

Recommendations

2025 EULAR recommendations for the management of polymyalgia rheumatica and primary large vessel vasculitis

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Handling editor Josef Smolen

<https://doi.org/10.1016/j.ard.2026.06.009>

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ARTICLE INFO

Article history:

Received 31 March 2026

Received in revised form 10 June 2026

Accepted 11 June 2026

ABSTRACT

Objectives: This study aimed to update the European Alliance of Associations for Rheumatology (EULAR) recommendations for management of polymyalgia rheumatica (PMR), giant cell arteritis (GCA), and Takayasu arteritis (TAK).

Methods: Following EULAR standard operating procedures, systematic literature reviews identified data published since the previous versions for PMR (2015) and for GCA/TAK (2018). An international task force discussed the evidence, and following a structured voting process, created overarching principles, recommendations, and quality indicators.

Results: The task force agreed on 4 overarching principles, 12 recommendations, and 2 quality indicators. All patients with suspected PMR, GCA, or TAK should be referred for specialist assessment and those with suspected GCA within 24 hours. In patients with a strong clinical suspicion of GCA, treatment with glucocorticoids (GCs) should be commenced without delay, while waiting for the results of confirmatory investigations. For most patients with suspected PMR or TAK, treatment with GC can be delayed until the diagnosis is confirmed. For induction of remission, GC should be initiated at a dose of 15 to 25 mg/day prednisone-equivalent for PMR and 40 to 60 mg for GCA or TAK. Guidance on GC tapering is provided. Adjunctive therapy is recommended for selected patients with PMR or GCA using either interleukin (IL)-6 receptor inhibitors for PMR and GCA or upadacitinib for GCA. Methotrexate may be an alternative. GC-sparing agents should be given in combination with GC to all patients with TAK. All overarching principles and recommendations met with high levels of agreement.

Conclusions: Updated guidance on management of PMR and large vessel vasculitis is provided in a single set of practical recommendations and algorithms.

INTRODUCTION

Polymyalgia rheumatica (PMR) is one of the commonest rheumatic diseases with an annual incidence of >110/100 000 population over the age of 50 in a northern European population [1,2]. Takayasu arteritis (TAK) and giant cell arteritis (GCA) are the 2 most recognised forms of primary large vessel vasculitis (LVV). Primary LVV have an annual incidence of <6/100 000 [3]. The incidence of GCA is much higher in people ≥50 years of age and is highest in Scandinavia (14.6–43.6/100 000) [4]. The worldwide annual incidence of TAK is 0.1/100 000 [5].

European Alliance of Associations for Rheumatology (EULAR) first endorsed recommendations for the management of LVV in 2009 and for PMR in 2015 [6,7]. The LVV

recommendations were updated in 2018 [8]. Therapeutic and diagnostic advances have necessitated the update of these recommendations. There are significant similarities in the pathophysiology of GCA and TAK [9,10] and the clinical presentations of PMR and GCA [11,12]. This overlap has led to this effort of addressing the management of PMR, GCA, and TAK in a single set of recommendations. These recommendations do not include the management of secondary large vessel vasculitides (eg, IgG4-related disease), mimics (eg, paraneoplastic presentations), or iatrogenic causes (eg, checkpoint inhibitor-related syndromes). The recommendations are meant for use by clinicians caring for patients with PMR and LVV, including nurses and other health professionals; trainees at all levels; and funding and regulatory authorities.

METHODS

These recommendations have been developed according to EULAR standardised operating procedures [13]. CBM and BH convened a task force of 28 members represent 13 European countries, Canada, India, and the USA (Supplementary Table S1). A steering committee consisting of the convenors, methodologists, fellows, and 2 additional task force members (SM and GD) guided the development of the project.

