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Systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis: focus on giant cell arteritis

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ABSTRACT

Objectives To analyse the current evidence for the management of large vessel vasculitis (LVV) to inform the 2018 update of the EULAR recommendations.

Methods Two systematic literature reviews (SLRs) dealing with diagnosis/monitoring and treatment strategies for LVV, respectively, were performed. Medline, Embase and Cochrane databases were searched from inception to 31 December 2017. Evidence on imaging was excluded as recently published in dedicated EULAR recommendations. This paper focuses on the data relevant to giant cell arteritis (GCA).

Results We identified 287 eligible articles (122 studies focused on diagnosis/monitoring, 165 on treatment). The implementation of a fast-track approach to diagnosis significantly lowers the risk of permanent visual loss compared with historical cohorts (level of evidence, LoE 2b). Reliable diagnostic or prognostic biomarkers for GCA are still not available (LoE 3b).

The SLR confirms the efficacy of prompt initiation of glucocorticoids (GC). There is no high-quality evidence on the most appropriate starting dose, route of administration, tapering and duration of GC (LoE 4). Patients with GCA are at increased risk of dose-dependent GC-related adverse events (LoE 3b). The addition of methotrexate or tocilizumab reduces relapse rates and GC requirements (LoE 1b). There is no consistent evidence that initiating antiplatelet agents at diagnosis would prevent future ischaemic events (LoE 2a). There is little evidence to guide monitoring of patients with GCA.

Conclusions Results from two SLRs identified novel evidence on the management of GCA to guide the 2018 update of the EULAR recommendations on the management of LVV.

Key messages

What is already known about this subject?

- The previous EULAR recommendations for the management of large vessel vasculitis (LVV) were published in 2009. Since then, significant evidence to support the diagnosis and treatment of LVV has been produced.

What does this study add?

- This was the first thorough review of available evidence published until December 2017 guiding diagnosis, monitoring and treatment of giant cell arteritis (GCA).
- Results of the systematic literature review (SLR) revealed the importance of early diagnosis, including the advantages of a fast-track approach to reduce ischaemic complications.
- Rapid initiation of treatment with glucocorticoids (GC) is pivotal; the addition of methotrexate or tocilizumab reduces relapse rates and GC requirements.
- There is inconsistent evidence supporting the use of antiplatelet agents to prevent future ischaemic events.
- There is no high-quality evidence guiding monitoring and duration of treatment in GCA.

How might this impact on clinical practice?

- The results of this SLR will significantly impact the future practice on the best diagnostic, monitoring and therapeutic approach to GCA. The evidence summarised in this study formed the basis for a substantial revision of the EULAR recommendations for the management of LVV, which was recently published. The updated EULAR recommendations will provide guidance on diagnosis, monitoring and treatment of GCA in the future years.

INTRODUCTION

The management of large vessel vasculitis (LVV) has rapidly changed in the recent years. Imaging is becoming increasingly recognised

as a reliable tool to diagnose LVV.[1 2] However, we still lack prognostic markers (either derived from baseline characteristics or useful biomarkers) to tailor the intensity of treatment to individual patients. Moreover, less common types of LVV (eg, isolated aortitis, vascular involvement in IgG4-related disease) are emerging, thereby expanding the spectrum of disease and adding complexity to their diagnosis and management. New therapeutic options are available for giant cell arteritis (GCA), offering opportunities, but also challenges in the best treatment approach and timing, appropriate concomitant glucocorticoids (GC) dose and tapering scheme, as well as potential safety concerns.

The aim of this systematic literature review (SLR) was to collect evidence on the therapeutic management of LVV to inform the Task Force responsible for the 2018 update of the EULAR LVV recommendations.[3] This, together with a second SLR focused on diagnostic and monitoring aspects in LVV, provided the Task Force with the current state of evidence. This paper will provide the evidence that emerged from both SLRs, focusing on the evidence in GCA. A second publication will deal with results of the two SLRs regarding Takayasu arteritis (TAK) and other types of LVV.

METHODS

Two SLRs were performed according to the EULAR operating procedures.[4] MEDLINE, EMBASE and Cochrane CENTRAL library were searched from inception of each database (1946, 1974 and 1993, respectively) to 31 of December 2017. Detailed description of search strategies is provided in the online supplementary material (online supplementary file 1). There was no language restriction. References from included studies were screened. Two SLRs were performed by two different reviewers according to research topic (table 1). We included all study designs (except case reports of single patients). Meta-analyses and SLRs were reviewed and included if relevant. Diagnostic and monitoring aspects regarding the use of imaging in LVV were excluded due to the recent publication of dedicated EULAR recommendations and a SLR on the use of imaging for LVV.[1 2]

Two reviewers (SM and AFA) independently screened all titles and abstracts to identify eligible studies to be assessed by full text. Both reviewers independently extracted data from eligible papers and summarised the evidence into summary of evidence (SoE) tables using a standardised data extraction form. Complete SoE tables are published in the online supplementary material. Included studies were organised according to diagnosis (GCA vs TAK vs other forms of LVV) and according to research question (type of diagnostic tool, biomarkers, monitoring tools, outcome assessment or type of drug or surgical intervention). Following the 2014 operating procedures and the 2017 additional guidance document on the development of EULAR recommendations, levels of evidence (LoE) were assigned according to the 2009 Oxford Centre for Evidence-Based Medicine LoE.[5] Risk of bias (RoB) was assessed using the Cochrane Risk of Bias Assessment Tool[6] for randomised controlled trials (RCTs) and the Newcastle-Ottawa scale for observational studies.[7] The Quality Assessment of Diagnostic Accuracy Studies II and the Quality In Prognosis Studies were used for observational studies according to specific outcomes studies.[4 6 8]

