).

Features that reduce the likelihood of TAB positivity:

- Absence of TA abnormality: negative LR 0.53 (0.38–0.75).
- Normal ESR: negative LR 0.2 (0.08–0.51) [8].

Differential diagnosis

- Herpes Zoster.
- Migraine.
- Serious intracranial pathology, such as infiltrative retro orbital or base of skull lesions.
- Other causes of acute vision loss, e.g. transient ischaemic attack.
- Cluster headache.
- Cervical spondylosis.
- Other upper cervical spine disease.
- Sinus disease.
- Temporo-mandibular joint pain.
- Ear problems.
- Other systemic vasculitides and CTDs.

Complications of GCA

Disease related

Early. Neuro-ophthalmic complications, such as vision loss and stroke [7]. If one eye is affected there is high risk (20–50%) of bilateral vision loss and total blindness with any delay or stoppage of treatment.

Late. Inflammatory aorto-arteritis—development of aortic aneurysm, aortic dissection [24].

Glucocorticosteroid related. Weight gain, bruising, osteoporosis and fractures, diabetes, cataracts, glaucoma, hypertension, accelerated atherosclerosis and hyperlipidaemia.

Recommended investigations (minimum data set) in GCA

- Full-blood count, urea and electrolytes (U&E), liver function tests, CRP and ESR:

an acute-phase response is characteristic of GCA (raised ESR, CRP, anaemia and thrombocytosis, abnormal liver function tests, particularly raised alkaline phosphatase, raised α -1 and α -2 globulins on serum electrophoresis).

- Chest radiograph.
- Urinalysis.
- Other relevant investigations to exclude mimicking conditions.

Pitfalls in the diagnosis of GCA

Cardinal ischaemic features of GCA, such as jaw and tongue claudication and visual symptoms, may go unrecognized or be attributed to other conditions especially if not accompanied by headaches. Patients at highest risk of neuro-ophthalmic complications do not always mount high-inflammatory responses [3–5]. PMR is also associated with GCA in 50% of the cases at presentation [7]. An acute-phase response can occur in other settings, such as other rheumatological conditions, neoplasia and infection.

- (2) Urgent referral for specialist evaluation is suggested for all patients with GCA. We recommend that a TAB

should be considered whenever a diagnosis of GCA is suspected. This should not delay the prompt institution of high-dose glucocorticosteroid therapy [11]. (Level of evidence 3, strength of recommendation C.)

Patients either fulfilling three or more of the five ACR criteria or historical features of impending neuro-ophthalmic complications, e.g. jaw claudication, amaurosis fugax and other visual symptoms, should be urgently referred to a rheumatologist or ophthalmologist, and the laboratory investigations listed above should be performed.

Early TAB in all patients with suspected cranial GCA is desirable [11, 12], since it is of prognostic as well as diagnostic importance. This should be performed preferably within 1 week of starting glucocorticosteroids [12]. However, reports suggest that TAB may remain positive for 2–6 weeks following initiation of glucocorticosteroids [12, 13], and glucocorticosteroids should not be delayed while awaiting TAB. It is the only specific diagnostic test routinely available to all hospital units. A trial of glucocorticosteroids is not an alternative diagnostic test as it may be misleading due to a non-specific response. This is relevant in view of the toxicity associated with long-term glucocorticosteroid use and missing an alternative diagnosis [14]. Patients with isolated large-vessel GCA and no cranial involvement may not require TAB.

Technical considerations

A number of technical issues may influence the likelihood of biopsy positivity [15]. Therefore, we recommend a regular link with a local dedicated surgical unit experienced in regular TAB.

Biopsy specimens should be no less than 1 cm, ideally >2 cm, in length [16]. Contra-lateral biopsy is usually not required [17] unless the size of the original biopsy specimen was suboptimal. The need to examine the specimen at multiple levels is controversial [18].

The prognostic value of TAB

Ischaemic neuro-ophthalmic complications are nearly always associated with TAB positivity, and the severity of intimal hyperplasia on TAB is associated with increasing neuro-ophthalmic complications [19].

Biopsy-negative GCA

TAB may be negative in some patients with GCA, due to the presence of skip lesions in some cases, and suboptimal biopsy in others. Therefore, patients with negative biopsies should be managed as having GCA, if there is a typical clinical and laboratory picture and response to glucocorticosteroids, or typical findings on ultrasound, or ischaemic complications typical of GCA (such as anterior ischaemic optic neuritis).