After studying the previous versions of the recommendations, a survey of the task force was conducted to identify potential topics for a systematic literature review (SLR) based on key questions from the SLRs informing the previous recommendations. Following collation, a prioritisation exercise allowed final selection of the topics that were converted into conceptual domains used to build questions in the form of Population, Intervention, Comparator, Outcome format to underpin the SLR. Three SLRs were performed from the date of the SLRs for the previous recommendations [14–16] and updated to December 31, 2024 [17,18]. The identified literature was appraised using the Cochrane risk of bias 2 tool for randomised controlled trials (RCTs) and the Newcastle-Ottawa scale for cohort and case–control studies [19]. The results were discussed with the task force at an online meeting and converted into draft statements which were refined at a face-to-face meeting. The statements were created de novo but maintaining the sentiment and phraseology of previous recommendations where possible. Consensus was defined as $\geq 75\%$ vote in favour of the recommendations in the first round (or $\geq 67\%$ and $\geq 50\%$ in a second and third round, respectively). If multiple rounds of voting were necessary, discussion took place in between voting rounds to modify the drafted recommendations. Following the face-to-face meeting, the Oxford Centre of Evidence-Based Medicine (2011) levels of evidence were used to determine the level of evidence (LoE) for each recommendation [20]. The final level of agreement (LoA) for each of the recommendations was conducted after the meeting via an anonymous survey. This was based on a numeric rating scale ranging from 0 (do not agree at all) to 10 (fully agree). Following scoring for feasibility/implementation and impact, 2 recommendations with high scores for both domains were selected for determining quality indicators.

The final manuscript was reviewed and approved by all task force members, as well as the EULAR Council.

RESULTS

The task force suggested 76 topics, of which 42 were selected for conversion into 12 conceptual domains to underpin the SLRs [17,18]. The task force presents a single set of recommendations with 4 overarching principles and 12 recommendations summarised in Figures 1 to 3 and Table 1. Five recommendations are completely new, and 7 recommendations, although created new, are updates of previous versions. A new research agenda has been proposed (Box 1). Throughout this document, the dosages of GC refer to prednis(ol)one equivalents.

Overarching principles

A. All decisions regarding management should be made in partnership between the clinician and the patient after an informed discussion highlighting the pros and cons, considering efficacy, safety and costs.

The diagnoses of PMR, GCA, or TAK are distressing and are compounded by the effects of glucocorticoid (GC) therapy. This includes both early (increased infection risk, emotional lability,

neuropsychiatric effects, etc.) and late (osteoporosis, glucose intolerance, cardiovascular complications, etc.) effects. The introduction of adjunctive immunosuppressive treatment is associated with its own set of problems, including self-injection, planning life around monitoring of the drug, access to medications, etc. The clinician–patient relationship ideally helps address these difficult decisions with the help of information, unbiased discussion of the pros and cons of medication, and explanation of the realities of navigating the health care system.

B. A diagnosis of PMR, GCA, or TAK is based on signs and symptoms, and, in patients with suspected GCA or TAK, confirmed by imaging or biopsy findings. Classification criteria should not be used for diagnosis. A best fit diagnosis can be used to follow these recommendations.

Clinical context is paramount but there is need to base diagnosis on objective measures such as imaging and/or histopathology. Signs and symptoms of PMR and LVV can be nonspecific and need a complement of tests that allow confirmation of diagnosis and appreciation of disease extent. PMR does not have a diagnostic test; the diagnosis is based on the combination of typical signs and symptoms and ruling out mimickers. Classification criteria are used to identify homogenous patient groups for research that most accurately represent the disease in question, thereby enhancing the confidence of the study results. Such criteria are typically intended to be highly specific, thus leaving some patients without a diagnostic label unless clinicians use a best fit diagnosis. The use of classification criteria may inform the clinician, but they cannot be used to make a diagnosis.

C. Patients should have access to education focusing on the impact of PMR, GCA, or TAK, key warning symptoms, and treatment, including treatment-related complications.