Table 1 Topics addressed by the two SLRs

SLRs informing the 2018 update of EULAR recommendations for the management of LVV	
Participants were patients with the following diagnoses: giant cell arteritis or Takayasu arteritis, or other types of LVV (isolated aortitis or IgG4-related disease with vasculitis).	
SLR 1: Diagnosis, prognosis and monitoring	**SLR 2: Drug and surgical treatment**
► Diagnosis: recognition, referral criteria, fast-track diagnosis, role of imaging for diagnosis, role of biopsy for diagnosis, interdisciplinary workup, considerations for subtypes of disease such as cranial/ischaemic/large vessel, isolated aortitis, IgG4related disease, LVV disease in other vasculitides. ► Prognostic and therapeutic implications of disease phenotypes: cranial versus extracranial, isolated aortitis, other forms including IgG4-related disease, imaging, other biomarkers, comorbidities and complications, disease damage versus activity. ► Long-term follow-up of patients: clinical assessments and frequency, imaging, patient-reported outcomes, physical therapies and management of complications. ► Patient education and other aspects of patients-centred care.	► Drug therapy: dosing, length of therapy, outcome and treatment-related side effects for the following drugs: glucocorticoids, methotrexate and other non-biological immunosuppressive agents (csDMARDs), tocilizumab and other biological DMARDs (bDMARDs). ► Specific treatment of organ complications: loss of vision and stroke), relapsing, refractory, glucocorticoid-dependent disease. ► Revascularisation procedures: indications for referral, management of aneurysms and/or vessel stenosis. ► Adjunctive therapies and prophylaxis: aspirin, cardiovascular and cerebrovascular disease, infections, vaccination, osteoporosis.

bDMARDs, biological DMARDs; csDMARDs, conventional synthetic antirheumatic drugs ; LVV, large vessel vasculitis; SLRs, systematic literature reviews.

RESULTS

The SLR focused on diagnosis and monitoring of all types of LVVs yielded 4389 articles and the one focused on treatment yielded 6226 articles (after removal of duplicates). One hundred and twenty-two and 165 studies, respectively, were finally included for full-text review. Of these, 62 and 76 studies, respectively, focused on GCA. Details are described in the online supplementary file 1. A meta-analysis of the collected evidence was not performed due to pronounced heterogeneity of the included studies in terms of design, inclusion criteria, methodology, type of intervention and outcome.

General management and diagnosis

Disease patterns of GCA

Standardised definitions for different disease patterns are lacking, leading to difficulties in comparability between studies. Nevertheless, 12 papers focusing on disease subtypes in GCA and on their clinical and prognostic implications were retrieved. Patients with large vessel GCA (LV-GCA) are more likely to be younger[9–11] and female[12 13] and suffer from a longer diagnostic delay[11 12 14] compared with those with exclusively cranial involvement. Headache, jaw claudication, scalp tenderness and visual complications are less frequent,[11–13 15] as opposed to a higher frequency of limb claudication and symptoms of polymyalgia rheumatica (PMR).[11 13 14] Relapse rates have been reported to be higher in LV-GCA (4.9 vs 3.0/10 person-years; p<0.001)[14 15] with discordant results on the need for more intensive immunosuppressive regimens.[11 12 14–17] LV involvement with aortic aneurysm/dissection is associated with increased mortality in GCA.[18]

In summary, disease patterns of GCA are mainly represented by cranial and LV-GCA. This distinction may have clinical and prognostic implications (LoE 3b).

Fast-track clinics for the diagnosis of GCA

There were two retrospective cohort studies (total number of patients n=189) comparing conventional clinical practice to a fast-track approach (FTA) integrating clinical evaluation with ultrasonographic assessment of the temporal (TA) and axillary arteries (table 2).[19 20] Compared with historical cohorts, the FTA has been associated with a significant reduction in the rates of visual loss,[19 20] inpatients costs[20] and need for temporal artery biopsy (TAB)[21] (LoE 2b).

Role of TAB in GCA

The SLR retrieved 13 retrospective observational cohort papers[22–34] and only three prospective studies,[35–37] focusing on the diagnostic role of TAB and on the associated clinical features. The data showed the importance of performing TAB as soon as possible, since in one large study including 381 patients sensitivity decreased rapidly with high dose of GC treatment (48% within 3 days vs 33% ≥7 days).[35] Nevertheless, another study on a large cohort of 535 consecutive patients had shown similar rates of TAB positivity regardless of previous GC treatment (31% in untreated patients vs 35% in patients exposed to GC before TAB; p=0.4). The frequency of positive TABs reduced with ongoing GC therapy >7 days but persisted in 28% of cases treated with GC for over 2 weeks. Interestingly, TABs were re-evaluated by a pathologist blinded to clinical and treatment information. Moreover, one small longitudinal pathological study (40 patients with initial positive TABs) has shown that vasculitis may still be demonstrated on repeated biopsies obtained after 3 (n=10), 6 (n=12), 9 (n=9) or 12 months (n=9) of GC therapy but with decreasing probability: 70% at 3 months, 75% at 6 months, 44% at 9 and 12 months, respectively.[36]

The recently published study on the Role of Ultrasound compared with Biopsy of Temporal Arteries in the Diagnosis and Treatment of GCA (TABUL) has reported a TAB sensitivity against clinical diagnosis of 39%, with 100% specificity.[35] Assessing the diagnostic performance of TAB has some limitations in GCA since an absolute reference standard for diagnosis is still lacking. The reference clinical diagnosis used in TABUL incorporated TAB results as part of ACR criteria, but also clinician's final diagnosis, emergence of complications consistent with GCA during follow-up or the emergence of alternative diagnosis and the validation by an expert review panel.

The length of TAB is crucial for optimising diagnostic performance. The cut-off with the highest positive predictive value for a positive TAB has been reported to be ≥0.7 cm after specimen fixation.[22 35] A single retrospective multicentre study has suggested that in the presence of

Table 2 Retrospective cohort studies comparing a fast-track diagnostic strategy for GCA to conventional practice

Study ID	N	Variable assessed	FTA	Conventional practice	P value	NOS scale
Patil *et al*, 2015[19]	113	Permanent visual impairment (n; (%))	6 (9%)	17 (37%)	0.001	2
		Time from symptoms to diagnosis (median (range) days)	17.5 (0–206)	21.0 (1–196)	>0.2	
Diamantopoulos *et al*, 2016[20]	75	Permanent visual impairment(n)	1 (1.3%)	6 (8%)	0.01*	2

*Relative risk: 0.12 (95% CI 0.01 to 0.97).
.FTA, fast-track approach; GCA, giant cell arteritis; NOS, Newcastle-Ottawa Scale.

inflammatory infiltrate involving the media and media–intima junction (excluding lymphocyte infiltration isolated to the adventitial or periadventitial tissue) the cut-off to optimise sensitivity for an histological confirmation of GCA should be ≥0.5 cm.[38]

Histological patterns of inflammatory infiltrate distribution (eg, transmural) on TAB have been correlated with specific clinical manifestations (eg, typical cranial symptoms for GCA).[23] Discordant evidence was found in regard to the presence of giant cells on TAB with the risk of blindness or cranial ischaemic events.[24–26] The presence of giant cells and calcifications on TAB have been described as independent predictors for the development of permanent visual loss.[32] Giant cells have also been linked with a relapsing disease course,[27–29] but not with GC requirements.[24 30 37]

In summary, TAB is a highly specific test to confirm a diagnosis of GCA (LoE 1b), however, diagnostic yield depends on timing after treatment initiation and correct sampling. There are no consistent data supporting a prognostic role for TAB on disease course or outcome.

