RHEUMATOLOGY

Guideline

British Society for Rheumatology

British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis

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Introduction

Background

GCA is a large vessel vasculitis affecting older people, with the highest incidence among persons 70–79 years of age [1]. Due to forecasted demographic changes, it has been estimated that between 2014 and 2050, >3 million people will have been diagnosed with GCA in Europe, North America and Oceania [2].

In GCA there is inflammation within the walls of medium and large-sized arteries, with associated intimal hyperplasia [3]. The ischaemia to end organs results in characteristic clinical features such as jaw or limb claudication [4]. Visual loss or stroke may occur in GCA, attributed to vascular occlusion; most GCA-associated visual loss occurs prior to glucocorticoid treatment or shortly after treatment initiation, underlining the importance of immediate treatment if the disease is strongly suspected [5, 6]. The reported proportion of patients with visual loss in GCA varies depending on the GCA case-finding method and method of ascertainment of visual loss; for example, in a UK study recruiting from a rheumatology setting, 17% of 271 patients with GCA reported irreversible visual loss and 1% had stroke [7]. Headache, scalp tenderness, jaw claudication, visual loss and stroke are all classified as cranial manifestations of GCA [4]. In addition, inflammation of the aorta and/or its proximal branches is common in GCA; this is often called large vessel vasculitis outside the head and neck (LV-GCA) and may be asymptomatic or produce non-specific systemic symptoms, such as fever or weight loss. Vascular imaging in GCA demonstrates large vessel involvement, usually with some degree of aortitis, in up to 83% of cases [8]. This large vessel inflammation may lead to later development of vascular stenosis, aneurysm or dilatation, dissection or rupture [9]. A subset of patients with LV-GCA presents with symptoms of a systemic inflammatory syndrome, which can have features of PMR without the classic cranial clinical features of GCA [4]. The true prevalence of this is unknown, as vascular imaging is not routinely performed in PMR at presentation.

Need for the guideline

As GCA is considered a medical emergency, it is treated at the point of diagnosis by clinicians in primary and secondary care who have a wide variety of clinical backgrounds. It is therefore necessary to provide clear guidance about current best practice and the underlying evidence including areas of uncertainty.

Recent years have seen new evidence emerge regarding the diagnosis and treatment of GCA. For this reason, a major revision to the 2010 British Society for Rheumatology (BSR) guideline for the management of GCA [10] was required. We also broadened the remit of the previous guideline to include diagnostic imaging for GCA.

Objectives of the guideline

The objective is to provide guidance for clinicians in the diagnosis and treatment of GCA. The guideline is supported by evidence wherever some evidence exists and by expert consensus where current evidence alone cannot provide a definite answer. The patient population covered by the guideline includes those patients in whom GCA is suspected sufficiently strongly that a decision to initiate glucocorticoid treatment is made. The guideline is not limited to GCA-related temporal (cranial) arteritis but also includes patients presenting with LV-GCA and limited forms of GCA with or without an association with PMR.

The evidence search was restricted to adult humans with GCA or suspected GCA, not limited by ethnicity, age or sex; however, since GCA is extremely rare in patients <50 years of age [1], generalizability below this age limit cannot be assured.

Areas the guideline does not cover

Takayasu arteritis and other forms of vasculitis (e.g. secondary large vessel vasculitis) are not covered by this guideline. The treatment of uncomplicated PMR is outside the scope of this guideline; readers are referred to the most recent BSR and ACR/EULAR guidance on the management of PMR [11, 12]. Guidance regarding immunizations and prophylaxis of glucocorticoid-induced osteoporosis is available elsewhere [13, 14].

Target audience

This guideline is intended for doctors and allied health professionals who work in a primary or secondary care setting and manage patients with suspected and/or established GCA. From a diagnostic perspective, early recognition of suspected GCA by the non-specialist is encouraged, but definitive diagnosis of GCA can be challenging and therefore prompt onward referral to an appropriate specialist is recommended. From a treatment perspective, this guideline is intended to provide a framework by which specialists, general practitioners and patients can work together to deliver optimal care tailored to the individual patient.

Stakeholder involvement

The guideline was developed in accordance with the BSR Guidelines Protocol. Members of the working group co-authored this guideline and are listed at the end of this document with their affiliations. Important stakeholder representation included patient groups (PMRGCAuk, PMR and GCA North East, PMR-GCA Scotland) and the Royal College of Ophthalmology. Individuals on the working group had a range of expertise, including rheumatology, general practice, ophthalmology, specialist rheumatology nursing and systematic review and guideline development methodology, and included patients with personal experience with GCA. There was no representation from industry. Informal feedback was sought at open meetings held at several international rheumatology conferences to ensure that the guideline development process took account of

current practice and important clinical questions within the wider rheumatology community, particularly regarding general principles of management.

Prior to defining the Population, Intervention, Comparator, Outcome (PICO) questions, stakeholders were consulted regarding outcomes of importance in GCA [15]. A list of candidate outcomes was identified after feedback from all the stakeholders and from a scoping literature review. A survey was undertaken to prioritize candidate outcomes. A total of 67 patients, 45 rheumatologists, 10 generalists (general practitioners or hospital based) and 7 ophthalmologists responded to the questionnaire. Each outcome was graded based on its relative importance for clinical decision making on a 1–9 point scale [15]. Scores from 1–3 indicated limited importance (not important for decision making), 4–6 indicated important (important, but not critical for decision making) and 7–9 indicated critical (critical for decision making). Outcomes deemed as critical (i.e. score $\geq$7) by at least 70% of physicians and/or patients were considered as candidate outcome measures and this list was refined by the guideline working group for the purpose of defining a list of 'outcomes' for the PICO questions (Supplementary Files, available at *Rheumatology* online).

The GCA Guideline Working Group developed the PICO questions, discussed the evidence collated, iteratively refined the wording of draft recommendations and voted on the final recommendations.

Rigour of development

Scope of literature search and strategy employed

PICO questions
The systematic literature review (SLR) was directed according to predefined questions in PICO. These were written by the working group and feedback was explicitly invited from the patients within the group. The PICO questions were structured as follows:

1. For recommendations on diagnostic imaging tests, the (P) target population comprises patients with suspected GCA, the (I) intervention is the diagnostic test of interest, the (C) comparator is the comparator test or the reference standard and the (O) outcomes are true positives, true negatives, false positives, false negatives, complications related to tests, resource use, inconclusive results and the implication of these items on patient-important outcomes as listed below [16].
2. For recommendations on treatment, the (P) target population comprises patients with a diagnosis of GCA/patients with a high suspicion of GCA above the treatment threshold, (I) intervention and (C) comparator are the alternative management strategies and (O) outcomes as listed below [16].
3. For prognostic factors, the (P) target population comprises patients with a diagnosis of GCA, (I) the presence and (C) the absence of a prognostic factor and (O) outcomes as listed below [17].

A preliminary list of PICO questions was identified by a face-to-face discussion at the first guideline development group meeting followed by an e-mail-based survey of the working group. These preliminary questions were refined and grouped together where appropriate at the second guideline development group meeting. This resulted in a final list of PICO questions (Supplementary Files, available at *Rheumatology* online).

The PICO questions were used to formulate a protocol for the SLR, which was approved by BSR before commencing searches. Screening of the search output was performed by two group members for each topic (diagnostic tests: C. Duftner, S. Appenzeller; therapeutic strategies: C. Dejaco, D. Camellino; prognostic factors: S. Gonzalez-Chiappe, A.W. de Souza) who independently selected full texts, extracted data and performed quality appraisal. Any disagreements between the two group members were resolved by discussion, consulting a third member (S. Mackie, A. Hutchings or A. Mahr, respectively) when no consensus could be reached. The literature search was last updated on 18 June 2018 by G. Reynolds and the outputs appraised by the same group members as before for consistency.

The search strategy of electronic databases is given in the Supplementary Files, available at *Rheumatology* online. Further published studies were identified by hand-searching the reference list of full and review articles and by contacting experts in the field. In addition to this, ClinicalTrials.gov, ISRCTN and the European Union Clinical Trials Register were searched and the literature tracked to identify published trial results. Criteria for selecting articles for full-text review are given below.

Diagnostic studies
We included full research articles of prospective studies involving >20 patients and investigating the index test in patients with suspected GCA. We did not evaluate temporal artery biopsy as an index test because of incorporation bias in relation to the reference standard. We excluded diagnostic case–control studies because this type of study design produces estimates of diagnostic accuracy that are not applicable to routine clinical practice [18]; studies where the index (imaging) test had been performed in >10% of patients upon treatment with glucocorticoids for >1 week (because imaging tests for GCA suffer significant loss of sensitivity after commencing high-dose glucocorticoids; having an imaging test within 1 week of initiating glucocorticoids appears feasible in practice [19]); studies with a reference standard other than clinical diagnosis (without formal criteria), ACR classification criteria and/or temporal artery biopsy result and studies that could not be assigned to any of the PICO questions.

Interventional studies
We included randomized controlled trials (RCTs) involving >20 patients with GCA. Observational or non-randomized studies or studies that could not be

assigned to any of the interventional PICO questions were excluded.