PMR, GCA, and TAK are life-changing diseases. The burden of these diseases and their treatments may mean that it is not possible to reach premorbid levels of functioning. Ongoing availability of information regarding the impact of the disease, the goal of treatment, the warning symptoms of relapse including the potential for PMR to relapse as GCA, and damage from disease and treatment, will help a patient navigate the uncertainties that they face. This could be done by a physician, a specialist nurse, or other health care specialists with relevant expertise to set realistic expectations and improve the patient experience.

D. Patients with LVV should be screened for treatment-related and cardiovascular comorbidities. Prophylactic treatment and lifestyle interventions may reduce cardiovascular risk and treatment-related complications.

Patients with LVV are at a higher risk of cardiovascular disease as a function of their exposure to GC as well as widespread vascular inflammation. The use of high-dose GC leading to sudden and significant weight gain could be mitigated by prophylactic dietary and lifestyle measures. Advice about diet, exercise, monitoring of cardiovascular risk factors, glycated haemoglobin, and bone protection all help to mitigate the impact of comorbidities. The management of cardiovascular risk is covered by separate EULAR recommendations [21]. National recommendations for diabetes screening and bone health should be followed.

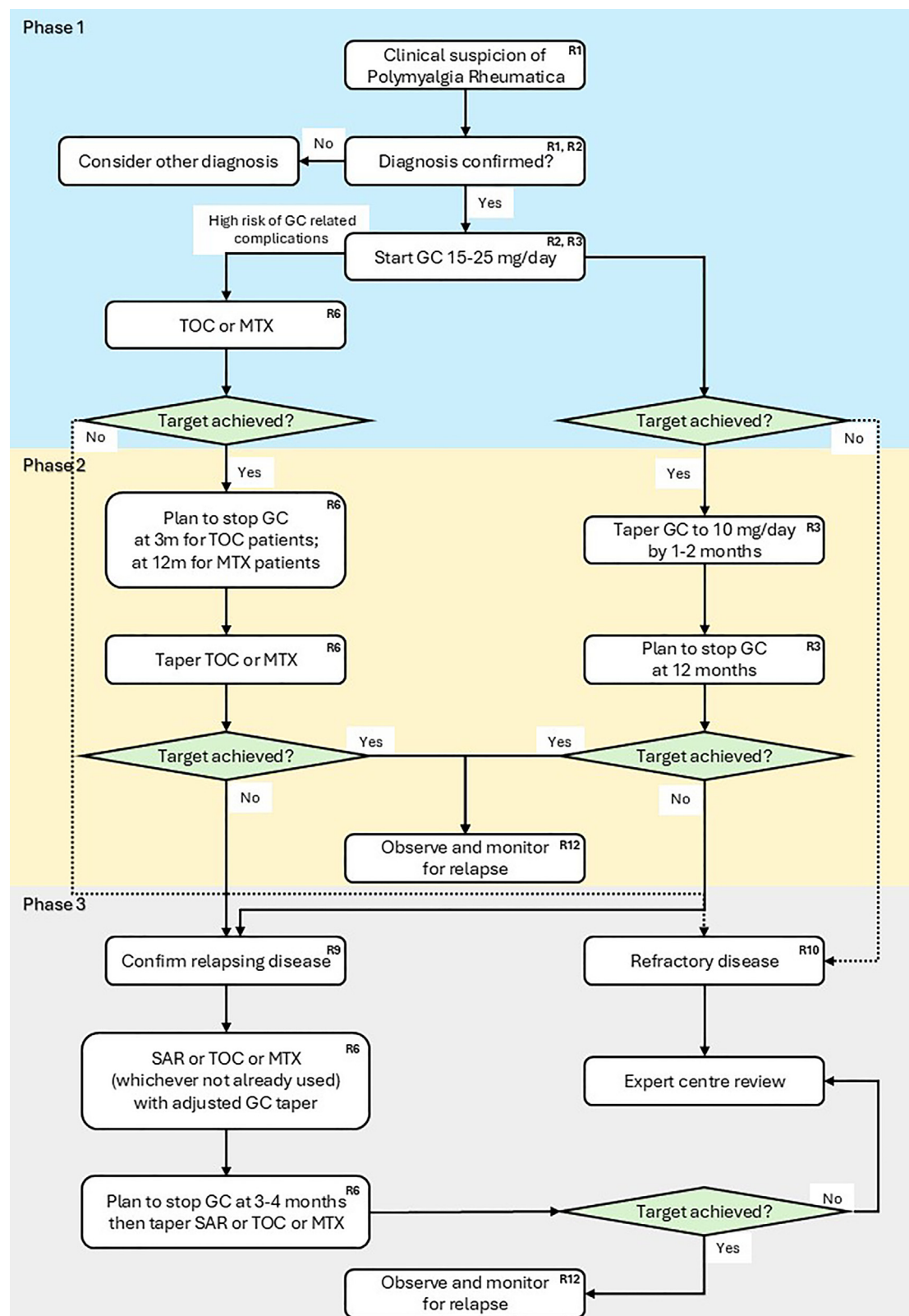


Figure 1. Management of polymyalgia rheumatica. The target is remission induction or maintenance. R, Recommendation Statement; GC, glucocorticoid therapy (dosages given in prednisolone or prednisone equivalents); TOC, tocilizumab 162 mg/week subcutaneously; MTX, methotrexate; SAR, sarilumab 200 mg every 2 weeks subcutaneously.

Recommendations

Recommendation 1

All patients with suspected PMR, GCA, or TAK should be referred for assessment to a specialist with appropriate expertise. Patients with suspected GCA should be urgently referred.

This recommendation from the 2018 update has been updated to include PMR. GCA is a medical emergency with a potential to present with and/or rapidly progress to irreversible ischaemic damage. Patients with cranial symptoms are at high risk of permanent vision loss and should be referred immediately. All patients with suspected GCA should be referred within 24 hours of presentation. The SLR identified 2 new studies

Table 1

Recommendations for the management of polymyalgia rheumatica and large vessel vasculitis showing levels of evidence and agreement in the task force, feasibility, and impact scores