Implications of disease activity, damage, comorbidities and complications on GCA

Several observational studies have explored potential predictors of ischaemic complications in GCA. Transient visual ischaemic symptoms,[39 40] cerebrovascular accidents,[41] jaw claudication,[39 42] headache, TA tenderness[39] and an increased platelet count[39] have been reported as risk factors for visual complications. On the other hand, PMR, upper limb artery involvement, constitutional symptoms, elevated C reactive protein (CRP) and low haemoglobin (Hb) levels conferred a reduced risk.[39 43 44] Cerebrovascular accidents in GCA have been associated with the presence of comorbidities, namely hypertension[45–47] and hyperlipidaemia,[45] but negatively correlated with anaemia and female sex.[45 46]

Relapses are more frequent in the first year after diagnosis[48] and are more common among patients presenting with scalp tenderness, PMR and evidence of a strong inflammatory response (at least three of the following: fever >38°C, weight loss ≥4 kg, Hb <11 g/L and erythrocyte sedimentation rate (ESR) ≥85 mm/hour).[49–51] A relapsing course is associated with higher GC requirements and higher rates of methotrexate (MTX) use.[49]

The rate of occurrence of vascular complications in GCA is high within the first year from diagnosis (5 events per 100 person-years). The risk of development of aortic aneurysms/dissection increases over time, particularly after 5 years from diagnosis, and has been reported to occur up to 20%–30% of patients. The aortic diameter (assessed by CT) increases over time and is more significant in the ascending and descending aorta, occurring mostly at the expense of patients with aortic structural damage at the first CT. In a cohort of 54 patients with GCA, followed prospectively for a median of 10.3 years after initial screening, reassessments with contrast-enhanced thoracic CT and ultrasound of the abdominal aorta performed at least every 4 years, or according to clinical judgement in the presence of abnormal findings at first assessment, allowed to detect aortic structural damage in 33.3% of patients. Aortic damage was defined as a focal dilatation, or a diffuse dilatation with a diameter ≥4 cm in the thoracic aorta and ≥3 cm in the abdominal aorta). Surgical repair, although indicated in at least 50% of cases, was only feasible in about one-third, mainly due to advanced age and comorbidities.[52] Interestingly, the size of the aneurysm has not been associated with the risk of dissection/rupture in patients with GCA, and a role of ongoing active inflammation of the vessel wall has been suggested.[18]

Aortic involvement is associated with a fivefold increase risk of death, while the mortality of GCA in general is not increased.[18 52] Mortality has also been associated with male sex and visual loss.[53 54] Severe infections and GC dose above 10 mg/day of prednisone after 12 months of treatment represent a significant mortality risk (HR 3.19, 95% CI 1.76 to 5.53; p=0.025 and HR 1.93, 95% CI 1.08 to 3.47; p=0.0001, respectively). An increased risk of infection-related mortality was confirmed in diabetic patients, further enhancing the need for careful management of comorbid conditions in patients with GCA.[55]

Overall, evidence points to a possible prognostic and predictive role of specific presenting symptoms with ischaemic complications and poor outcome (LoE 3b). Comorbidities can influence GCA-related complications and their management should be integrated in the treatment of GCA (LoE 2b).

Biomarkers for GCA

The SLRs found 24 observational studies that analysed (mostly circulating) biomarkers and their relation to disease outcome (online supplementary file 2, tables 19–24). The most widely used biomarkers for GCA have been ESR and CRP. A stronger inflammatory response (including systemic symptoms and/or markedly increased ESR or CRP) is associated with a decreased risk of ischaemic events,[56 57] but higher risk of relapse.[51 58]

Although infrequent, there are reports of patients with GCA with active disease that present with normal or near-normal ESR and/or CRP. In a prospective series of 25 untreated patients,[59] four presented ESR levels below 20 mm/hour with no clinical differences from the patients with high ESR. On this study, IL-6 levels were measured, and despite appearing more sensible than ESR to detect disease activity, of the four patients with normal ESR, two also had normal IL-6 levels. CRP closely followed IL-6 trend. As tocilizumab (TCZ) suppresses the CRP and other acute phase reactants production in the liver, CRP, and indirectly, ESR levels (eg, secondary to fibrinogen and acute phase reactants reduction) may not accurately reflect disease activity in TCZ treated patients with GCA and the search for alternative biomarkers is desirable.

Circulating levels of several cytokines (eg, IL-6 and TNF-alpha) have been associated with a relapsing course

of GCA, with levels falling once remission had been obtained.[60–62] High IL-6 levels have been inversely associated with ischaemic events.[63] Osteopontin has recently been proposed as a marker of active disease especially in patients treated with TCZ.[64] Although osteopontin levels correlate with IL-6 levels, its production in cultured arteries was shown not to be significantly modified by TCZ.[64] Therefore, osteopontin is an interesting candidate biomarker for TCZ-treated patients with GCA, but prospective clinical data correlating osteopontin levels with imaging and clinical outcomes are yet lacking.

The association between antiphospholipid antibodies and ischaemic complications in GCA is controversial.[65–68] Genetic biomarkers for GCA are still under investigation (online supplementary file 2; table 19).

In summary, validated, reliable biomarkers for GCA are still not available. ESR and CRP are the most widely used and correlate to some extent with disease activity (LoE 3b), but the reliability of CRP in TCZ-treated patients with GCA still needs to be addressed.

Long-term follow-up of patients including clinical assessment, physical therapy

The SLRs could not find evidence regarding the best timings/frequency of follow-up visits nor was there any data on the role of physical therapy.