(3) Although imaging techniques show promise for the diagnosis and monitoring of GCA, these do not currently replace TAB for cranial GCA. They should be reserved for investigation of suspected large-vessel

GCA. Their role in early diagnosis of cranial GCA is an important area of future research. (Level of evidence 1A, strength of recommendation B.)

Duplex ultrasonography for GCA diagnosis [20]

Ultrasonography shows promise in diagnosis of GCA. It can detect the characteristic ultrasonographic appearance of a hypoechoic 'halo' around affected temporal arteries, representing vessel wall oedema (positive for 16 days after glucocorticosteroid commencement) and arterial stenosis and occlusion. In meta-analysis, the halo sign had a pooled sensitivity of 69% and specificity of 82% compared with biopsy [21]. The sensitivity and specificity of any suggestive vessel abnormality were 88 and 78%, respectively.

Ultrasonography cannot be recommended as a replacement to TAB at present. It does not have the prognostic value of histology. It is user dependent and requires a high level of expertise, which is not yet widespread. The possible role for ultrasound in cranial GCA may be in the selection of which patients should have a TAB. In cases with large-vessel GCA, ultrasound is a sensitive technique for assessment of axillary artery vasculitis. The use of PET and MRI scanning in large-vessel vasculitis is discussed below.

Management of GCA

(4a) We recommend the immediate initiation of high-dose glucocorticosteroid treatment after clinical suspicion of GCA is raised [11]. (Level of evidence 3, strength of recommendation C.)

Visual loss occurs early in the course of disease and, once established, rarely improves. Early treatment with high-dose glucocorticosteroids is imperative to prevent further visual loss and other ischaemic complications. Although there is little systematic evidence, the consensus for glucocorticosteroid initiation is as follows:

Uncomplicated GCA (No jaw or tongue claudication or visual symptoms):

- Prednisolone 40–60 mg (not <0.75 mg/kg) daily until resolution of symptoms and laboratory abnormalities [26, 27].

Complicated GCA:

- Evolving visual loss or history of amaurosis fugax: i.v. methylprednisolone 500 mg to 1 g daily for 3 days [28, 29].
- Established vision loss—at least 60 mg prednisolone daily [30, 31].

Bone protection (weekly bisphosphonate and calcium or vitamin D supplementation) should be co-prescribed with glucocorticosteroid therapy. See the Royal College of Physicians guidelines on glucocorticoid induced osteoporosis for further details [32].

Proton pump inhibitors should be used for gastrointestinal protection.

- (4b) Glucocorticosteroid reduction should be considered only in the absence of clinical symptoms, signs and laboratory abnormalities suggestive of active disease.

However, it is important to use only the minimum effective dose and consider patient's choice, acceptability and glucocorticosteroid side effects. Steroid reduction may also be appropriate if the acute-phase response is deemed to be due to another cause.

Suggested tapering regimen

- 40–60 mg prednisolone (not <0.75 mg/kg) continued for 4 weeks (until resolution of symptoms and laboratory abnormalities).
- Then dose is reduced by 10 mg every 2 weeks to 20 mg.
- Then by 2.5 mg every 2–4 weeks to 10 mg.
- Then by 1 mg every 1–2 months provided there is no relapse [46, 47].

For patients preferring enteric coated prednisolone, the reduction <10 mg should be as follows: 10/7.5 mg alternating for 2 months, then 7.5 mg daily for 1–2 months, then 7.5/5 mg alternating for 1–2 months, then 5 mg daily for 1–2 months, etc.

Some patients may benefit from a more gradual glucocorticosteroid taper, or a period of treatment at a stable dose, such as 5 mg prednisolone for 3 months. There are also some patients who will require long-term low-dose glucocorticosteroid therapy. The dose may also need adjustment, due to disease severity, comorbid factors (e.g. diabetes, cardiorespiratory or renal disease), fracture risk, patient wishes and adverse events.

- (5) Low-dose aspirin should be considered in patients with GCA, if no contraindications exist. (Level of evidence 3, strength of recommendation C.)

Low-dose aspirin has been shown to decrease the rate of visual loss and cerebrovascular accidents in GCA [odds ratio (OR) 0.22 (95% CI 0.06, 0.8), compared with patients not treated with aspirin] [44]. However, there are also conflicting reports regarding its efficacy at preventing ischaemic events in GCA [45].