	LoE	LoA	% of Votes with ≥ 8/10 LoA	Feasibility ^a Mean ± SD	Impact ^b Mean ± SD
Overarching principles					
A. All decisions regarding management should be made in partnership between the clinician and the patient after an informed discussion highlighting the pros and cons, considering efficacy, safety, and costs.	NA	9.8	100		
B. A diagnosis of PMR, GCA, or TAK is based on signs and symptoms, and, in patients with suspected GCA or TAK, confirmed by imaging or biopsy findings. Classification criteria should not be used for diagnosis. A best fit diagnosis can be used to follow these recommendations.	NA	9.8	100		
C. Patients should have access to education focusing on the impact of PMR, GCA, or TAK, key warning symptoms, and treatment, including treatment-related complications.	NA	9.6	100		
D. Patients with LVV should be screened for treatment-related and cardiovascular comorbidities. Prophylactic treatment and lifestyle interventions may reduce cardiovascular risk and treatment-related complications.	NA	9.6	100		
Recommendations					
1. All patients with suspected PMR, GCA, or TAK should be referred for assessment to a specialist with appropriate expertise. Patients with suspected GCA should be urgently referred.	PMR 3 GCA 2 TAK 5	9.8	100	7.9 ± 2.0	9.7 ± 0.7
2. In patients with a strong clinical suspicion of GCA, treatment with GC should be commenced without delay, while waiting for the results of confirmatory investigations. In most patients with suspected PMR or TAK, treatment with GC can be delayed until the diagnosis is confirmed.	PMR 4 GCA 4 TAK 5	9.5	96.4	8.9 ± 1.3	9.0 ± 1.2
3. In patients with new-onset PMR, oral GCs should be used for induction of remission, at an initial dose of 15 to 25 mg/day, tapered to 10 mg/day within 1 to 2 months, with the aim of stopping GC within 1 year. In patients with relapsing PMR, therapy with GC should be restarted or escalated to at least the last effective dose, followed by individualised tapering. The GC regimen should account for patient and disease factors, and use of adjunctive therapies, to use the minimum effective dose.	4	9.9	100	9.0 ± 1.3	9.1 ± 1.2
4. In patients with new-onset GCA, GC should be used for induction of remission, at an initial dose of 40 to 60 mg/day, tapered to 15 to 20 mg/day within 2 to 3 months, with the aim of stopping therapy with GC within 12 to 18 months. In case of major relapse, therapy with GC should be reinstituted or the dose escalated as for new-onset disease. For minor relapses, the dose of GC should be increased to at least the last effective dose. Subsequent tapering should be individualised.	4	9.6	92.9	9.2 ± 0.9	9.3 ± 0.9
5. In patients with newly diagnosed active TAK, GC should be used for induction of remission, at an initial dose of 40 to 60 mg/day, tapered to 15 to 20 mg/day within 2 to 3 months, with the aim of stopping therapy with GC within 12 to 18 months. In case of major relapse, therapy with GC should be reinstituted or the dose escalated as for new-onset disease. For minor relapses, the dose of GC should be increased to at least the last effective dose. Subsequent tapering should be individualised.	5	9.6	92.9	8.9 ± 1.4	9.1 ± 1.1
6. Adjunctive therapy with an IL-6R inhibitor (tocilizumab) may be considered in selected patients with new-onset PMR. Adjunctive therapy with an IL-6R inhibitor (preferably sarilumab, or tocilizumab as an alternative) should be considered in selected patients with relapsing or refractory PMR. Methotrexate may be used as an alternative to IL-6R inhibitors in both groups of patients.	1	9.5	100	8.0 ± 1.5	8.8 ± 1.1
7. Adjunctive therapy with tocilizumab or upadacitinib should be considered in patients with GCA, especially those with refractory or relapsing disease, or at an increased risk of GC-related adverse effects. Current guidance on safety of both agents must be considered. Methotrexate may be used as an alternative.	1	9.5	96.4	8.6 ± 1.2	9.3 ± 1.0
8. Adjunctive therapy with nonbiologic disease-modifying agents should be given to all patients with TAK. Tocilizumab or TNF inhibitors can be considered in case of relapsing or refractory disease despite therapy with conventional DMARD.	4	9.7	96.4	9.0 ± 1.2	9.2 ± 1.0
9. The diagnosis of relapse of PMR and GCA should be based on the assessment of clinical signs, symptoms, and laboratory markers, supported by imaging where needed. In TAK, the diagnosis of relapse is substantially based on imaging in conjunction with clinical and laboratory assessment.	5	9.8	100	8.8 ± 1.3	9.2 ± 1.1
10. Patients with refractory PMR, GCA, or TAK should undergo a re-evaluation of their diagnosis and be considered for referral to a specialist centre.	5	9.8	100	8.9 ± 1.3	9.6 ± 0.9
11. In GCA and TAK, elective endovascular interventions or reconstructive surgery should be performed in phases of stable remission. Arterial vessel dissection or critical vascular ischaemia requires urgent referral to a vascular team.	3	10.0	100	8.8 ± 1.0	9.2 ± 1.0
12. In patients with PMR, GCA and TAK, regular follow-up and monitoring of disease should be based on symptoms, clinical findings, and acute phase markers. Imaging should be used to assess for damage on an individual basis in patients with GCA, and to assess for activity and damage in all patients with TAK.	5	9.5	92.9	8.8 ± 1.3	9.2 ± 1.3

^a Feasibility assessed as follows: 'Please rate the recommendation on its feasibility to be implemented (NRS 0-10)'

^b Impact was asked as follows: 'Please rate the recommendation on its impact on quality of care (NRS 0-10)'

LoE, level of evidence; LoA, level of agreement; NA, not applicable; PMR, polymyalgia rheumatica; GCA, giant cell arteritis; TAK, Takayasu arteritis; LVV, large vessel vasculitis; GC, glucocorticoid therapy; IL-6R, interleukin-6 receptor; DMARD, disease-modifying antirheumatic drug.