Patient-reported outcome measures and patient-centred care in GCA

One prospective study looked at the efficacy of a patient education programme for patients with different types of vasculitis (including nine patients affected by GCA). A significant increase in the awareness on the disease was confirmed 1 and 12 months after the training.[69]

Drug therapy

Glucocorticoids

The SLRs yielded four RCTs assessing the use of GC, all including newly diagnosed patients with GCA.[70–73] Details are presented in table 3. Two RCTs investigated the GC-sparing effect of high-dose pulse intravenous methylprednisolone induction therapy; one of these had a high RoB as the study was not blinded.[73] Notably, both RCTs on the use of high-dose intravenous GC excluded patients with recent vision loss or ocular/vascular complications. The GC regimens used differed between the two studies: 15 mg/kg intravenous methylprednisolone for 3 days followed by 40 mg/day oral prednisone with rapid tapering,[71] or 240 mg intravenous single pulse of methylprednisolone, followed by 0.5–0.7 mg/kg/day oral prednisone with rapid tapering, respectively.[73] Only the first study met the primary endpoint allowing a more rapid GC tapering in patients treated with 3 days of intravenous pulses at diagnosis, with 71% of patients reaching a prednisone dose ≤5 mg/day by week 36 compared with 15% for patients not receiving pulse intravenous methylprednisolone; p=0.003 and a reduction by 2224 mg in the cumulative prednisone dose (dose of GC pulses not counted).[71]

One small RCT, including seven patients in the active group and five in the control group, analysed the efficacy and safety of modified-release prednisone with immediate-release prednisolone in newly diagnosed GCA suggesting a similar outcome profile, but with worse sleeping scores in the modified-release GC. However, the small sample size does not permit definitive conclusions.[70] The differential effect on bone mass loss of deflazacort versus prednisone was assessed in an RCT showing no difference between the two GC compounds.[72]

Data on the most effective initial GC dose to treat GCA derive from uncontrolled observational studies with no conclusive evidence to be drawn and no apparent influence on the maintenance dose.[74–76] In a retrospective review of 286 TAB +patients with GCA, a higher initial oral prednisone dose (>40 mg/day) was associated with greater chances of reaching a low dose sooner (HR 1.46; 95% CI 1.09 to 1.96) and of discontinuing GC (HR 1.56; 95% CI 1.09 to 2.23).[48]

The incidence of visual loss (defined as new onset of permanent reduction of visual acuity or visual field loss) with respect to early diagnosis and GC initiation compared with delayed treatment was assessed in a prospective longitudinal cohort study of 68 patients with GCA, suggesting the importance of prompt treatment in reducing the rate of permanent visual loss. This approach did not have any effect on the frequency of relapses.[77] Further evidence from a retrospective, multicentre study supports the concept that partial improvement of visual acuity is associated with the very early initiation of GC within 1 day from the onset of visual symptoms, regardless of the route of administration.[78]

The effect of the best route of administration of GC (intravenous vs oral) on visual loss in GCA was assessed in a retrospective longitudinal cohort study. Patients either received 150 mg dexamethasone sodium phosphate every 8 hours for 1–3 days, followed by oral prednisone 80–120 mg/day, or they were given oral prednisone, starting with doses ≥80 mg/day. Visual improvement only occurred in a very limited number of cases (only in 4% of eyes and only for overall visual acuity and not for central vision) with no differences in the route of GC administration. Earlier GC initiation was associated with a trend for greater likelihood of improvement.[79] Another retrospective longitudinal study compared the route of GC administration during the first week of treatment on visual loss at presentation of GCA. Different intravenous schemes were used (intravenous methylprednisolone pulses 1000 mg per day, 250 mg 2–4 times per day, 500 mg 1–2 times per day for a median of 3 days (range 2–5 days)) compared with oral GC prednisolone (50–100 mg/day). There was an increased likelihood for improved visual acuity in the group treated with intravenous GC (40%) compared with the oral route (13%); in all except for four patients, vision remained stable 1 month after presentation, supporting the idea that improvement

Table 3 Randomised controlled trials of GC in GCA

Study ID	Study design	GCA subtype	n	Intervention	Control	Primary outcome	Results (i)	Results (c)	P value
Raine *et al*[70] 2018	Feasibility study, prospective, randomised, open-label, blinded evaluator	New	**12** 7 (i) vs 5 (c)	MR prednisolone	Prednisolone	Persistent clinical disease control week 26	6/7	4/5	NA
Mazlumzadeh *et al*[71] 2006	Double-blind, placebo-controlled, randomised prospective controlled trial	New	**27** 14 (i) vs 13 (c)	GC i.v. 15 mg/kg/day for 3 days → 40 mg/day PRED p.o.	i.v. saline for 3 days+40 mg/day PRED	GC ≤5 mg/day week 36	10/14 (71%)	2/13 (15%)	0.003
Cacoub *et al*[72] 2001	Double-blind, randomised prospective controlled trial	New	**74** 37 (i) vs 37 (c)	Prednisolone 0.7 mg/kg/day	Deflazacort (equivalent dose)	Bone mass loss (g/cm^2) month 12	0.026±0.007	0.03±0.005	NS
Chevalet *et al*[73] 2000	Randomised prospective controlled trial (not blinded)	New	**146** 61 (i) vs 53 (c2) vs 50 (c3)	GC i.v. 240 mg → 0.7 mg/kg/day PRED p.o.	(C2): 0.7 mg/kg/day PRED p.o. -(C3): GC i.v. 240 mg → 0.5 mg/kg/day PRED p.o.	Mean cumulative PRED dose (mg) mo 12	5777	5578 (c2); 5168 (c3)	0.38

c, control; GC, methylprednisolone; GCA, giant cell arteritis; i, intervention; i.v., intravenous; mo, month; MR, modified release; NA, not applicable; New, newly diagnosed giant cell arteritis;NS, non-significant; p.o., oral route; PRED, prednisolone.

only occurs in the very initial phases of the ischaemic process.[80] Notably, both studies were characterised by high RoB; different baseline characteristics of the two cohorts and different GC doses limited the comparability and possibility to achieve firm conclusions.

The most effective GC tapering scheme was not specifically assessed in any study included in the SLRs. In the trial of TCZ in GCA (GiACTA),[81] two standardised prednisone-taper protocols (52 week and 26 week taper) were tested in an RCT. Patients who enrolled in the placebo group with more rapid tapering protocol experienced more flares (68% vs 49%) and a greater need for prednisone escape therapy (74% vs 55%), with a comparable safety profile. Nevertheless, the cumulative GC dose was numerically lower for the group treated with a more rapid GC taper (3296 vs 3818 mg).