Prognostic studies

We included prospective and retrospective studies on >100 GCA patients investigating primarily the relevance of any of the prognostic factors of interest. Studies with another research focus (e.g. description of a cohort, interventional trials) were excluded for this part of the SLR. We further excluded studies that did not report the result of a statistical test for association with the outcome. The prognostic factors being investigated should have been in routine clinical use without requiring sophisticated equipment or complex analysis. A minimum time for follow-up in eligible studies was set at 6 months. Because the aim of this part of the SLR was to identify factors that could be used to risk-stratify patients in routine clinical practice, studies that reported exclusively on imaging or laboratory tests with no reference to patient presentation were excluded.

Data extraction

Study details and results were extracted using a data extraction form from included articles by two members of the literature review team according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [20]. The preliminary data extraction form was piloted in five identified articles and evaluated for completeness and handling. This data extraction form included the following items: authorship and publication, design, main study population, primary study objective(s), links/overlap with other studies, study inclusion criteria, characteristics of participants, definition of intervention/exposure and control, definition of outcome, method of statistical analysis, length of follow-up, losses to follow-up, missing data, discrete/continuous data (counts, means, standard deviations etc.), measures of effect and uncertainty and any other information relevant to quality assessment.

Additional parameters extracted relevant to diagnostic studies included the use of glucocorticoids before performance of imaging, disease characteristics [number (%) of patients fulfilling clinical criteria for GCA, number (%) of patients with positive temporal artery biopsy, number (%) of patients with large vessel GCA], technical aspects (imaging devices used, elementary lesions and structures investigated, blinding of the index test to a reference standard), index test, reference standard, diagnostic performance [raw data to calculate sensitivity, specificity, positive (LR+) and negative likelihood ratio (LR−)] and parameters required for assessment of study quality (risk of bias). Additional data extracted relevant to prognostic factors included adjusted and unadjusted odds ratios (ORs), relative risks (RRs) or hazard ratios (HRs) and information relevant to quality assessment.

Quality assessment

We evaluated the quality of evidence using the approach set out by GRADE [20, 21] and implemented as follows:

1. Risk of bias: Confidence in the estimate of the effect decreases if studies have major limitations that may bias their results. For diagnostic studies, risk of bias was assessed using the QUADAS-2 tool [22]. For interventional studies, the following factors were considered [20]: randomization procedure and sequence generation, allocation concealment, blinding of patients and assessor, completeness of outcome reporting (attrition bias: losses of follow-up, adherence to the intention-to-treat analysis or stopping the trial early for benefit) and selective outcome reporting. For prognostic studies, risk of bias was investigated using the following questions [17]:
   - Was there a representative and well-defined sample of patients? Was selection bias avoided?
   - Was follow-up sufficiently long and complete?
   - Were objective and unbiased outcome criteria used? Were methods used to determine/measure outcomes adequate?
   - Were all characteristics of patients known or suspected to affect the outcome recorded?
   - Was there adjustment for important prognostic factors, including age, sex, ESR, ischaemic manifestations (amaurosis fugax, jaw claudication, limb claudication), extracranial manifestations, symptom duration, comorbidities, constitutional symptoms and smoking?
2. Inconsistency of results: Confidence in the estimate of the effect decreases if there is variability in results (heterogeneity) across studies and investigators fail to identify a plausible explanation.
3. Indirectness of the evidence: Confidence in the estimate of the effect decreases if there are differences between the population, intervention, comparator or outcome of interest and those included in the systematic review studies.
4. Imprecision: Confidence in the estimate of the effect decreases if the systematic review includes relatively few patients and few events and thus has wide confidence intervals and/or the extremes of the confidence intervals are close to the null effect.
5. Publication bias: Confidence in the estimate of the effect decreases if there is evidence that some studies were not reported.

Evidence generated from prospective diagnostic accuracy studies, RCTs and longitudinal cohort studies investigating prognostic factors started as high quality but was downgraded if any of the above limitations was present.

After assessing these five domains the overall quality of evidence (QoE) was assessed as:

1. High quality evidence [indicated by ++++ (A) – further research is very unlikely to change our confidence in the estimate of effect]

2. Moderate quality [indicated by +++ (B) – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate]
3. Low quality [indicated by ++ (C) – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate]
4. Very low quality [indicated by + (D) – any estimate of effect is very uncertain]

Preparing the evidence report

Evidence tables were prepared by the literature review team for each PICO question using Review Manager (RevMan; Cochrane Collaboration, London, UK) and GRADE profiler (GRADEpro) software. The evidence profiles contained the following specific information:

Diagnostic studies

Diagnostic studies included direct outcomes (true positives, true negatives, false positives, false negatives, sensitivities and specificities; complications of the index test and of the reference standard; resource use), the number of studies and quality assessment related to each of these outcomes and the effect estimate (i.e. number of individuals classified per 1000 people) according to different pretest probabilities [low (<20%), intermediate (20–50%) and high (>50%) pretest probability].

Interventional studies

Interventional studies included benefits and harms for each outcome across studies, the assumed and corresponding risk for comparators and interventions (95% CI), the absolute and relative effect (95% CI), the number of participants/number of studies, the number needed to treat and the QoE, including quality factors for each critical and important outcome.

Prognostic studies

Prognostic studies included ORs, RRs or HRs as well as corresponding P-values, both unadjusted and (where available) adjusted for confounders. Results of quality appraisal were also reported.

Whenever possible, meta-analyses using fixed effects methods (interventional studies) or random effects methods (diagnostic, prognostic studies) were conducted to combine the results of studies for each PICO question.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $P < 0.1$ and an I^2 inconsistency statistic of >50% to indicate significant heterogeneity. Where significant clinical heterogeneity was present, analysis of individual studies and/or subanalyses investigating studies with comparable design and quality was conducted.

Methods used to formulate the recommendations

General principles statements

GRADE recommends that where certain principles of diagnosis and treatment of a disease are generally agreed upon by the medical community, these should be stated in terms of 'good practice statements' [23]. Here we call these 'general principles' and they are a description of generally accepted best medical practice as evidenced by consensus within our Guideline Working Group. They are not necessarily evidence-based, but form the clinical context within which the evidence-based recommendations should be understood.

General principles statements in relation to GCA were drafted and iteratively refined by means of multiple rounds of e-mail consultation within the guideline working group, including patient representatives, as well as wider consultation by presentation and discussion at international rheumatology meetings. The final versions were voted on by the working group and a consensus score generated for each statement, defined as the mean value of scores of all the individual working group members.

Forming guideline recommendations

Using the evidence profiles, recommendations were proposed for each key question according to the GRADE methodology [24]:

The GRADE system offers two grades of recommendations: 'strong' and 'conditional'.

This grade is determined by the QoE, balance between desirable and undesirable effects, values and preferences of patients and use of resources.

The evidence on prognostic factors was used to build subgroups of GCA patients with different risk profiles concerning patients' important outcomes rather than formulating individual recommendations on prognostic factors. Treatment recommendations have been tailored to these subgroups given that the trade-off between benefit and harm, values and preferences as well as consideration regarding resource use may vary according to the presence or absence of risk factors.

The recommendations process was conducted in two stages:

1. The quality of evidence was discussed at international meetings and webinars.
2. Recommendations were formulated that were iteratively refined via webinars and e-mail.

Finally, the working group voted by scoring each recommendation on a 0–10 scale. The consensus score was defined as the mean of all scores received.

The overall QoE for each recommendation was summarized using the GRADE QoE scale, as per the BSR Guidelines Protocol 2017.

Limits of search and search dates

The following electronic databases were searched from their inception dates, noted in parentheses, to the

present: Ovid MEDLINE (1946), Embase (1988), Cochrane Central Register of Controlled Trials (1996) and Cochrane Systematic Reviews (1993). The search was last updated on 23 June 2018.

Because of the need for quality appraisal by a consistent team of reviewers, the search was limited to articles published in English.

When will the guideline be updated?

The guideline will be updated after 3 years; publication of a major new clinical trial may trigger a partial revision.

The guideline

Eligibility
- Patients with suspected GCA (for diagnostic tests)
- Patients with confirmed GCA (for treatment recommendations)

Exclusions
- Takayasu arteritis
- PMR (unless there is also a diagnosis of GCA)

General principles

General principles are not the same as evidence-based recommendations, but are presented here to summarize best practice.

How should suspected GCA be treated?
1. Patients in whom GCA is strongly suspected should be immediately treated with high-dose glucocorticoids. Consensus score: 9.61.

'Strongly suspected' GCA means that in the assessing clinician's judgement, GCA is a more likely explanation for the patient's symptoms than any other condition. The assessing clinician may take into account GCA symptoms, signs and laboratory tests (such as acute phase markers) [25, 26]. The risk of toxicity caused by short-term glucocorticoid treatment commenced in patients with initial strong suspicion of GCA but then diagnosed with an alternative condition is acceptably low as long as a full diagnostic evaluation is performed promptly and it is acknowledged that a suspicion of GCA is not the same as a diagnosis of GCA. For doses, see below.

How quickly should patients with suspected GCA be referred for evaluation?
2. GCA is a medical emergency. Each local healthcare organization should have information available to frontline clinicians, such as general practitioners and clinicians working in acute care, on how to refer patients with suspected GCA urgently for local specialist evaluation. Patients should be evaluated by a specialist ideally on the same working day if possible and in all cases within 3 working days. Consensus score: 9.17.