- (6) Large-vessel GCA should be suspected in patients with prominent systemic symptoms, limb claudication or persistently high-inflammatory markers despite adequate glucocorticosteroid therapy. Imaging techniques such as PET and MRI scanning should be reserved for the assessment of suspected large-vessel involvement. (Level of evidence 3, strength of recommendation C.)

Patients with GCA can suffer ischaemic complications in non-cranial vascular territories. The incidence and predictors of large-vessel involvement were studied in a cohort of 168 patients over 50 years [23]. Twenty seven per cent patients experienced

large-artery complications of GCA (18% aortic aneurysm or dissection, 13% large-artery stenosis), with an incidence of 30.5/1000 person-years at risk [12]. Patients with cranial symptoms were less likely to have large-vessel involvement [hazard ratio (HR) 0.1 (95% CI 0.03, 0.35)] and high ESR [HR 0.8 (95% CI 0.67, 0.95)].

In this cohort, thoracic aortic dissection was associated with a marked increase in mortality, but otherwise, survival was similar between patients with and without large-vessel involvement and the local population in general [24].

Imaging in large-vessel GCA

Fluoro-deoxyglucose PET. Fluoro-deoxyglucose-PET (FDG-PET) may have a promising role in assessing disease activity and extent in GCA. Blockmans *et al.* [25] described vascular FDG uptake at diagnosis, in 29 (83%) of 35 patients with GCA. FDG uptake in the shoulders at diagnosis correlated significantly with the presence of PMR ($P=0.005$). Vascular uptake decreased with treatment, although it was unhelpful in identifying relapse.

Large-vessel GCA may present with fever, cachexia or an unexplained inflammatory response, and PET has revealed clinically unsuspected large-vessel vasculitis when performed to exclude infection or malignancy.

MRI. High-resolution multi-slice 3T MRI using intravenous contrast has been used for non-invasive imaging of GCA to image superficial cranial and extra-cranial arterial disease [22]. MRI demonstrated increased vessel wall thickness and oedema, with increased mural enhancement post-contrast and luminal stenosis in suspected large-vessel GCA. These findings correlate with disease activity and colour Doppler ultrasonography. It is observer independent and has the advantage of an extended field of view.

- (7) Monitoring of therapy should be clinical and supported by measurement of inflammatory markers. (Level of evidence 4, strength of recommendation D. This is a consensus statement.)

Symptoms to monitor

- Headaches.
- Jaw and tongue claudication.
- Visual symptoms.
- Vascular claudication of limbs, bruits, pulses and blood pressure.
- Proximal pain and morning stiffness.
- Disability related to GCA.
- Adverse events.
- Osteoporotic risk factors and fractures.
- Other glucocorticosteroid-related complications, e.g. weight gain, hypertension, diabetes, cataract, glaucoma and dyslipidaemia.
- Other symptoms that may suggest an alternative diagnosis.

Laboratory monitoring

The following investigations should be performed:

- At each visit—full blood count, ESR/CRP, urea and electrolytes, glucose.
- Every 2 years—chest radiograph to monitor for aortic aneurysm (echocardiography, PET and MRI may also be appropriate).
- Bone mineral density may be required.

Imaging

- Aortic imaging should be considered in suspected large-vessel disease (as discussed above) as subclinical involvement is common and may progress to form aneurysm or dissection. This should be undertaken after discussion with radiologists.
- Patients should have a chest radiograph every 2 years to monitor for aortic aneurysm. If large-vessel involvement is suspected, this may need supplementation with echocardiography or other imaging.

Frequency of follow-up

We recommend the following follow-up schedule: Weeks 0, 1, 3, 6 and then Months 3, 6, 9, 12 in the first year. Extra unscheduled visits may be necessary in the event of relapse or adverse events. Later (Month 3 onwards) follow-up can be undertaken under shared care.

Disease relapse

The following features should prompt the suspicion of disease relapse [33]:

- Sustained fever of $>38^{\circ}\text{C}$ for >1 week not attributable to a cause other than GCA.
- New or recurrent headache or scalp or temporal artery pain or tenderness.
- New, recurrent or worsening ischaemic retinopathy, optic neuropathy or visual loss not attributable to other causes.
- New or recurrent tongue or jaw pain and/or claudication.
- New or recurrent extremity claudication.
- New, recurrent or worsening thickness, tenderness or ulcers or nodules over the temporal or occipital arteries.
- New, recurrent or worsening angiographic abnormalities compatible with vasculitis of the aorta and/or its primary branches.
- New, recurrent or worsening transient cerebral ischaemia or stroke not attributable to cardiac arrhythmias or atherosclerotic disease.
- New, recurrent or worsening of classic PMR-like symptoms, including malaise and fatigue that were unexplained by processes other than GCA.
- ESR/CRP is usually raised with relapse, but relapse can be seen with normal inflammatory markers.
- All patients in whom relapse is suspected should be treated as below, and discussed or referred for specialist assessment.