The safety of GC treatment was evaluated in a large nested case–control analysis demonstrating a strict correlation between prednisone dose (average daily GC dose >30 mg/day) and the development of diabetes with an adjusted OR of 4.7 (95% CI 2.8 to 78), glaucoma 3.5 (2.0–6.1), osteoporosis 1.9 (1.2–2.9), fractures 2.6 (1.6–4.3), serious infections 3.3 (2.2–5.2) and death 2.1 (1.3–3.5).[82] Similar concerns regarding the significant rate of GC-related adverse events (AEs) were confirmed in a retrospective medical claims data analysis, reporting an increase in HR by 3% for every 1000 mg increase in prednisone-equivalent exposure.[83]

Evidence for GC discontinuation and drug-free remission was evaluated in a retrospective cohort study demonstrating that the following factors were associated with higher chances of obtaining long-term remission: a lower number of flares, lower cumulative GC dose at 1 year, lower duration of GC treatment and more rapid achievement of low-dose GC.[84]

In summary, the prompt initiation of GC therapy is consistently associated with a better outcome, including visual complications (LoE 4). Only low to moderate quality evidence with conflicting results exists on the most appropriate initial dose and route of administration (LoE 4). The most appropriate tapering scheme has not been standardised yet, with evidence from one high-quality RCT suggesting a higher risk of flares in more rapid tapering regimens (LoE 1b). Nevertheless, safety concerns related to GC are dose dependent (LoE 3b), underlying the need to optimise the dose and duration of GC treatment.

MTX and other non-biological immunosuppressive drugs

The role of MTX in addition to GC for the treatment of GCA has been tested in four RCTs.[85–88] All studies included newly diagnosed patients. The fourth RCT enrolled only a limited number of untreated GCA (n=6) and/or patients with PMR and presented a significant RoB.[88] Only one of the RCTs had an overall low RoB.[87] Just one trial met the primary endpoint (reduction in number of relapses and total cumulative dose of GC during follow-up).[86] No effect on the relapse rate, total dose and duration of GC was reported by the RCT from Hoffman *et al*.[85] In all studies, the dose of MTX was generally low, administered orally and differed significantly among the RCTs: maximum dose ranged from 15 mg/week, down to 7.5 mg/week (for two RCTs), respectively. Moreover, the concomitant GC dose was not standardised among the studies, nor was the GC duration and tapering scheme.

An individual patient data meta-analysis pooling information from 161 patients enrolled in the three RCTs performed exclusively on patients with GCA[85–87] re-evaluated the efficacy and safety of adjunctive low-dose MTX in GCA.[89] HRs compared with placebo for a first disease relapse are 0.65 (95% CI 0.44 to 0.98; p=0.004), for a second relapse: 0.49 (95% CI 0.44 to 0.98; p=0.02). A superiority of the treatment effect of MTX over placebo becomes apparent after 24–36 weeks, suggesting that the duration of follow-up might have influenced the possibility to reach the endpoint in the individual trials. At least 3.6 (95% CI 2.2 to 56.8) and 4.7 (95% CI 3.3 to 21.9) patients need to be treated with MTX to prevent a first and second relapse, respectively. The adjunctive use of MTX resulted in a significant reduction in the cumulative GC dose by 842 mg within 48 weeks. Finally, MTX was associated with higher probability of reaching a sustained drug-free remission (HR 2.84; p<0.001). The overall incidence of AEs was not significantly different between patients treated with MTX versus placebo.

The effectiveness and safety of MTX in real life has been reported by one observational retrospective longitudinal study describing the role of long-term (up to 8.4 years) continuation of MTX in routine clinical practice for patients with GCA (both as first line in newly diagnosed patients or as add-on treatment in relapsing cases).[90] In this study, the maximum MTX dose was 15 mg/week, and the drug proved to be safe and with low discontinuation rates due to inefficacy (incidence rate for discontinuation: 2.8/100 patient-years). However, the RoB is high due to the study design and lack of a comparator group.

Cyclosporine was not efficacious and did not display a GC-sparing effect in two open RCT including newly diagnosed and refractory cases of GCA.[91 92] Azathioprine (AZA) efficacy was tested in an RCT with significant methodological issues influencing the results of the study.[93] Dapsone was tested in an open, prospective randomised trial versus GC alone but did not demonstrate a GC-sparing effect. Haematologic toxicity with dapsone is relevant and warrants periodic monitoring.[94] A summary of the RCTs of non-biological immunosuppressants in GCA is presented in table 4.

Leflunomide and cyclophosphamide effectiveness and safety were only assessed in retrospective cohort studies not allowing for definitive conclusions.[95–99]

In summary, MTX can reduce the risk of relapse and exposure to GC in patients with GCA (LoE 1a). No high-quality evidence supports the efficacy of other conventional synthetci disease modifying antirheumatic drugs (csDMARDs) (LoE4).

Table 4 Randomised controlled trials of non-biological immunosuppressants in GCA

Study ID	Study design	GCA subtype	n	Intervention	Control	Primary outcome	Results (i)	Results (c)	P value
MTX									
Hoffman *et al*[85] 2002	Randomised, double-blind, placebo-controlled trial	New	**98** 51 (i) vs 48 (c)	PRED p.o. (1 mg/kg/day)+MTX p.o. (maximum 15 mg/week)	PRED +placebo	First disease relapse (six mo)	68.9%	66.1%	0.31
Jover *et al*[86] 2001	Randomised, double-blind, placebo-controlled trial	New	**42** 21 (i) vs 21 (c)	PRED p.o. (60 mg/day) +MTX p.o. (10 mg/week)	PRED +placebo	No of relapses Cumulative PRED dose (mg)	9 (45%) 4187±1529	16 (84.2%) 5489.5±1396	0.018 0.009
Spiera *et al*[87] 2001	Randomised, double-blind, placebo-controlled trial	New	**21** 12 (i) vs 9 (c)	PRED p.o. (1 mg/kg/day)+MTX p.o. (7.5 mg/week) when PRED dose of 30 mg/day	PRED +placebo	Cumulative GC dose (mg)	6469±2024	5908±2131	0.6
van der Veen *et al*[88] 1996	Randomised, double-blind placebo-controlled trial	New PMR or GCA or both	**40** 20 (3 GCA) (i) vs 20 (3 GCA) (c)	PRED p.o (20 mg/day)+MTX p.o. (7.5 mg/day)	PRED +placebo	Time to remission (days)	48	45	NS
Cyclosporine									
Schaufelberger *et al*[91] 1998	Open-label, randomised controlled trial	Refractory	**22** 11 (i) vs 11 (c)	PRED (mean 11.8±10 mg/day)+CsA (2 mg/kg/day)	PRED (mean 11.1±7 mg/day)	Cumulative GC dose (g) six mo	1.41	1.44	NS
Schaufelberger *et al*[92] 2006	Open-label, randomised controlled trial	New	**59** 29 (i) vs 30 (c)	PRED (mean 40±11 mg/day)+CsA (2–3.5 mg/kg/day)	PRED (mean 40±12 mg/day)	Cumulative GC dose 12 mo	NSP	NSP	NSP
Dapsone									
Liozon *et al*[94] 1993	Open-label, randomised controlled trial	New	**47** 24 (i) vs 23 (c)	PRED (0.7 mg/kg/day-1 mg/kg/day if ocular)+Dapsone	PRED (0.7 mg/kg/day-1 mg/kg/day if ocular)	Total duration of GC	14 mo	13 mo	NS
AZA									
De Silva and Hazleman[93] 1986	Randomised, double-blind, placebo-controlled trial	Established PMR/GCA	**31** 16 (i) vs 15 (c)	PREDNL maintenance dose p.o. (8.1 vs 7.4 mg/day)+AZA p.o. (100–150 mg/day)	placebo	GC dose 52 weeks (mg)	1.9±0.84	4.2±0.58	<0.05