Rapid specialist evaluation is a key principle of management of GCA, therefore 'fast-track' referral pathways for urgent specialist evaluation of suspected GCA are beneficial. On suspicion of GCA, primary care providers should initiate glucocorticoids alongside an urgent referral to the local GCA pathway. In retrospective reports from centres that have set up fast-track referral pathways, initial diagnostic evaluation and treatment of patients with suspected GCA within 24 h of referral has been associated with a reduction in reported rates of GCA-related sight loss compared with conventional care pathways [27, 28]. In a prospective, multicentre UK study, clinical evaluation, vascular ultrasound and temporal artery biopsy were all undertaken within 1 week of commencing high-dose glucocorticoid therapy for suspected GCA [19]. The success of fast-track referral pathways depends on appropriate selection of patients for referral and therefore education of clinicians in primary and secondary care is crucial.

To whom should patients with suspected GCA be referred?
3. Patients with suspected GCA should be evaluated by a clinician with appropriate specialist expertise, usually a rheumatologist. Patients presenting with a history of new visual loss (transient or permanent) or double vision should be evaluated as soon as possible on the same calendar day by an ophthalmologist. Consensus score: 9.61.

The reason for needing a full, prompt diagnostic evaluation by a clinician with appropriate specialist expertise is that undiscerning use of high-dose glucocorticoids may mask other diseases and can complicate the diagnostic workup [12, 25]. Where the diagnosis is difficult, opinions from specialists from multiple disciplines can be of value. This includes the interpretation of specialized investigations for GCA and consideration of alternative diagnoses. Ophthalmological evaluation is essential where there is visual loss, of which there are various possible causes in GCA [29, 30].

What evaluations should be performed when starting treatment?
4. When starting glucocorticoids for suspected GCA, diagnostically relevant symptoms and signs should be documented. Blood should be taken for full blood count, CRP and ESR before or immediately after commencing high-dose glucocorticoids. If GCA is strongly suspected, the first dose of glucocorticoid can be given without waiting for laboratory results. Consensus score: 9.61.

Diagnostically relevant symptoms and signs of GCA include headache; scalp tenderness/hyperaesthesia; jaw or tongue claudication; temporal artery tenderness, nodularity or reduced pulsation; visual manifestations including diplopia or changes to colour vision; limb claudication; PMR (pain and stiffness of the shoulder and hip girdles) and fever, sweats or weight loss. Less commonly, patients may have carotidynia, audiovestibular symptoms, dry cough or indications of tongue or scalp ischaemia that may precede necrosis.

However, as none of the above-mentioned symptoms is entirely specific (or pathognomonic) for GCA, and many are very non-specific, each is of limited use if

TABLE 1 A proposed list of clinical assessments that could be carried out at or near diagnosis of GCA

History and examination	Investigations
• Height and weight • Features of GCA relevant to prognosis: fever, sweats or weight loss; ischaemic manifestations (jaw claudication, tongue claudication) • Signs and symptoms indicating involvement of extracranial arteries, e.g. bruits, different blood pressures in the two arms and limb claudication • Ophthalmological evaluation for patients with transient or permanent visual loss or diplopia • History of comorbidities and medications that might predispose to glucocorticoid-related adverse effects, including infection, hypertension, diabetes, osteoporosis, low-trauma fracture, dyslipidaemia, peptic ulcer and psychiatric adverse effects • Features that may suggest an alternative diagnosis, e.g. neurological deficits, very severe constitutional symptoms or localised ear, nose and throat signs	• Measures of activity of GCA: laboratory markers of inflammation (CRP for all patients, plus either ESR or plasma viscosity) and full blood count (platelet count may be elevated in GCA) • Consider serum protein electrophoresis and urine Bence–Jones protein/serum free light chains if ESR elevated out of proportion to CRP • Baseline laboratory tests of major organ system function (plasma glucose, renal and liver function tests, calcium and alkaline phosphatase) • Screening tests for risk of serious infection[a] (may include urine dipstick, chest radiograph and tests for latent tuberculosis according to local or national protocol) • Screening tests for osteoporosis risk[a] (may include TSH, vitamin D, bone density test, DXA)

[a]Screening tests for infection and osteoporosis to be considered in light of relevant local and national guidelines. TSH, thyroid stimulating hormone; DXA, dual-energy X-ray absorptiometry.

taken in isolation [26], and the differential diagnosis must also be considered. GCA causes an elevation in platelet count, CRP and ESR. Plasma viscosity can be used where ESR is unavailable. These markers all decrease with glucocorticoid therapy, therefore all patients should have blood drawn prior to starting treatment, unless there is evidence of critical ischaemia such as visual loss or diplopia and no immediate access to phlebotomy.

What evaluations should be performed soon after starting treatment for GCA?

5. Patients treated for GCA should be evaluated for features of the disease relevant to the prognosis, such as clinical and laboratory features of a marked inflammatory response at diagnosis, ischaemic manifestations such as transient visual loss or jaw/tongue claudication and signs or symptoms indicating involvement of the aorta and its proximal branches, and for comorbidities relevant to treatment, such as diabetes mellitus, hypertension and bone fracture risk. Consensus score: 9.53.

Assessments to be performed in all patients with GCA are detailed in Table 1. As well as confirmatory tests for GCA (see Key Recommendation 1), alternative explanations for patients' symptoms should be considered, particularly if these confirmatory tests are negative. Factors relating to prognosis [risk factors (prognostic) PICO questions 1–6] were reviewed. Overall, insufficient evidence was found to be able to stratify patients with proven GCA to different management strategies on the basis of risk factors considered: age, sex, acute phase reactants, PMR status, large vessel involvement in GCA, atherosclerotic disease, glucocorticoid responsiveness or histological features of GCA. Nonetheless, these features remain important diagnostically and/or when assessing for risk of glucocorticoid-associated adverse effects.

Risk factors for visual loss: Studies reporting risk factors for permanent visual loss in GCA yield variable results. In a single-centre study of 339 consecutive biopsy-proven cases presenting over a 39-year period, in which clinical features were prospectively recorded by an internist in a 176-item structured questionnaire, 53 patients had permanent visual loss. In multivariable regression modelling, older age, history of transient visual loss and jaw claudication were independent predictors of visual loss, while fever and rheumatic symptoms were protective [31]. Similar findings were reported in an earlier retrospective study of irreversible cranial ischaemic complications in 200 patients, with transient diplopia also identified as a potential risk factor [32].

Hypertension and ischaemic heart disease were also identified as potential risk factors for cranial ischaemic complications in studies from Italy and Spain [33, 34]. In an international multicentre observational study reporting data from 433 GCA patients from 26 countries, 34 patients developed complete loss of vision in one or both eyes at 6 months. After adjusting for age and sex, the strongest risk factor for this was peripheral vascular disease recorded at baseline (the effect size was similar when restricting the case definition to biopsy-proven GCA) [35].

Risk factors for aortic aneurysms: Inflammation of the aorta is associated with subsequent development of aortic dilatation or aneurysm [36], and those GCA patients with dilatation of the subclavian arteries were found to be more likely to have subsequent aortic aneurysm than those with GCA-related subclavian stenosis [37]. Possible risk factors for aneurysm development in GCA are smoking, male sex, hypertension and pre-existing cardiovascular disease as well as inflammation of the aorta or its proximal branches [37–41]. However, the evidence about risk factors for aneurysm development in GCA is at present not sufficient to define high-

risk subgroups to select GCA patient subgroups for aortic imaging.

Chest radiography involves minimal radiation exposure but is insensitive to early thoracic aortic aneurysms [42]. French recommendations suggest routine aortic imaging at GCA diagnosis and every 2–5 years thereafter [43]. However, aortic imaging as a routine screening test for all GCA patients remains of uncertain cost-effectiveness and the optimal method and timing of imaging in this context is still unclear [44]. Therefore clinicians are advised to use their own discretion regarding selection of patients for aortic imaging.

Risk factors for prolonged treatment course: A 'strong inflammatory response' (defined as three or four of the following features: fever, weight loss, ESR $\geq$85 mm/h and haemoglobin <11 g/dl) has been associated with a higher relapse rate and prolonged treatment course [45–47]. Imaging evidence of LV-GCA may be associated with prolonged glucocorticoid treatment compared with patients with cranial GCA who did not have imaging evidence of LV-GCA [36, 48].

It is best practice for the prescriber of glucocorticoid therapy to ensure that patients are evaluated for hypertension and hyperglycaemia (blood glucose for acute changes and/or HbA1c to identify patients that might be at greater risk) within the first 2 weeks of commencing high-dose glucocorticoids. Comorbidities relevant to glucocorticoid toxicity include diabetes mellitus, osteoporosis and bone fracture. Generally, toxicity increases with glucocorticoid dose and duration [49]. Symptoms of and/or exposure to serious infections should be assessed in all patients starting glucocorticoids, considering the local prevalence of these infections. It is suggested that a chest radiograph and dipstick urinalysis should be performed. Exposure to tuberculosis should be discussed and screened according to national guidelines [50].

Oral glucocorticoids can rarely increase intraocular pressure or worsen pre-existing primary open-angle glaucoma. If there is glaucoma or ocular hypertension present, or a history of being a glaucoma suspect or glaucomatous risk factors (such as connective tissue disease, type I diabetes, a first-degree relative with primary open-angle glaucoma or high myopia), screening should be performed by a suitably trained eye professional [51].