Box 1

Research agenda for PMR, GCA, and TAK

1. To understand the clinical and prognostic significance of the presence of imaging changes suggestive of vasculitis in patients with PMR.
2. To optimise GC tapering for each of the 3 diseases based on clinical and laboratory parameters.
3. To comparatively study the available therapies, including combinations, in head-to-head trials for each of the 3 diseases using laboratory parameters, disease-specific outcome measures, imaging to assess structural damage and patient-reported outcome measures.
4. To determine the length of adjunctive immunosuppression needed based on clinical and health-economic outcomes for each of the 3 diseases.
5. To determine the long-term benefits of adjunctive immunosuppression with respect to GC-related complications in each of the 3 diseases.
6. To determine the impact of treatments on structural vascular damage including aortic aneurysm and vessel stenosis in GCA and TAK.
7. To discover disease-specific biomarkers for monitoring of each of the 3 diseases.
8. To determine the utility and periodicity of repeat imaging to assess structural damage and/or disease activity for each of the 3 diseases.
9. To develop and validate activity and damage scores for each of the 3 diseases using outcome measures in rheumatology (OMERACT) methodology.
10. To determine the value of antifibrotic therapies to prevent and/or reverse vascular structural damage in patients with GCA and TAK.

GCA, giant cell arteritis; TAK, Takayasu arteritis.

where fast-track clinics reduced the incidence of permanent vision loss in GCA from 18.7% and 26.8% to 11.5% and 12.7% respectively [17,22]. The residual risk of vision loss can be related to delay in seeking medical attention [23] and vision loss being the presenting manifestation [24]. Diagnostic pathways for GCA have commonly been guided by ultrasonography as the primary diagnostic modality [25]. Sequential multimodal diagnostics, which include histopathology and other imaging modalities, will improve the diagnostic yield [24,26]. The full guidance on the use of imaging tools for the diagnosis of GCA has been covered by a separate EULAR recommendation [27].

Referral for patients with suspected PMR or TAK is less urgent, but equally important [28]. PMR is often diagnosed and treated in primary care [29]. In an international survey of 394 general practitioners from 11 countries, 30% used >25 mg/day GC at diagnosis, and 25% of patients were referred for diagnostic confirmation [29]. In another survey of >1200 UK general practitioners, only 55% would routinely check C-reactive protein levels, and half would consider a trial of GC in the absence of an acute phase response [30]. In addition to overdiagnosis, another potential risk of a minimalist diagnostic strategy in PMR is the under-recognition of vascular involvement. Imaging with ultrasonography and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) scanning can demonstrate vascular inflammation in a subset of patients with PMR [17,31,32]. Unrecognised vascular involvement in this clinical context is associated with higher risk of relapses, greater use of GC, and greater progression to the use of adjuvant immunosuppression [17,33]. In the absence of prospective interventional studies, there is ongoing academic debate about the need for more aggressive treatment in these patients. The role of imaging in this subgroup needs individual consideration. There are no new data on diagnostic pathways for TAK. A thorough clinical and radiological vascular assessment for patients with suspected TAK remains essential [6].

Recommendation 2

In patients with a strong clinical suspicion of GCA, treatment with GC should be commenced without delay, while waiting for the results of confirmatory investigations. In

most patients with suspected PMR or TAK, treatment with GC can be delayed until the diagnosis is confirmed.