AZA, azathioprine; c, control;CsA, cyclosporine; GC, glucocorticoid; GCA, giant cell arteritis;I, intervention; mo, month; MTX, methotrexate; New, newly diagnosed giant cell arteritis; NS, non-significant; NSP, non-specified; PMR, polymyalgia rheumatica; p.o., oral route; PRED, prednisone; PREDNL, prednisolone.

TCZ and other biological immunosuppressive drugs

The SLRs revealed two multicentre double-blind, placebo-controlled RCTs on the use of TCZ for patients with GCA (newly diagnosed/relapsing/LV-GCA)[81 100] (table 5). One RCT (n=251 patients) tested two schemes of TCZ s.c. (162 mg every week or every other week) with two GC tapering protocols (26 weeks or 52 weeks). The other study (n=30 patients) assessed the use of intravenous TCZ (8 mg/kg/monthly). The primary outcome was met in both studies. In the larger Trial of Tocilizumab in Giant Cell Arteritis (GiACTA) trial, sustained GC-free remission at week 52 was 56% (TCZ/weekly) and 53% (TCZ/every other week) vs 14% (26 week GC taper) or 18% (52 week GC taper); p<0.001. The HR for flares was 0.23 (99% CI 0.11 to 0.46) vs 0.28 (0.12 to 0.66); p<0.001 compared with patients receiving a 26-week taper (of GC alone). Sensitivity analyses excluding CRP normalisation from the definition of remission confirmed the results. The weekly TCZ dose was more efficacious in preventing flares in relapsing disease compared with the every-other-week regimen. The cumulative median GC dose over 52 weeks was significantly lower for the group receiving TCZ (1862 mg) compared with both GC schemes (3818 mg for the 52-week taper and 3296 for the 26-week taper); p<0.001 for both comparisons.[81]

In the trial from Villiger *et al*, complete remission was achieved by week 12 in 12/20 (85%) patients treated with TCZ (at a GC dose 0.1 mg/kg/day) vs 4/10 (40%) in the comparator group; risk difference was 45% (95% CI 11% to 79%; p=0.03). The cumulative prednisolone dose after 52 weeks was 43 mg/kg in the TCZ group vs 110 mg/kg in the placebo group (p=0.005).[100] No safety issues arose from the two RCTs. The RoB was low for both studies (online supplementary file 3; table 37).

Three retrospective open-label cohort studies[101–103] and two case series[104 105] were identified assessing the role of intravenous TCZ in patients with refractory GCA, GC-dependent disease or those with AE to GC. Effectiveness was confirmed in these observational studies, with few serious AE reported (five serious infections with two deaths, one tuberculosis infection). One of these case series reported on the long-term (median follow-up of 2 years) good tolerability of intravenous TCZ in eight patients with GCA. The RoB was high for all these studies.

The optimal duration of TCZ therapy to ensure sustained remission has not been assessed yet, with data on case series suggesting frequent relapses after TCZ discontinuation (up to 35% after 3.5±1.3 months).[101 106]

The efficacy of intravenous abatacept (ABA) (10 mg/kg on days 1,15, 29 and then every 8 weeks) was assessed in a multicentre, double-blind placebo-controlled RCT enrolling 41 newly diagnosed or relapsing patients with GCA or LV-GCA. After 12 weeks of treatment with ABA, patients were randomised to either continue with the active drug or with placebo (GC). The trial demonstrated a marginally significant reduction in the risk of relapse compared with GC alone (relapse-free survival rate at 12 months: 48% vs 31%; p=0.049) and a longer median duration of remission (9.9 months vs 3.9 months; p=0.023), without increased toxicity. GC-sparing effect of ABA was not assessed.[107] The RoB was generally low (online supplementary file 3; table 37), however, the results obtained by the study were at the limits of statistical significance.

The SLRs identified three multicentre, double-blind placebo-controlled RCTs of TNF inhibitors (TNFi)–adalimumab (ADA), etanercept (ETA) and infliximab (IFX) for GCA.[108–110] Efficacy in terms of GC-sparing effect, disease activity and GC withdrawal or reduction of GC cumulative doses and AE was not confirmed by any of the studies using TNFi, with two of them (ETA, IFX) being limited by the low number of patients included. All studies, but the one on IFX,[110] had a high RoB.

An open-label proof-of-concept study testing the steroid-sparing effect of ustekinumab in 14 patients with refractory GCA was identified, showing promising results in terms of GC dose reduction from baseline to last follow-up (from 20 to 5 mg/day; p=0.001).[111]

In summary, TCZ significantly enhances the chances of achieving remission, preventing flares and reducing GC requirements in newly diagnosed and relapsing patients with GCA (LoE 1b). The duration of treatment (beyond 1 year) and long-term safety have not yet been prospectively assessed.

Specific treatment of organ complications (including visual loss and stroke)

Evidence for specific treatment of visual loss was only found for GC treatment and has been described in the section above. There was no evidence regarding the management of other ocular complications resulting from treatment (eg, cataract and glaucoma). There was no evidence for specific treatment to prevent cerebrovascular accidents associated with GCA.