Treatment of relapse

- Headache: treat with the previous higher glucocorticosteroid dosage.
 - Headache and jaw claudication: treat with 60 mg prednisolone.
 - Eye symptoms: treat with either 60 mg prednisolone or i.v. methylprednisolone.
 - Large-vessel GCA (prominent systemic symptoms, limb claudication, persistent high-inflammatory markers): investigate with imaging techniques as above and consider treatment using systemic vasculitis protocols. This is another important area of future research.
- (8) The early introduction of MTX or alternative immunosuppressants should be considered as adjuvant therapy. (Level of evidence 1A, Strength of recommendation B.)

Although there are conflicting messages from randomized controlled trials of MTX as a glucocorticosteroid-sparing agent in GCA [34–36], a meta-analysis of three studies does suggest that MTX allows a small reduction in the cumulative glucocorticosteroid dose, and a higher probability of glucocorticosteroid discontinuation without relapse [37]. The numbers-needed-to-treat to prevent a first and second relapse were 3.6 and 4.7, respectively. Other disease-modifying drugs used in GCA include AZA [38]. A recent abstract also suggests the possibility of encouraging results with LEF use in difficult-to-treat GCA and PMR [39].

Biological therapies have shown promise in small series and case report [40–42]. However, this has not been replicated in systematic studies to date [33, 43] and currently their routine use cannot be recommended.

- (9) Patient education. (Level of evidence 4, Strength of recommendation D.)

We suggest a new ARC booklet on GCA incorporating the new guidelines group recommendations. This is being developed with recommendations from various patient representatives and members of Polymyalgia Rheumatica and Giant Cell Arteritis UK (PMRGCAUK). The approach to diagnosis and management of GCA is summarized in appendix 3.

Key recommendations

- Use key presenting symptoms, examination and investigation results to make an urgent diagnosis of suspected GCA. New headache, jaw claudication, visual symptoms, temporal artery abnormalities, scalp tenderness, polymyalgic symptoms and raised ESR/CRP should be recorded.
- Commence immediate high-dose glucocorticosteroid treatment with 40–60 mg prednisolone daily.
- Initiate urgent referral for specialist evaluation and TAB.
- Monitor symptoms, signs and laboratory features of disease relapse and large-vessel GCA.

- Monitor and treat disease and glucocorticosteroid-related complications (such as osteoporosis).
- Disease relapse should be managed by glucocorticosteroid re-escalation, with the dose dependent on the clinical features of the relapse. Adjunctive therapies, e.g. MTX should be considered early in relapsing disease.
- Provide patient education.

Audit standards

Measures of process and adherence to guidelines:

- Minimum data set recorded prior to glucocorticosteroid therapy:
 - Clinical features, e.g. headaches, jaw claudication, visual symptoms, temporal artery abnormalities, limb claudication and bruits, proximal pain and stiffness.
 - Investigations; as specified in guidelines especially TAB.
- Initial glucocorticosteroid dose and taper.
- Monitoring frequency.
- Bone protection: co-prescription of calcium, vitamin D and bisphosphonates (DXA as required).
- Patient education provided.

Areas for future research

The group felt that quality prospective studies were needed for evaluation of initial management approach to GCA as a critical ischaemic process. This includes study of earlier recognition and referral, different glucocorticosteroid doses, administration routes and tapering, TAB and role of specific histological features, e.g. intimal hyperplasia. The role of glucocorticosteroid-sparing agents, such as LEF and biological therapies, needs to be established with well-designed randomized controlled trials.

More studies are also required for early diagnosis and the identification and management of large-vessel GCA. This relates to the use of imaging techniques such as ultrasound, MRI and PET.

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Appendix 1

Literature review on GCA

Search strategy. In order to obtain all the relevant literature, a sensitive search with appropriate search strings (for treatment in GCA or TA, TAB, duplex ultrasonography in GCA or TA, MRI and PET scans in GCA or TA) was undertaken in the most common databases of published medical literature:

- The Cochrane database of randomized controlled trials (RCTs) (up to January 2007).
- MEDLINE (through OVID; 1966 to January 2007).
- CINAHL (through OVID; 1982 to January 2007).
- EMBASE (through OVID; 1980 to January 2007).