For ongoing care via a shared care model, patients with GCA should see a clinician with appropriate expertise at least every 2–8 weeks during the first 6 months, then every 12 weeks during the second 6 months, every 12–24 weeks during the second year and additionally as indicated in case of relapse or as glucocorticoid therapy is tapered and discontinued. This visit schedule is based on the higher likelihood of new treatment-related adverse events and the need for treatment dose adjustment early in the treatment course while glucocorticoid doses are still high. However, this should be adapted for the individual patient. Each follow-up visit should include at least a full history, targeted physical examination and measurement of at least a full blood count, ESR and/or CRP, plus follow-up of any abnormalities relevant to the individual patient as well as drug-specific screening for toxicity.

How should ongoing management of GCA be individualized?

6. Full assessment of the disease and comorbidities and consideration of the patient's personal priorities should inform decisions about glucocorticoid tapering and initiation of additional treatments such as glucocorticoid-sparing therapies. Involvement of and clear communication with primary care physicians is critical, especially for management of multimorbidity. Consensus score: 9.67.

Management of patients with GCA should include attention to comorbidities and the impact of glucocorticoid toxicities in order to individualize the standard glucocorticoid tapering schedule (Table 2). PICO questions on the prevention of glucocorticoid-induced osteoporosis and immunization in GCA were not included; there are published guidelines on these matters [13, 14]. Although it is customary to co-prescribe proton pump inhibitors with high-dose glucocorticoid therapy, especially in older patients, it has recently been suggested that lower glucocorticoid doses may not always routinely need co-prescription of a proton pump inhibitor [53]. Local or national guidance should be followed.

Glucocorticoid therapy increases susceptibility to infections but may also decrease the efficacy of vaccinations; live vaccines are contraindicated in patients receiving high-dose glucocorticoid therapy (>20 mg prednisolone daily for $\geq$2 weeks) [54]. Patients without a history of chicken pox (varicella zoster virus infection) should be advised to avoid close contact with people who have chickenpox or shingles and to seek urgent medical advice if they have been exposed.

What education should patients be offered?

7. All patients with GCA should be provided with information about GCA and its treatment. Patients should receive advice on diet, physical activity and stopping smoking. Consensus score: 9.47.

Information should be available in written format and ideally in multiple formats. Dietary considerations include mitigating the potential effects of glucocorticoid therapy on body weight, post-prandial glycaemia and bone fracture risk. Recommendations on physical activity in inflammatory arthritis and osteoarthritis are available [55] and there have also been suggestions of benefit in other inflammatory vascular diseases [56], but advice needs to be tailored to the individual patient with GCA, particularly if there are comorbidities.

Particular considerations in GCA may include physical deconditioning as a result of the inflammatory disease, vascular stenosis to the limbs and the role of exercise in stimulating collateral formation and the psychological benefits of exercise in mitigating the impact of the disease on the patient. Particular considerations with patients receiving long-term glucocorticoid treatment

TABLE 2 A typical glucocorticoid tapering schedule for GCA

Daily prednisolone dose	Example rate of reduction in daily prednisolone dose	Notes
40–60 mg oral prednisolone: initial dose for patients with active GCA	Continue at same dose until GCA symptoms and acute phase markers resolve	Purpose: induction of clinical remission
In clinical remission and >20 mg prednisolone	Reduce daily dose by 10 mg every 2 weeks	Aim to reach 20 mg prednisolone once the patient has been in remission for 4–8 weeks
In clinical remission, >10 mg prednisolone but <20 mg	Reduce daily dose by 2.5 mg every 2–4 weeks	If symptoms suggestive of GCA relapse occur during taper, consult Table 3
In clinical remission and on ≤10 mg prednisolone	Reduce daily dose by 1 mg every 1–2 months	

This is an example of a typical glucocorticoid taper schedule, based on that described in the 2010 BSR guidelines for GCA [10] and similar to the control arm of a recent GCA clinical trial [52]. High-quality evidence comparing different glucocorticoid taper schedules in GCA is not available. Alternative approaches include, for example, reducing prednisolone by 10 mg/week in patients who are in remission at >20 mg daily and/or reducing the dose slower than stated here in patients who are on ≤5 mg daily. In all cases, taper schedules should be individualized based on the patient. For relapse management, see Table 3.

TABLE 3 Examples of symptoms that may signify relapse of GCA during glucocorticoid taper that require further evaluation and, if judged to be due to GCA relapse, escalation of glucocorticoid treatment

Symptom	Possible significance in a patient with GCA	Action to consider if symptom is judged to be due to GCA relapse
Return of headache symptoms	Possible GCA relapse without ischaemic manifestations	Return to previous higher prednisolone dose
Jaw or tongue claudication	Possible GCA relapse with ischaemic manifestations	Consider high-dose oral prednisolone (40–60 mg) with or without glucocorticoid-sparing agent
Weight loss, fever, night sweats, anaemia, persistent acute phase response, new/recurrent PMR symptoms, limb claudication, abdominal pain or back pain	Possible GCA-related inflammation of the aorta and/or its proximal branches	Investigate with vascular imaging (MRI, CT or FDG-PET/CT); consider increasing oral prednisolone and/or adding glucocorticoid-sparing agent

This table outlines how new symptoms in GCA patients, in the absence of other risk factors or significant comorbidities, may influence management decisions. New visual loss or diplopia should be urgently evaluated by an ophthalmologist. Acute phase markers should be measured and, if found to be elevated, may increase the clinical suspicion of GCA relapse. At present, the only agents with any evidence for glucocorticoid-sparing in GCA are methotrexate and tocilizumab.

may include myopathy, which typically develops after weeks or months of glucocorticoid therapy (particularly at high doses); insulin resistance limiting the ability of skeletal muscle to take up glucose and store glycogen; bone fragility and central adiposity. Exercise can also be beneficial for improving balance and general mobility, which may be affected by alterations to vision and biomechanics.

The role of exercise programmes in GCA has not been formally evaluated in clinical studies. Patients should be signposted to relevant patient support groups or charities as sources of peer support. Patients should be advised of potential symptoms of glucocorticoid withdrawal, although these are uncommon in practice. Patients should be advised about alteration of their glucocorticoid dose in intercurrent illness, especially including advice for seeking emergency attention if they suffer a vomiting illness necessitating parenteral glucocorticoid.

What plans should be made for possible future GCA relapses?
8. During glucocorticoid taper and after glucocorticoid cessation, patients should be informed what symptoms may suggest GCA relapse and what action the patient should take in these circumstances, including the first point of contact for medical advice and how to contact the team providing specialist care. Consensus score: 9.81.

Examples of actions to consider if new GCA-attributable symptoms develop are given in Table 3.

Specific recommendations for diagnostic tests in suspected GCA

As affirmed in the 2010 BSR/British Health Professionals in Rheumatology guideline, there is an urgent need for confirmation of disease in every suspected case of GCA [10]. In the 2010 guidance, it was recommended that

temporal artery biopsy was desirable in every case of suspected GCA. In this edition, this recommendation has been updated in view of new evidence regarding imaging tests for diagnosis of GCA.

Which additional confirmatory diagnostic tests should be performed in all patients with suspected GCA? (PICO 1, 2)

Diagnostic accuracy may be expressed as sensitivity and specificity, or as a likelihood ratio; this information can be combined with the pretest probability (established on clinical grounds) to select and interpret the results of confirmatory diagnostic tests. Compared with biopsy, imaging tests such as ultrasound have the advantage of access to both superficial temporal arteries in their entirety. Most diagnostic accuracy studies have focussed on the role of ultrasound ($n = 16$) or MRI ($n = 7$). One study addressed the role of FDG-PET and another study examined the role of FDG-PET and CT angiography (CTA) for GCA diagnosis.

Seven studies (519 patients with suspected GCA, of whom 169 were diagnosed with GCA) compared the ultrasound 'halo' sign with a clinical diagnosis of GCA, giving a pooled sensitivity of 79% (95% CI 73, 84) and pooled specificity of 94% (95% CI 90, 96) [57–63]. The QoE was +++; downgrading was performed because of risk of bias in four of seven studies. One of these studies included 12 patients with a final diagnosis of LV-GCA [58].

Five studies (185 patients with suspected GCA, of whom 57 were diagnosed with GCA) compared the ultrasound 'halo' sign with temporal artery biopsy, giving a pooled sensitivity of 74% (95% CI 63, 83) and pooled specificity of 81% (95% CI 73, 88) [61–65]. The QoE was +; downgrading was performed because of high risk of bias in all five studies and because of inconsistency. Patients with LV-GCA were not evaluated in these studies.

Two studies (140 patients with suspected GCA, of whom 67 were diagnosed with GCA) compared the ultrasound 'compression' sign of temporal arteries with ACR criteria–based diagnosis of GCA, giving a pooled sensitivity of 79% (95% CI 67, 88) and a pooled specificity of 100% (95% CI 95, 100) [57, 66]. The QoE was ++; downgrading was performed for risk of bias in one of the studies and because both studies were performed by the same research group. The ACR criteria for GCA, which are not suitable for clinical diagnosis, served as the reference standard in both studies.

Three studies (560 patients with suspected GCA, of whom 327 had a clinical diagnosis of GCA) compared the diagnostic performance of ultrasound abnormality (defined as any one of halo, stenosis or occlusion) with clinical diagnosis of GCA, giving a pooled sensitivity of 61% (95% CI 56, 67) and pooled specificity of 86% (95% CI 81, 90) [19, 63, 67]. The QoE was ++; downgrading was performed for risk of bias in all three studies and for inconsistency.