Relapsing and refractory GCA

We identified descriptive longitudinal cohorts assessing the treatment and outcome of patients with relapsing GCA. Most relapses occurred during GC monotherapy with increasing risk at lower doses ≤10 mg/day.[112] A relapsing course was associated with higher and more prolonged GC requirements and related GC side effects, particularly osteoporosis.[27 49] MTX 15 mg/week was often added for relapses, particularly in cases with ≥2 relapses or the presence of GC side effects together with an increase in GC dose by 10–15 mg/day above the previous effective dose.

The individual patient data meta-analysis from Mahr *et al* provided evidence supporting the role of MTX in the prevention of a second relapse.[89] The GiACTA trial (described above) included a specific analysis of patients with refractory/relapsing disease, showing that the only effective dose of TCZ in this group was 162 mg/weekly and not every other week.[81]

Overall, TCZ (LoE 1b) and MTX (LoE 1a) have shown evidence for reduction of further relapses in GCA.

Table 5 Randomised controlled trials of biologic immunosuppressants in GCA

Study ID	Study design	GCA subtype	n	Intervention	Control	Primary outcome	Results (i)	Results (c)	P value
Stone *et al*[81] 2017	Randomised, double-blind placebo-controlled trial	New/relapse	**251** 100 (i1); 50 (i2) vs 50 (c1);	(i1): TCZ 162 mg/week s.c +26 week GC taper (i2): TCZ 162 mg/2 weeks s.c. +26 weeks GC taper	(c1): placebo +26 week taper GC (c2): placebo +52 weeks taper GC	Rate of sustained GC-free remission week 52 vs placebo +26 week GC taper	56%(i1) 53% (i2)	14% (c1) 18% (c2)	<0.001
Villiger *et al*[100] 2016	Phase 2, randomised, double-blind, placebo-controlled trial	New/relapse	**30** 20 (i) vs 10 (c)	i.v. TCZ 8 mg/kg/4 weeks+PREDNL 1 mg/kg p.o.	placebo	Complete remission at a PREDNL 0.1 mg/kg/day week 12	17 (85%)	4 (40%)	0.0301
Langford *et al*[107] 2017	Randomised, double-blind placebo-controlled trial	New/relapse	**41** 20 (i) vs 21 (c)	i.v. ABA 10 mg/kg on day 1,15, 29 and weeks 8+GC 40–60 mg/day with 28 weeks taper	GC 40–60 mg/day with 28 weeks taper +placebo	Duration of remission (relapse-free survival rate) mo 12	46%	31%	0.049
Seror *et al*[108] 2014	Randomised, double-blind placebo-controlled trial	New	**70** 34 (i) vs 36 (c)	ADA s.c. 40 mg/2 weeks+PRED 0.7 mg/kg/day	PRED 0.7 mg/kg/day+placebo	Percentage of patients in remission with <0.1 mg/kg/day PRED week 26	20 (58.9%)	18 (50%)	0.46
Martínez-Taboada *et al*[109] 2008	Randomised, double-blind placebo-controlled trial	Established with AE to GC	**17** 8 (i) vs 9 (c)	PRED ≥10 mg/day+ETA 25 mg /twice week s.c.	PRED ≥10 mg/day+placebo	Ability to withdraw GC and control disease mo 12	50%	22.2%	NS
Hoffman *et al*[110] 2007	Randomised, double-blind placebo-controlled trial	New in remission	**44** 28 (i) vs 16 (c)	IFX (5 mg/kg) weeks 0, 2, 6 then every 8 weeks+GC	GC +placebo	Relapse-free rate through week 22	43%	50%	0.65

ABA, abatacept; ADA, adalimumab; AE, adverse events; c, control; ETA, etanercept; GC, glucocorticoids;GCA, giant cell arteritis; I, intervention; IFX, infliximab; i.v., intravenous; mo, month; p.o., oral route; PRED, prednisone; PREDNL, prednisolone; TCZ, tocilizumab.

Revascularisation procedures (aneurysm and stenosis treatment)

Two studies retrospectively assessed the treatment of aortic aneurysms (and/or dissection) in GCA.[113 114] The surgical outcome and short-term survival were good, but with the need for frequent surveillance and occasional requirement for repeated intervention (8%–10% of cases).

There were no studies addressing the role of preventive medical treatment or timing for screening for aortic complications.

One retrospective case series (n=10 LV-GCA patients) described the outcome of percutaneous transluminal balloon angioplasty (PTA) in combination with GC, csDMARDs and antiplatelet agents for symptomatic upper limb stenosis/occlusion resistant to medical treatment. The rate of restenosis was high (primary patency rate 65.2%), but repeated PTA was effective (secondary patency rate 82.6%).[115]

A retrospective case series including 10 patients with LV-GCA or TAK analysed the safety and effectiveness of PTA for occlusive arterial disease in LVV, which were in accord with previous evidence. Technical success was good for stenotic lesions and moderate for occlusive lesions; the cumulative primary clinical success rate was 67.6%. There is an important risk of arterial injury during PTA, reported in 36% of patients.[116]

Overall, we found only limited and low-quality data to guide revascularisation procedures in patients with GCA (LoE 4).

Adjunctive therapy and prophylaxis (aspirin, other cardiovascular complications, infections, osteoporosis)

The SLRs identified six retrospective longitudinal cohorts studies investigating the role of antiplatelet agents to prevent ischaemic complications in GCA.[47 117–121] The results of the studies are controversial, with three suggesting no effect of acetylsalicylic acid (ASA) in preventing ischaemic events when prescribed before or at the time of GCA diagnosis[117 118]; and one suggesting an association with increased risk for severe cranial ischaemic events.[47] By contrast, two studies reported that antiplatelet/anticoagulation therapy might reduce ischaemic complications at diagnosis and during follow-up without any increased risk of bleeding.[119 122] There have been no RCTs assessing the use of low-dose ASA for GCA.[123] A meta-analysis of six retrospective studies (including 914 patients) concluded that established antiplatelet/anticoagulants given prior to diagnosis do not reduce the risk of ischaemic events. The heterogeneity of the studies was moderate/high.

The role of statins in GCA is unclear. Contradictory results were obtained from two population-based incident cases cohorts[124 125] and two retrospective longitudinal cohorts.[126 127] The first two studies (characterised by a lower RoB) reported that statin therapy, given prior to[126 127] or within 1 year from the diagnosis of GCA,[127] was associated with reduced hospitalisation due to cardiovascular events in GCA (HR 0.993; 95% CI 0.986 to 0.999; p=0.0467). There was no effect of statins on the inflammatory process or on the rapidity of GC reduction. The retrospective observational studies did not demonstrate any reduction in the incidence of severe ischaemia and/or any steroid-sparing effect.