Reference lists of retrieved articles were examined and experts in the field of PMR research were contacted for additional references. Hand searches were not conducted.

Methodological problems commonly encountered

- (i) Dearth of studies conducted within primary care.

- (ii) Studies commonly not powerful enough to measure differences in clinically important outcomes with high precision.
- (iii) Diversity of measurement instruments—very few validated.
- (iv) Problems with internal validity—absence of strict randomization and blind assessment of observer-rated outcomes. There were very few RCTs.
- (v) Inadequate information on content and quality of intervention. Quality checks and protocol adherence hardly ever mentioned.
- (vi) Few studies report patient data pre-glucocorticosteroid intervention, with blurred distinction between isolated GCA and GCA with PMR.
- (vii) Few studies of long-term outcome.

Initial treatment in GCA

There are no RCTs comparing different initial oral glucocorticosteroid doses. There are a few trials comparing oral vs i.v. followed by oral glucocorticosteroids. There are several observational studies. The initial dose favoured is 40–60 mg prednisolone daily with a few suggesting 1 mg/kg [23, 24]. Daily glucocorticosteroid doses or divided doses were more useful in controlling symptoms compared with alternate day regimens [40].

Some observational papers mentioned using i.v. glucocorticosteroids in patients with evolving visual symptoms or amaurosis fugax (250 mg to 1 g daily for 3 days) followed by oral glucocorticosteroids to prevent visual deterioration [25, 26]. There is no evidence that i.v. glucocorticosteroid use results in visual improvement in patients with established visual loss. Aspirin use is recommended unless contraindicated. Acetylsalicylate has also shown *in vitro* to reduce IFN- γ secretion by a cyclo-oxygenase-independent mechanism.

Disease course, duration of treatment and adverse events

Observational studies indicate that ~46% of relapses occur in the first month due to rapid glucocorticosteroid tapering and that almost 96% of relapses occur in the first year. The mean duration of glucocorticosteroid treatment is between 2 and 3 years [41].

The benefits from treatment with glucocorticosteroids need to be balanced with the increased risk of adverse outcomes, such as diabetes and fractures [43]. In the UK, one study reported glucocorticosteroid-related side effects in one-third (two-thirds if weight gain is included) of patients.

Disease-modifying drugs in GCA

MTX has been tried in four RCTs with varying results. In a study of 98 patients over 12 months, Hoffman *et al.* reported no difference in relapses, GCA-related morbidity, glucocorticosteroid dosage, treatment toxicity between MTX and placebo [34]. However, in a study of 42 patients over 24 months, Jover *et al.* showed a significant decrease in glucocorticosteroid dosage and relapses with MTX compared with placebo [35].

AZA, CSA, dapsone and HCQ have also been used as glucocorticosteroid-sparing agents with reports of limited benefits. Rituximab has been reported successful in a single case.

There are five case reports of successful anti-TNF use in resistant GCA (three infliximab and two etanercept) although a recent Phase II study was ended prematurely when an interim analysis did not show any benefit. There appears to be a great unmet need for well-designed studies of novel biological therapies in GCA.

Appendix 2

Quick reference guide

(i) Suspect diagnosis of GCA:

Symptoms: patients aged >50 years presenting with

- Abrupt-onset headache (usually unilateral in the temporal area and occasionally diffuse or bilateral).
- Scalp pain (diffuse or localized), difficulty in combing hair.
- Jaw and tongue claudication.
- Visual symptoms (amaurosis fugax, blurring and diplopia).
- Systemic symptoms of fever, weight loss, loss of appetite, depression and tiredness.
- Polymyalgic symptoms.
- Limb claudication.
- Raised ESR, CRP, e.g. evidence of an acute-phase response.

(ii) Examination:

- Abnormal superficial temporal artery: may be tender, thickened with reduced or absent pulsation.
- Scalp tenderness.
- Reduced visual acuity [transient or permanent loss (partial or complete) in up to 20%].
- Visual field defect.
- Relative afferent papillary defect on swinging flashlight test.
- Pale, swollen optic disc with haemorrhages on fundoscopy (anterior ischaemic optic neuritis).
- Unilateral or bilateral central retinal artery occlusion.
- Upper cranial nerve palsies.
- Features of large-vessel GCA: asymmetry of pulses and blood pressure and bruits (usually of the upper limb).