Four studies (563 patients with suspected GCA, of whom 180 had a positive temporal artery biopsy) compared the diagnostic performance of ultrasound abnormality (defined as any one of halo, stenosis or occlusion) with temporal artery biopsy, giving a pooled sensitivity of 81% (95% CI 74, 86) and pooled specificity of 74% (95% CI 70, 79) [19, 63, 67, 68]. The QoE was ++; downgrading was performed for risk of bias in three of the four studies and for imprecision.

Neither clinical diagnosis nor temporal artery biopsy are perfect reference standards for evaluating the diagnostic accuracy of ultrasound for GCA, because neither of these are themselves 100% accurate. Clinical diagnosis is based on clinical symptoms, signs and laboratory tests, each of which are imperfect markers for GCA.

A positive temporal artery biopsy showing features of inflammation characteristic of GCA such as giant cells or panarteritis [69] confirms the diagnosis of GCA. Although the true sensitivity of temporal artery biopsy is not precisely known, it is accepted that its sensitivity is substantially <100%; this is supported by the histological observation of skip lesions in some cases. An imperfect reference standard would result in underestimation of the diagnostic accuracy of ultrasound. When using clinical diagnosis as a reference standard it is important that this is made independently of the index test result in order to avoid bias. This may be done by blinding of the diagnostician to the index test result. Notably a large prospective UK study assessing the diagnostic value of ultrasound addressed this issue by blinding the patient, the treating clinician and the investigator to the ultrasound result [19].

Ultrasound was found to be more sensitive but less specific than biopsy for diagnosis of GCA, was cost effective and provided a method for reducing the number of patients who need a temporal artery biopsy [19]. Overall, the pooled positive and negative likelihood ratios for ultrasound appear to support its use either for ruling out GCA in low-probability cases or for confirming GCA in high-probability cases (Supplementary Files, available at *Rheumatology* online and Fig. 1). Ultrasound of the axillary arteries might add extra diagnostic information to ultrasound of the temporal arteries [70].

Six studies (500 patients with suspected GCA, of whom 268 were finally diagnosed with GCA) compared cranial artery MRI (vessel wall oedema and contrast enhancement) with clinical diagnosis, giving a pooled sensitivity of 75% (95% CI 69, 80) and a pooled specificity of 89% (95% CI 84, 93) [71–76]. The QoE was ++; downgrading was performed for risk of bias in five of the studies and because five of the six studies were performed by the same research group; sensitivity was somewhat lower in the study performed by a separate group [76].

Five studies (397 patients with suspected GCA, of whom 171 had positive temporal artery biopsy) compared cranial artery MRI (vessel wall oedema and contrast enhancement) with temporal artery biopsy, giving a pooled sensitivity of 94% (95% CI 90, 97) and specificity of 79% (95% CI 73, 84) [71–74, 76]. The QoE was +; downgrading was performed for risk of bias in five of the studies, for inconsistency and for likely publication bias.

Fig. 1 A possible approach to using rapid-access vascular ultrasound to assist in clinical diagnostic decision making in suspected cranial GCA
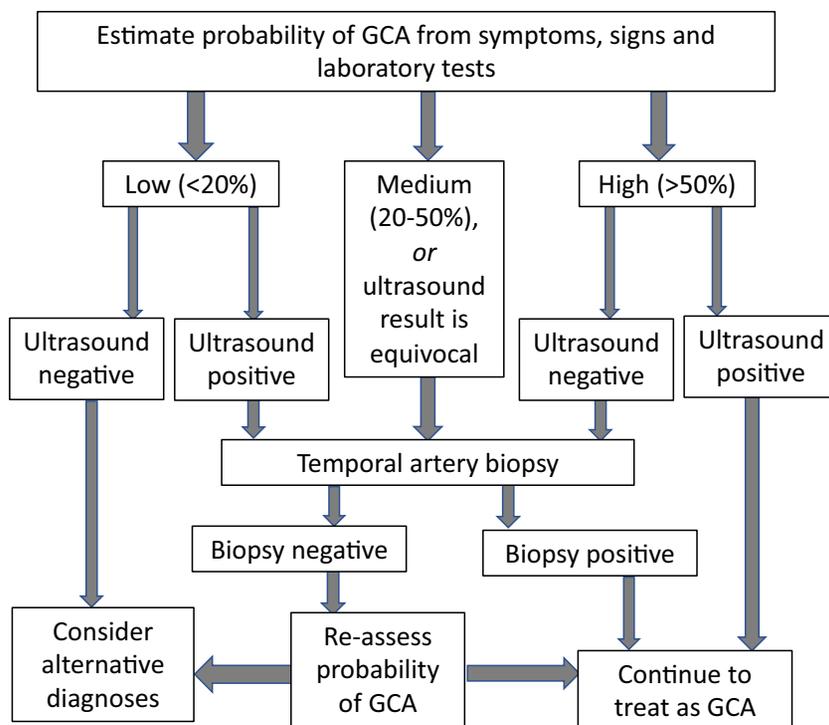
This figure illustrates a possible approach to using rapid-access vascular ultrasound, if available, in suspected GCA. Estimation of the probability of GCA is based on all information available (symptoms, signs, laboratory tests and alternative non-GCA explanations for the clinical picture) and can be updated based on new information (clinical course, result of temporal and axillary ultrasound and/or results of temporal artery biopsy). This assessment is based on clinical judgement and should ideally be performed by an individual with specialist expertise. Note that for a medium (20–50%) estimated probability of GCA, it may be useful to perform an ultrasound prior to biopsy, in case the biopsy is negative. For a high clinical probability of GCA, a positive ultrasound alone may be sufficient, as illustrated here; however, in these cases it is still acceptable to perform biopsy in addition to ultrasound in order to further increase diagnostic certainty. In the absence of clinical features of cranial GCA, temporal artery biopsy can still be positive, but imaging of the extracranial large vessels may be considered instead of, or in addition to, temporal artery biopsy. Recently, various clinical prediction rules have been proposed to assist clinicians in the estimation of probability of GCA; the performance of a clinical prediction rule developed in another setting should ideally be checked using local audit data prior to adopting into local clinical practice. If rapid-access vascular ultrasound is not available, patients treated for suspected GCA should all have a temporal artery biopsy. None of these tests should delay the prescribing of high-dose glucocorticoid therapy for patients with strongly suspected GCA.

Overall, MRI of the cranial arteries appears to be potentially useful for ruling out GCA if the result is negative, but false-positive test results could occur, such that MRI of the cranial arteries would not be first choice for a confirmatory test in GCA [76]. Other issues of relevance to cranial vascular MRI are low availability of high-resolution 3T MRI equipment and expertise, higher costs and possible adverse effects of contrast agents.

In contrast to the 2010 guideline, where the authors outlined that imaging techniques are promising for diagnosis and monitoring of GCA [10], in this guideline there is now sufficient evidence, taken together, to state that all patients with GCA should have at least one confirmatory diagnostic test, which could be either temporal artery biopsy or temporal and axillary artery ultrasound.

However, temporal artery biopsy and ultrasound differ in their positive and negative likelihood ratios for GCA, with biopsy having relatively greater 'rule-in' value and ultrasound having relatively greater 'rule-out' value (Supplementary Files, available at *Rheumatology* online). Selection of the most appropriate confirmatory diagnostic test(s) therefore requires an assessment of the pretest probability as outlined elsewhere [77]; if both ultrasound and biopsy are possible, an approach to this is suggested in Fig. 1.

The ultrasound halo diminishes in size during the first week of glucocorticoid therapy, indicating that the sensitivity of the test is likely to depend on the delay between initiation of glucocorticoid therapy and the ultrasound test [19]. Ultrasound is operator-dependent and requires

adequate training. Ultrasound performs best in the 'fast-track' setting, assuming rapid access, good technical equipment and high expertise with this method. With ultrasound, the non-compressible 'halo' sign is the most important finding suggesting GCA [78]. Temporal artery biopsy should be performed by a surgeon experienced in this procedure and samples should be at least 1 cm in length post-fixation. The pathologist evaluating the biopsy should be experienced in diagnosing GCA.

Data from the Temporal Artery Biopsy versus Ultrasound in the Diagnosis of Giant Cell Arteritis study [19] suggested significant variation between pathologists in the interpretation of temporal artery biopsy histology, so where biopsy findings are ambiguous (e.g. low-level inflammation restricted to the adventitia), discussion between the requesting clinician and the pathologist is desirable. In the absence of inflammatory infiltrate, a report of healed arteritis is not sufficient to diagnose GCA. Isolated vasa vasorum vasculitis is not diagnostic of GCA. Contralateral biopsy may slightly increase the yield of temporal artery biopsy, but is usually unnecessary. Biopsy may remain positive for several weeks after initiation of glucocorticoid therapy [79].

If neither vascular ultrasound nor biopsy is possible, and local MRI facilities and radiology support are available, then high-resolution 3T MRI of the cranial arteries could be used instead. In interpreting the results of these diagnostic tests, pretest probability (established on clinical grounds) should be taken into account (Fig. 1).

1. Strong recommendation: Patients with suspected GCA should have a confirmatory diagnostic test. This could be either a temporal artery biopsy at least 1 cm in length or an ultrasound of the temporal and axillary arteries, or both. QoE: +++. Consensus score: 9.33.

Which tests can be used to evaluate involvement of the aorta and its proximal branches in GCA? (PICO 2, 3)
One study (24 patients with suspected GCA, of whom 15 were diagnosed with GCA) compared FDG-PET with clinical diagnosis of GCA, giving a sensitivity of 67% (95% CI 38, 88) and a specificity of 100% (95% CI 66, 100) [80]. The QoE was ++; downgraded because of indirectness and publication bias.