Concomitant treatment with angiotensin receptor blockers (ARB) but not with ACE inhibitors (ACEI) was associated with lower relapse rate and more prolonged disease-free survival in GCA in a single prospective, open-label controlled study (adjusted HR for relapses with ARB 0.32; 95% CI 0.12 to 0.81; p=0.017).[128] Of the 106 patients included, only 36 received ACEI and 14 were treated with ARB. Although patients had been followed up prospectively, data were analysed retrospectively. Finally, duration, dose and type of ARB treatment were heterogeneous. Therefore, these results need confirmation by further studies.

The SLRs identified two studies assessing the role of prophylaxis against *Pneumocystis jiroveci* pneumonia (PJP). In one prospective cohort of 62 patients treated with GC (20–50 mg/day) combined with MTX (15–20 mg/week), there were 4 (6%) cases of PJP. The main risk factor identified for PJP infection was the presence of lymphopaenia. The other study was a retrospective case series (seven patients) reporting 29% mortality in patients with GCA who developed PJP infections.[129 130] Although both studies raised the issue of infection screening and the risk of infection in these elderly patients treated with intensive immunosuppressive regimens, they did not provide any clear evidence on the modality or timing of antibiotic prophylaxis to prevent infectious complications.

The prevention and treatment of osteoporosis, the management of medium to high-dose GC therapy and vaccinations have not been assessed specifically for GCA. International consensus recommendations on the management of osteoporosis and vaccinations in rheumatic diseases in general have been published.[131 132]

In summary, there is no consistent evidence that antiplatelet agents given at the time of GCA diagnosis prevent future ischaemic events (LoE 2a). Otherwise there is no strong evidence on other adjunctive or prophylactic therapies specifically for GCA.

DISCUSSION

The management of GCA has recently been improved as a result of more standardised and widespread introduction of diagnostic imaging tools, newer therapies (particularly bDMARDs) and optimised therapeutic and monitoring strategies. Two SLRs were required to inform an update of the recommendations on the management of LVV supported by the EULAR Task Force. The SLRs provided more evidence than the previous recommendations[133] because they were conducted from inception of all available literature to ensure a more systematic assessment of the evidence in LVV. The Task Force agreed to include all study designs (except for case reports of

single patients) in the SLRs, in order to offer a comprehensive overview of all available evidence to support clinical decisions in a field of rare diseases with very limited numbers of RCTs/high LoE studies. The inclusion of observational studies reflecting routine care improves the generalisability of our results but introduces a higher RoB and confounding elements that need to be taken into account when interpreting these findings. Information from the online supplementary material should be considered together with the present paper. Moreover, it needs to be considered that research on LVV is an evolving field, but the SLR included evidence published until the 31 December 2017 in order to provide evidence for the 2018 update of the EULAR recommendations on the management of LVV.

The increasingly recognised role of imaging, especially ultrasound and fast-track clinics, in the diagnosis of GCA has been incorporated into the recently published EULAR recommendations on imaging of LVV[1] and should allow earlier diagnosis and better characterisation of the frequency and types of disease patterns in the future.

The SLR on the general management and monitoring mainly retrieved studies with a low LoE, underlying the need for future high-quality research aiming at clarifying the precise prognostic role of disease phenotypes (cranial vs LV-GCA),[134] the assessment of reliable predictors and preventive strategies for future complications (including ischaemic events and development of aneurysms), the optimal follow-up timing and tools to detect disease relapses. Moreover, the identification of biomarkers of disease severity and activity which could prove useful during treatment with TCZ (in view of its direct effect in suppressing CRP) is gaining increasing interest.

The SLR focusing on treatment confirmed the need to promptly initiate GC therapy as soon as the diagnosis of GCA is suspected, however, there are conflicting data on the optimal starting dose and route of administration of GC. There is a need to optimise future studies to define the minimum effective initial dose and a safe reduction approach for managing GCA with GC.[81] The treatment challenge of GC dependent or refractory/relapsing disease remains, particularly when reaching low-to-medium doses of GC (10–15 mg/day). The three RCTs conducted to assess the role of MTX in newly diagnosed patients with GCA have been criticised for the application of variable endpoints (time to first relapse, reduction of relapses or influence on cumulative GC dose), the use of different drug doses (maximum 15 mg/week) for a variable period of time, and for their heterogeneous adjunctive GC doses and tapering schemes. Only one of them had reached its primary endpoint.[86] However, a meta-analysis of individual patient data assessed the role of MTX in preventing the first and subsequent relapse, confirming the efficacy and safety of MTX in both disease states and highlighting the relatively slow action of the drug within 2–3 months. MTX was confirmed to reduce the cumulative GC dose.[89] Available evidence on the subsequent long-term use of MTX (although at a maximum dose of only 15 mg/week) in routine clinical care confirmed its efficacy and safety.[90]

The main novel therapeutic option for GCA in recent years has been TCZ.[81 100] TCZ proved to be efficacious in newly diagnosed and relapsing patients in terms of reducing the risk of relapse and allowing a GC-free or low-GC dose remission. Continuous surveillance and future studies are needed to assess the optimal dose, duration of treatment and tapering speed of GC when prescribed concomitantly to TCZ. We do not have any reliable monitoring tests in patients receiving TCZ, which very effectively suppresses acute phase reactants; this might be clarified by longer term registry data.

The studies on the two main add-on therapies supported by high-quality evidence (MTX and TCZ) are characterised by differences in study outcomes, definitions of relapse and remission, treatment duration, doses of concomitant GC and study effect sizes (lower for MTX) which do not allow direct comparisons between the two drugs. Only one of the three RCTs conducted on MTX reached its primary endpoint and the quality of the RCTs supporting the use of TCZ was higher. Nevertheless, no head-to-head comparative studies have been conducted to date. Moreover, there are no validated biomarkers of disease severity or extent to identify patients who should be treated more intensively from the onset of disease. All these questions will need to be addressed by the future studies.

In summary, the literature review confirms the need for prompt GC initiation in suspected GCA, the emerging role for imaging diagnostic tools, and the efficacy and safety of adjunctive therapy with MTX or TCZ. The review highlights some unresolved issues in terms of the optimal monitoring test(s), ability to detect complications and prophylactic treatment to prevent ischaemic, cardiovascular or infectious events.

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