(iii) Immediate initiation of glucocorticosteroid treatment without delay after clinical suspicion of GCA.

Uncomplicated GCA (without jaw or tongue claudication, visual symptoms):

- Prednisolone 40–60 mg (at least 0.75 mg/kg) daily until resolution of symptoms and laboratory abnormalities.

Complicated GCA:

- Evolving visual loss or history of amaurosis fugax: i.v. 500 mg to 1 g daily for 3 days.

- Established vision loss—at least 60 mg prednisolone daily—to protect the other eye.

In all patients:

- Low-dose aspirin 75 mg daily (if no contraindications).
- Bisphosphonates and calcium vitamin D supplementation.
- Proton pump inhibitor.
 - (iv) Urgent referral to specialist care.
 - (v) Urgent referral for a TAB.
 - (vi) Perform the laboratory investigations: full blood count, U&E, liver function test and ESR/CRP.

(vii) Tapering of glucocorticosteroids:

Principle: glucocorticosteroid reduction should be considered only in the absence of clinical symptoms, signs and laboratory abnormalities suggestive of active disease. However, it is important to use only the minimum effective dose and consider patient's choice, acceptability and glucocorticosteroid side effects.

Suggested tapering regimen: 40–60 mg prednisolone continued for 4 weeks (until resolution of symptoms and laboratory abnormalities), then dose is reduced by 10 mg every 2 weeks to 20 mg, then by 2.5 mg every 2–4 weeks to 10 mg, then by 1 mg every 1–2 months provided there is no relapse [38, 39].

For patients preferring enteric coated prednisolone, the reduction <10 mg should be as follows: 10/7.5 mg alternating for 2 months, then 7.5 mg daily for 1–2 months, then 7.5/5 mg alternating for 1–2 months, then 5 mg daily for 1–2 months, etc. The dose may need adjustment for disease severity, comorbid factors, fracture risk, patient wishes and adverse events.

(viii) Ongoing monitoring of:

- Headaches.
- Jaw and tongue claudication.
- Visual symptoms.
- Vascular claudication of limbs, bruits, pulses and blood pressures.
- Proximal pain and morning stiffness.
- Disability related to GCA.
- Osteoporotic risk factors and fractures.
- Other glucocorticosteroid-related complications, e.g. weight gain, hypertension, diabetes, cataract, glaucoma, dyslipidaemia and skin.
- Other symptoms that may suggest an alternative diagnosis.

Laboratory monitoring: full blood count, ESR/CRP, U&E, glucose and BMD if needed.

Imaging: Patients should have a chest radiograph every 2 years to monitor for aortic aneurysm. In suspected large-vessel GCA, this may need supplementation with echocardiography, PET, MRI/CT as appropriate.

Frequency of follow-up: Weeks 0, 1, 3, 6, then Months 3, 6, 9, 12 in the first year (extra visits: relapses, adverse events).

(ix) Relapses:

A rise in ESR > 40 mm/h, plus at least one symptom or sign of GCA including:

- Sustained fever of >38°C for >1 week not attributable to a cause other than GCA.
- New, recurrent or worsening headache, scalp or temporal artery pain or tenderness, ischaemic retinopathy, optic neuropathy, visual loss, tongue or jaw pain and/or claudication, extremity claudication, thickness/tenderness/ulcers or nodules over the temporal or occipital arteries, angiographic abnormalities compatible with vasculitis of the aorta and/or its primary branches, transient cerebral ischemia or stroke not attributable to cardiac arrhythmias or atherosclerotic disease, classic PMR-like symptoms, including malaise and fatigue that were unexplained by processes other than GCA.

Treatment of relapse:

- First and second relapse—increase glucocorticosteroids.
 - Headache: treat with the previous higher glucocorticosteroid dosage.
 - Headache and jaw claudication: treat with 40 mg prednisolone.
 - Eye symptoms: treat with either 60 mg prednisolone or i.v. methylprednisolone.
 - Large-vessel GCA (prominent systemic symptoms, limb claudication and persistent high-inflammatory markers): investigate with imaging techniques as above and consider treatment using systemic vasculitis protocols. This is another important area of future research.
- Third relapse—consider additional immunosuppression, e.g. MTX.

Consider alternative diagnosis in atypical cases and in glucocorticosteroid non-responders or partial responders.

Patient education

We suggest a new ARC booklet on GCA for the use of newly diagnosed patients.

Appendix 3

Pathway for management of GCA