One study (69 patients with suspected GCA/PMR, of whom 13 had biopsy evidence of GCA) compared vascular 18F-glucose uptake in the thorax and legs on FDG-PET with temporal artery biopsy, giving a sensitivity of 77% (95% CI 46, 95) and specificity of 66% (95% CI: 52%, 78%). Comparing vascular 18F-glucose uptake in the thorax on FDG-PET with temporal artery biopsy gave a sensitivity of 54% (95% CI 25, 81) and a specificity of 86% (95% CI 74,94). The QoE was +; downgraded because of risk of bias, indirectness and imprecision [81].

One study (24 patients with suspected GCA, of which 15 were diagnosed with GCA) compared CTA with clinical diagnosis of GCA, giving a sensitivity of 73% (95% CI 45, 92) and a specificity of 78% (95% CI 40, 97) [80].

The QoE was ++; downgraded for indirectness and publication bias. CTA can reveal wall thickening with contrast enhancement in biopsy-proven GCA [82]. There is also experience with CTA for accurate assessment of luminal diameter for large vessel stenosis in Takayasu arteritis [83].

No studies of magnetic resonance angiography (MRA) for the diagnosis of LV-GCA were found the met our criteria, but there is experience with MRI for the detection of vessel wall oedema reflective of inflammation and accurate assessment of luminal diameter for large vessel dilatation and stenosis in diseases of the major arteries, such as Takayasu arteritis. Gadolinium-enhanced MRA may help identify aortitis in the large vessel vasculitides, but appears to be very sensitive to glucocorticoid therapy [84].

In addition to showing inflammation of the large vessels, FDG-PET/CT may detect malignancy or infection and thus can be of use in the differential diagnosis of GCA. Contrast-enhanced CT of the chest and abdomen is also often used in clinical practice to screen for deep infection or occult malignancy. Moreover, aortic wall thickening on a contrast CT might help to identify GCA, albeit with lower sensitivity than FDG-PET/CT, and could also potentially have uses in settings where FDG-PET/CT is unavailable [80, 85, 86]. Additional advantages of FDG-PET and CT therefore include potential value in the workup of alternative diagnoses such as malignancy and infection.

As well as detecting axillary artery involvement for diagnosis of large vessel involvement in GCA, vascular ultrasound may also be able to visualize the carotid arteries and obtain more limited views of the subclavian arteries, vertebral arteries and parts of the aorta, but a higher level of operator expertise is required for these studies.

Overall, there is indirect evidence for the use of imaging tests to evaluate involvement of the aorta and its proximal branches in GCA, but the published evidence is extrapolated from other diseases such as Takayasu arteritis [77] and there is currently insufficient evidence from prospective studies of suspected GCA to yield precise estimates of diagnostic accuracy for these tests.

2. Conditional recommendation: 18F-FDG-PET, MRA, CTA or axillary artery ultrasound may be used to evaluate involvement of the aorta and its proximal branches. QoE: +. Consensus score: 9.36.

Recommendations for treatment of GCA
What is the best dose and route of initial glucocorticoid therapy for GCA in the absence of ischaemic visual manifestations? (PICO 1–3). There are no clinical trials comparing different initial oral glucocorticoid doses for GCA. However, clinical experience suggests that the vast majority of patients with GCA respond symptomatically within 1–7 days to a 40–60 mg daily dose of prednisolone, apart from irreversible sequelae such as established visual loss, stroke or tissue necrosis. Failure to respond to this dose should prompt re-evaluation of the diagnosis.

In several clinical trials [87–89] the initial dose of oral prednisolone has been administered by weight rather than by a fixed dose, as is done for other systemic vasculitides in clinical practice. There was not enough direct evidence to be able to recommend dosing prednisolone strictly by weight, but nonetheless body weight (or at least size) remains a factor to be taken into account when deciding on an initial dose. Comorbidities also should be taken into account, since the toxicity of glucocorticoid therapy increases with the dose [49]. Clinicians should consider a higher dose within the 40–60 mg range for patients who have cranial ischaemic features of GCA such as ischaemic visual manifestations or jaw or tongue claudication, acknowledging that the evidence base for this is limited.

Two RCTs addressed the question of whether intravenous glucocorticoids should be given in patients with new-onset, uncomplicated GCA (i.e. those without any history of recent visual loss, amaurosis fugax or transient ischaemic attack): one was a single-centre, 78-week, double-blinded RCT ($n = 27$) and one was a 12-month open RCT ($n = 164$) [87, 90]. In the double-blinded RCT [90], patients received either 15 mg/kg body weight/day intravenous methylprednisolone for 3 days or placebo plus 40 mg/day oral prednisone. In the open RCT [87], the intervention group was treated with a single dose of 240 mg intravenous methylprednisolone followed by 0.7 mg/kg oral prednisone; one control group was treated with oral prednisone 0.7 mg/kg alone and a further control group was treated with a single dose of 240 mg intravenous methylprednisolone followed by 0.5 mg/kg oral prednisone. Due to the substantial differences in study design, efficacy outcomes were not meta-analysed. We pooled the data for treatment-related adverse events to increase the power to detect unwanted effects.

Moderate QoE (+++) from one study [90] suggested a reduction of the cumulative glucocorticoid dose at week 78 {median cumulative glucocorticoid dose 5636 mg [interquartile range (IQR) 4050–6690]} in the group that received 3 days of intravenous methylprednisolone compared with 7860 mg (IQR 7373–9005) in the control group. The glucocorticoid pulses were not counted for cumulative dose. In the other study, very low QoE (+) [87] indicated no benefit of pulse treatment at 1, 2, 6 and 12 months regarding cumulative glucocorticoid dose.

Low QoE (++) suggested that those in the methylprednisolone group had a higher probability of achieving remission while receiving ≤5 mg oral prednisone at three time points: week 36 [RR 4.64 (CI 1.24, 17.33)], week 52 [RR 5.11 (CI 1.39–18.81)] and week 78 [RR 2.57 (CI 1.12, 5.89)] [90].

No differences were found between pulse therapy and control groups as regards discontinuation of glucocorticoids at 12 months (QoE +) [87], patients with at least one relapse at 78 weeks and drug-free remission at 78 weeks (both with QoE ++) [90].

Comparing adverse events between treatment arms in these trials, no differences were observed between the intervention and control groups regarding infections, cushingoid habitus, psychiatric side effects, cardiovascular complications, diabetes, digestive disturbances, glucocorticoid-related ophthalmologic side effects, phlebitis/thrombosis, glucocorticoid-induced myopathy, abdominal bleeding, osteoporosis including fractures and mortality (all with QoE + or ++). Nonetheless, the small size of these two trials limits the power to show significant differences in adverse events between treatment arms.

In summary, there may possibly be a small benefit in terms of a reduced cumulative glucocorticoid dose in patients receiving glucocorticoid intravenous pulse therapy, but due to concerns over the likely increased risk of adverse effects with this therapy, the value of intravenous glucocorticoids in patients without acute or intermittent visual loss in GCA remains uncertain.

3. Conditional recommendation: The standard initial glucocorticoid dose for GCA is 40–60 mg oral prednis(ol)one per day. QoE: +. Consensus score: 9.44.

What is the best dose and route of initial glucocorticoid therapy for GCA in the presence of ischaemic visual manifestations? (PICO 4). Clinical trials have not been conducted in patients with acute ocular ischaemia, but observational data indicate that the vast majority of visual loss in GCA occurs before initiation of glucocorticoid therapy. Acute visual loss due to ocular ischaemia in GCA requires immediate action [29].

Intravenous glucocorticoid (methylprednisolone) therapy is used in systemic vasculitis for the treatment of life- or organ-threatening disease [91]. The intravenous formulation ensures rapid delivery of the drug to the site of action and, in addition, the very high doses required have rapid actions via non-genomic effects as well as on the genomic effects that take some hours to affect gene transcription [92, 93]. Intravenous glucocorticoid therapy is thus commonly used for patients with acute or intermittent visual loss due to GCA. If intravenous glucocorticoid therapy is not possible, 60–100 mg oral prednisolone may be given for up to 3 consecutive days.

4. Conditional recommendation: GCA patients with acute or intermittent visual loss may initially be given 500 mg–1 g intravenous methylprednisolone daily for up to 3 consecutive days before commencing oral prednis(ol)one therapy. If intravenous therapy is not immediately possible, this should not delay initiation of oral prednis(ol)one. QoE: +. Consensus score: 9.00.

How should glucocorticoid dose be tapered in GCA? (PICO 5). A single-centre, open, 2-month RCT compared different tapering regimens in 35 patients with new-onset GCA [94]. The same glucocorticoid dose was used in the first 5 days, but the rate of tapering thereafter differed between treatment groups. No significant difference was found between the groups at 2 months

concerning relapse rate (QoE +) or visual loss (QoE ++).

In a multicentre RCT of tocilizumab as a glucocorticoid-sparing therapy for GCA [52], in two arms of the trial patients received placebo rather than tocilizumab. In one of these trial arms prednisone was tapered to zero over 6 months and in the other prednisone was tapered to zero over 12 months; relapses were treated at the discretion of the investigator. Patients with new-onset GCA receiving the 6 month prednisone taper without tocilizumab had a numerically higher frequency of relapse during the first year than receiving the 12 month prednisone taper, whereas the cumulative glucocorticoid dose was similar in these two trial arms. Although patients and investigators were blinded to the tapering regimen, this trial was not designed specifically to compare different prednisone tapering regimens.