The recommendation to manage GCA as a medical emergency with high-dose GC [34] is unchanged from previous EULAR recommendations [6,8]. Therapy with oral GC remains the mainstay of treatment for patients with PMR and TAK without the urgency for preventing ischaemic manifestations. Patients with suspected PMR or TAK should ideally be referred to secondary care in the GC naïve state. Response to GC is not a sensitive test and a ‘diagnostic trial’ of GC is not recommended. Assessing patients on GC is uniquely exigent. It rapidly closes the window of opportunity for reliable interpretation of diagnostic tests and leaves secondary care with the highly unfavourable choice of continuing without definitive investigations or asking patients to rapidly reduce GC and re-experience pain. Even after coming off GC, establishing definitive diagnosis may remain challenging [35]. For TAK, few patients may present with severe and urgent ischaemic manifestations such as cerebrovascular accident. However, even in that situation, it is crucial to rule out more common causes.

In all situations, there needs to be a balance between performing diagnostic tests and timely commencement of GC. For GCA, it is in the patient’s best interest to start GC without delay, and there is the need to ensure that services are developed to expeditiously perform time-sensitive diagnostic investigations [36]. Traditionally, the presence of cranial symptoms such as headache, scalp tenderness, thickening of the superficial temporal artery or its branches, jaw claudication, visual disturbance, and others, raise a strong clinical suspicion of GCA and should be treated without delay. PMR is not a medical emergency, but the experience of pain should not be underestimated. In these and other recommendations, there is an aspirational element that recommends early and definitive diagnosis and discourages a trial of GC prior to specialist evaluation [28]. The creation of rapid access strategies for PMR may result in higher referral rates, but it would also result in lower proportion of patients commencing GC [37].

Recommendation 3

In patients with new-onset PMR, oral GC should be used for induction of remission, at an initial dose of 15 to 25 mg/day, tapered to 10 mg/day within 1 to 2 months, with the aim of stopping GC within 1 year. In patients with relapsing PMR, therapy with GC should be restarted or escalated to at least the last effective dose, followed by individualised tapering. The GC regimen should account for patient and disease factors, and use of adjunctive therapies, to use the minimum effective dose.

This recommendation has not changed much from the previous iteration [7]. After confirming the diagnosis of PMR, oral GC remain the mainstay of treatment. There is no consensus definition of remission, but at the very least it would be an absence of symptoms supported by the normalisation of acute phase markers. In the previous iteration, the dose range for initial therapy was 12.5 to 25 mg/day. In practice, the task force members felt that a dose <15 mg/day would rarely be used as initial therapy in clinical practice. New data were not found to amend the previous recommendation of tapering the dose to 10 mg/day by 2 months. Further tapering should consider patient and disease factors. Patients with comorbidities that are induced or exacerbated by GC may need faster taper. Analysis of placebo arms from recent RCTs in PMR demonstrate that shorter GC regimens of 11 weeks in new-onset PMR and 14 and 18 weeks in GC-dependent PMR were associated with GC-free remission rates of