5. Conditional recommendation: Glucocorticoid dose should be tapered to zero over 12–18 months, providing there is no return of GCA symptoms, signs or laboratory markers of inflammation. A more rapid dose reduction is appropriate for patients at high risk of glucocorticoid toxicity and/or those receiving concomitant glucocorticoid-sparing therapy. QoE: +. Consensus score: 8.81.

What dosing frequency of oral glucocorticoid should be used in GCA? (PICO 6, 7). A single-centre, open RCT with unclear length of follow-up compared the effects of 15 mg oral prednisone every 8 h with a single administration of 45 mg oral prednisolone/day. A third (alternate day) group received 90 mg oral prednisone every other day. Patients in all three groups were treated for the first 5 days with 20 mg oral prednisone every 8 h [95].

Remission and relapses at 4 weeks did not differ between groups of split-dose and single-dose prednisone treatment (QoE +). No difference was reported regarding hypercortisolism (which was not further defined), fractures, diabetes and glucocorticoid-induced myopathy (all with QoE +).

Comparing the single-daily and alternate-day treatment groups, at 4 weeks the single-daily group had higher remission rates at 4 weeks [RR 2.67 (CI 1.32, 5.39)] and lower relapse rates [RR 0.11 (CI 0.02, 0.80)] (QoE +). Hypercortisolism was more common in the single-daily group [RR 5.95 (CI 1.57, 22.57)]; fractures, diabetes and glucocorticoid-induced myopathy (all with QoE +) did not differ between groups.

This evidence, albeit low quality, raises concerns that alternate-day dosing may be associated with a higher relapse risk. Splitting the dose over the day does not seem to confer benefit and potentially carries risks of disturbance of diurnal rhythms, including sleep [96, 97]. In summary, in GCA there appears to be no reason to alter the standard guidance in other medical conditions to prescribe glucocorticoids as a single daily dose in the morning [12, 91].

6. Conditional recommendation: Patients should be prescribed a single daily dose of glucocorticoid rather than alternate day dosing or divided daily dosing. QoE: +. Consensus score: 9.53.

Should modified-release prednisone be used in place of standard therapy? (PICO 8). There was neither RCT data nor sufficient clinical experience to make any recommendation about modified-release prednisone in GCA.

7. No recommendation can be made for the use of modified-release prednisone in the treatment of GCA. QoE: insufficient evidence. Consensus score: 9.72.

When should further, non-biologic immunosuppression be added to glucocorticoid therapy for GCA? (PICO 9, 10). The effect of MTX has been investigated in three RCTs: a single-centre, 24-month, double-blinded RCT ($n = 42$) of patients with recent-onset GCA compared the addition of MTX 10 mg/week, *vs* placebo, to oral prednisone (initial prednisone dose of 60 mg/day) [98]. A multicentre, 12-month, double-blinded RCT ($n = 98$ instead of 300 originally planned) of patients with recent-onset GCA compared the addition of MTX 15 mg/week, *vs* placebo, to oral prednisone (initial prednisone dose of 1 mg/kg/day) [88]. A smaller single-centre, double-blinded RCT ($n = 21$) of patients with GCA whose prednisone dose had been reduced to 30 mg/day compared the adjunctive use of MTX 7.5 mg/week *vs* placebo; the initial glucocorticoid dose was at the discretion of the treating physician and some patients with visual symptoms received intravenous glucocorticoid pulse therapy [99].

Regarding efficacy data, the two larger trials [88, 98] could be pooled but the smallest trial [99] was considered separately because it substantially differed from the two other trials regarding design (lower MTX dose used, initiation of therapy upon reduction of glucocorticoid dose) and quality. Regarding adverse events, we combined the data from all three trials in order to increase the sensitivity to detect rare outcomes.

Pooling of the two larger studies indicated moderate QoE (+++) that MTX reduced the proportion with relapse at 12–24 months [RR 3.20 (95% CI 1.49, 6.87)] [88, 98]; the smallest trial showed no difference in relapse between the MTX and placebo groups (QoE +) [99]. In addition, the largest trial analysed 'treatment failure', defined as having two or more relapses or having a relapse that was not controlled by an increment of prednisone dose as scheduled: regarding this outcome, no difference was seen between the MTX and placebo groups (QoE ++) [88]. In none of the studies was a difference observed regarding cumulative glucocorticoid dose or the duration of glucocorticoid therapy (all outcomes with QoE + or ++); however, the largest trial reported only the median and IQR of the cumulative glucocorticoid dose rather than the mean and standard deviation, which reduced the validity of pooling the published data [88, 98, 99].

Regarding possible modification of glucocorticoid-related adverse effects by MTX, mortality, vision loss, malignancy, infections, psychiatric side effects, fractures, cataracts, diabetes, hypertension, cushingoid habitus, weight gain and skin fragility did not differ between groups (data from one to three studies, all with QoE + or ++, except for hypertension, with QoE +++) [88, 98, 99].

Regarding possible MTX-related adverse effects, there was no strong evidence to support that MTX was associated either with a higher rate of withdrawal due to any side effect, nor an increase in individual side effects, including alanine aminotransferase/aspartate transaminase elevation, nausea/vomiting, thrombocytopenia, oral ulcers, alopecia, diarrhoea or gastric discomfort (QoE + or ++) [88, 98, 99]. Nonetheless, these trials were not designed nor powered to detect differences in adverse effects.

An individual patient data meta-analysis relating to these three RCTs was also identified [100] and included in this review because it is a more efficient use of the data than meta-analysis using published reports. According to the individual patient data meta-analysis, compared with the placebo group, the MTX group had a modest reduction of the risk of first and second relapse (HR 0.65, $P = 0.04$ and HR 0.49, $P = 0.02$, respectively), higher rates of glucocorticoid-free remission (HR 2.8, $P = 0.001$ for ≥ 24 weeks sustained discontinuation of glucocorticoids) and lower cumulative glucocorticoid doses (mean difference -1.1 g, $P = 0.007$ at week 96) [100].

In summary, the data from these three small RCTs indicate that there might be a modest benefit of MTX in GCA in reducing relapse and cumulative glucocorticoid dose and the data are encouraging regarding reducing the risk of second relapse as well as first relapse; however, overall the evidence remains equivocal. MTX has been used at doses of 7.5–15 mg weekly in clinical studies and up to 25 mg weekly orally or by subcutaneous injection in clinical practice.

A single-centre, 52-week, double-blinded RCT ($n = 31$) compared azathioprine 150 mg/day vs placebo in patients with PMR, with or without GCA, who required ≥ 5 mg daily oral prednisolone to control disease activity [101]. A lower daily glucocorticoid dose at the end of the follow-up (52 weeks) was found in the intervention group compared with the control group [mean dose difference 3 mg (CI 4.32, 0.28), QoE +]. Adverse events were similar in both groups (QoE +). Thirty-one patients were recruited, but only 18 reached the 52 week time point. According to the inclusion criteria for this trial, patients had to satisfy the Hazleman criteria for PMR. Eleven of 31 of these had a positive temporal artery biopsy. This trial did not truly fulfil the inclusion criteria for this review (at least 20 patients with GCA) and therefore no recommendation could be made on the basis of this trial. However, it is included here for completeness since it is frequently mentioned by narrative reviews.

Dapsone was studied at a dose of 50–100 mg/day in an open, multicentre RCT ($n = 47$) with an unclear length of follow-up [102]. A lower relapse risk was found in the treatment group compared with the control group [RR 0.37 (CI 0.16, 0.84), QoE +] and there was a trend towards a higher probability of glucocorticoid-free remission [RR 3.81 (CI 0.92, 15.81), QoE +] in the dapsone group. Anaemia was more common in the dapsone group compared with the control group [RR 8.89 (CI 1.27, 61.99), QoE ++] and the dapsone group had two cases of agranulocytosis. Rash, diabetes, bone complications, cardiovascular complications, infections and loss of vision did not differ between groups (all QoE +).

Two open RCTs of ciclosporin ($n = 82$) were published in the format of a letter [103, 104]. Ciclosporin was used at a daily dose of 2.0–3.5 mg/kg for 6 or 12 months. No benefit of the drug was observed regarding cumulative glucocorticoid dose, acute phase reactants or patients' and physicians' global assessments (all QoE +). However, there was an increased risk of treatment discontinuation due to toxicity [RR 13.00 (CI 1.78, 95.1), QoE ++].

The potential toxicity of dapsone or ciclosporin is likely to outweigh any possible benefit and their use is not recommended. There has been no RCT of leflunomide in GCA despite anecdotal evidence of benefit in case series and open, non-randomized studies [105–107]. In clinical practice, mycophenolate mofetil or cyclophosphamide have been occasionally used as immunosuppressive agents for severe GCA by analogy with their use in other systemic vasculitides, but they have not been formally studied in GCA.

8. Conditional recommendation: MTX might be considered for GCA, in combination with a glucocorticoid taper, in patients at high risk of glucocorticoid toxicity or who relapse. There is insufficient evidence to recommend any other oral immunosuppressive agent in GCA, including azathioprine, leflunomide or mycophenolate mofetil. QoE: ++. Consensus score: 8.92.

Which biologic agents can be used for GCA in addition to standard therapy? (PICO 11, 12). Tocilizumab was approved for GCA by US and European regulatory authorities in 2017 based on the results of two RCTs of addition of 1 year tocilizumab, or placebo, to tapering glucocorticoid therapy [52, 89].

In the larger of these trials [52], both patients with new GCA and patients with relapsing GCA were included. Patients with relapsing GCA had to have been treated for GCA no longer than 4 years prior to enrolment. Tocilizumab was combined with a standardized prednisone taper according to which prednisone cessation occurred at 6 months. Patients receiving placebo were treated with one of two alternative prednisone tapering schedules, by which prednisone cessation was achieved at either 6 months or 1 year if the patient remained relapse-free. If a patient relapsed during the study, prednisone therapy was escalated according to the investigator's discretion.

The primary endpoint (sustained remission at 1 year plus adherence to the tapering protocol, using a definition of remission incorporating CRP levels) was

achieved in 56% of patients treated with weekly sub-cutaneous tocilizumab and in 53% of those treated every other week. In the placebo group, sustained remission at 1 year was achieved in 14% of those tapering prednisone over 6 months and 18% of those tapering prednisone over 1 year. Comparing weekly tocilizumab with placebo plus a 6 month glucocorticoid taper, the RR for sustained remission was 4.0 (95% CI 1.97, 8.12; QoE++++). Comparisons with other groups revealed similar results, with an RR of 3.01–3.79 (QoE ++++). Patients in the tocilizumab treatment arm also showed a higher rate of sustained remission using a modified definition of sustained remission that did not require CRP normalization [weekly tocilizumab compared with placebo plus a 6 month glucocorticoid taper: RR 2.95 (95% CI 1.66, 5.26), QoE +++; for other comparisons, RR 1.65–2.76, QoE+++].

In both this trial and in the smaller single-centre trial [89], an increase in relapse-free survival at 1 year [RR 3.57 (95% CI 2.29, 5.55), QoE ++++] was seen and a reduction in the 1 year cumulative glucocorticoid dose was observed in the tocilizumab treatment arms [mean difference −1434 mg (95% CI −2148, −720) in the weekly tocilizumab group compared with placebo plus 6 month tapering of glucocorticoids, QoE++++; mean difference from −1434 to −1956 mg in other comparisons, QoE++++]. Patient-reported outcomes were encouraging, although these were assessed using generic measures, since no disease-specific patient-reported outcome has yet been fully validated for GCA. Of note, although glucocorticoid-sparing efficacy was demonstrated, these studies were not designed or powered to demonstrate a reduction in glucocorticoid-related adverse events.

It has been argued that a glucocorticoid-sparing therapy such as tocilizumab would be more cost effective in the following GCA patient subgroups: first, GCA patients requiring escalation of glucocorticoid therapy due to relapse of disease, and second, GCA patients who are at high risk for adverse effects from further glucocorticoid treatment (e.g. on the basis of their comorbidity profile or other risk factors for glucocorticoid-related toxicity, including neuropsychiatric glucocorticoid-related adverse effects, previous fragility fractures or difficult-to-control diabetes mellitus).

UK prescribers should be aware that, at the time of writing, a limited duration of tocilizumab therapy for GCA has been approved by the Scottish Medicines Consortium and by NHS England for defined patient groups, taking into account cost-effectiveness data available at the time of the technology appraisal.

Tocilizumab has only been approved for weekly subcutaneous use, although it has also been studied in intravenous formulations [89]. In a multicentre RCT [52], one of the treatment arms received subcutaneous tocilizumab every 2 weeks rather than weekly; patients in this treatment arm also reached the primary endpoint, although it appeared to be less efficacious in relapsing patients. The trials in GCA have not demonstrated an increased risk of adverse events with tocilizumab [52, 89]; pooling of data from both trials indicated a lower rate of serious adverse events in patients treated with tocilizumab than those treated with placebo [RR 0.64 (95% CI 0.41, 1.00), QoE+++].

Abatacept was studied in a single, small trial [108]. All patients received abatacept initially in addition to glucocorticoid therapy. Those achieving remission were randomized in week 12 to either continue the drug or to switch to placebo. Time-to-relapse analysis, which was the primary endpoint, significantly favoured abatacept. A post hoc analysis to compare the proportion of patients in remission at 12 months did not show a significant difference between the treatment arms [RR 1.50 (CI 0.71, 3.17), QoE ++], likely due to the small size of the study. At present, abatacept is not approved for treatment of GCA.

TNF inhibitors have been studied in two RCTs [109, 110], both of which showed inefficacy but an increased incidence of infections. A third, small RCT of etanercept for GCA [111] did not fulfil the inclusion criteria for the literature review. Although it showed a lower cumulative glucocorticoid dose in the etanercept arm, this trial failed to show a significant result for its primary outcome. Based on this evidence, TNF inhibitors cannot be recommended for GCA.

9. Strong recommendation: Tocilizumab can be considered for GCA, in combination with a glucocorticoid taper, especially in patients at high risk of glucocorticoid toxicity or who relapse. TNF inhibitors are not recommended in GCA. QoE: +++. Consensus score: 9.61.

Should anticoagulant or antiplatelet agents be given for GCA? (PICO 12–15). No RCTs relating to aspirin or other anticoagulant/antiplatelet agents were found. A Cochrane review found no evidence from RCTs to determine the safety and efficacy of low-dose aspirin as an adjunctive treatment in GCA [112]. National and society guidelines for the secondary prevention of coronary and other atherosclerotic vascular diseases should be followed.

10. The routine use of antiplatelet or anticoagulant agents for GCA is not recommended. QoE: insufficient evidence. Consensus score: 9.28.

Should cholesterol-lowering agents be given for GCA? (PICO 16). No RCTs of cholesterol-lowering agents for GCA were found. National and society guidelines for the secondary prevention of coronary and other atherosclerotic vascular diseases should be followed.

11. The routine use of cholesterol-lowering agents such as statins for GCA is not recommended. QoE: insufficient evidence. Consensus score: 9.53.

Applicability and utility

This guideline represents a framework upon which clinical practice should be based. However, as with any guideline, individual patient circumstances can have important influences on clinical decision making and clinicians should continue to work alongside patients to make shared decisions about care. Failure to adhere to this guideline should not necessarily be considered

negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

Potential organizational barriers to implementation

In practice, constraints of the healthcare system may create challenges to widespread implementation of this guideline. For example, implementing rapid-access vascular ultrasound as a diagnostic test in GCA is dependent not only on local expertise and experience in the technique itself, but also on the entire care pathway for patients with suspected GCA, including appropriate, timely referrals and clinical expertise such that the results of the test can be interpreted appropriately.

As another example, follow-up every 2–8 weeks for the first 6 months (less frequently thereafter) may seem ambitious, but this could be delivered via a shared care model in collaboration with primary care by which the patient and general practitioner receive the information and support they need and have ready access to secondary care if need be. Nonetheless, it is also recognized that specific quality standards are necessary to drive clinical improvement.

Cost and cost-effectiveness implications for implementation

A formal health economic evaluation was not conducted as part of the guideline development process.

The use of additional imaging tests could incur healthcare costs. This has to be set against the advantages of accurate, timely diagnosis of GCA, in particular the potential cost savings of avoiding unnecessary treatment of patients without the disease.

A UK National Institute for Health and Care Excellence (NICE) technology appraisal has been conducted with regard to tocilizumab therapy for GCA [113], which has the potential to significantly increase the direct costs of drug treatment of GCA. Both biologic and non-biologic therapies used alongside glucocorticoid treatment would incur additional costs due to the requirements for regular blood monitoring. However, this must be set against the potential cost savings arising from a reduction in cumulative glucocorticoid doses and thereby a reduction in glucocorticoid-associated adverse events. On the basis of overall cost-effectiveness data, approval was granted by NHS England and the Scottish Medicines Consortium for tocilizumab treatment for defined GCA patient groups; readers are directed to the appropriate guidance for a more detailed explanation.

Mechanism for auditing compliance with the guideline

Quality standards have been defined based on the fundamentals of good clinical care, as outlined in the general principles. Audit should be performed on an unbiased (e.g. consecutive) sample of patients presenting to a clinic or service. A draft audit tool that may be adapted for local use is published as Fig.

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Statement of contribution of the literature review team

Christian Dejaco led the SLR team. The literature review team was split into three groups, each group consisting of three members: group 1 (Duftner, Mackie, Appenzeller) performed the SLR on diagnostic tests/strategies, group 2 (Dejaco, Camellino, Hutchings) performed the SLR on therapeutic interventions and group 3 (Mahr, Gonzalez-Chiappe, Wagner Silva de Souza) performed the SLR on prognostic factors. Two members of each group independently performed screening, inclusion/exclusion of articles, data extraction and quality appraisal. Results were compared between the two members and any discordance was resolved by discussion, then consulting the third member of the group where no consensus could be reached. Christian Dejaco supervised the progress of the SLR in each group and the preparation of the evidence tables. The searches underpinning the 2018 update to the SLR were conducted by Gary Reynolds, who also worked with the literature review team in the appraisal of new evidence.

Individuals who contributed to the guideline development but did not participate in the final voting are listed below and their contributions are gratefully acknowledged:

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Presentation and dissemination of final guidelines

The final guidelines will be disseminated by publication in the journal Rheumatology (Oxford) as well as by uploading onto the BSR homepage.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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