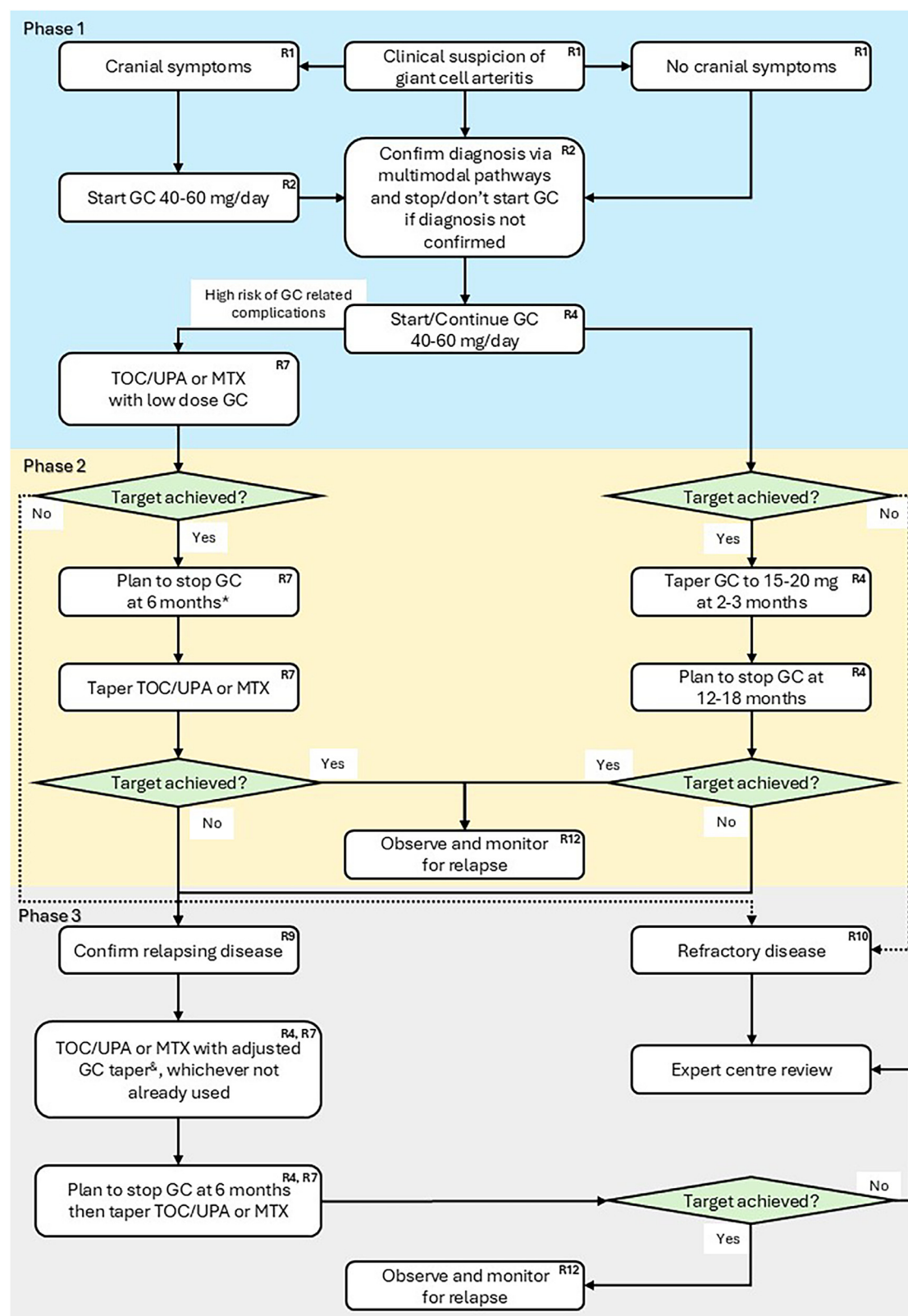


Figure 2. Management of giant cell arteritis. The target is remission induction or maintenance. R, Recommendation Statement; GC, glucocorticoid therapy (dosages given in prednisolone or prednisone equivalents); TOC, tocilizumab 162 mg/week subcutaneously; UPA, upadacitinib 15 mg once daily; MTX, methotrexate.

*Minor relapse: increase GCs to last effective dose; major relapse: treat as new disease.

<20 % [38–40]. Patients with persistent or recurring symptoms or acute phase response may need a slower taper but also need diagnostic re-evaluation. Earlier use of GC-sparing therapies may allow an accelerated taper. We do not routinely recommend the use of intramuscular GC, modified release GC, split dosing of

GC, or alternate-day GC dosing. It may be appropriate in some instances for variable daily dosing of GC during the week to achieve average decimal point dosing at doses <5 mg/day to avoid or manage adrenal insufficiency. The ultimate goal of treatment should be GC-free remission.

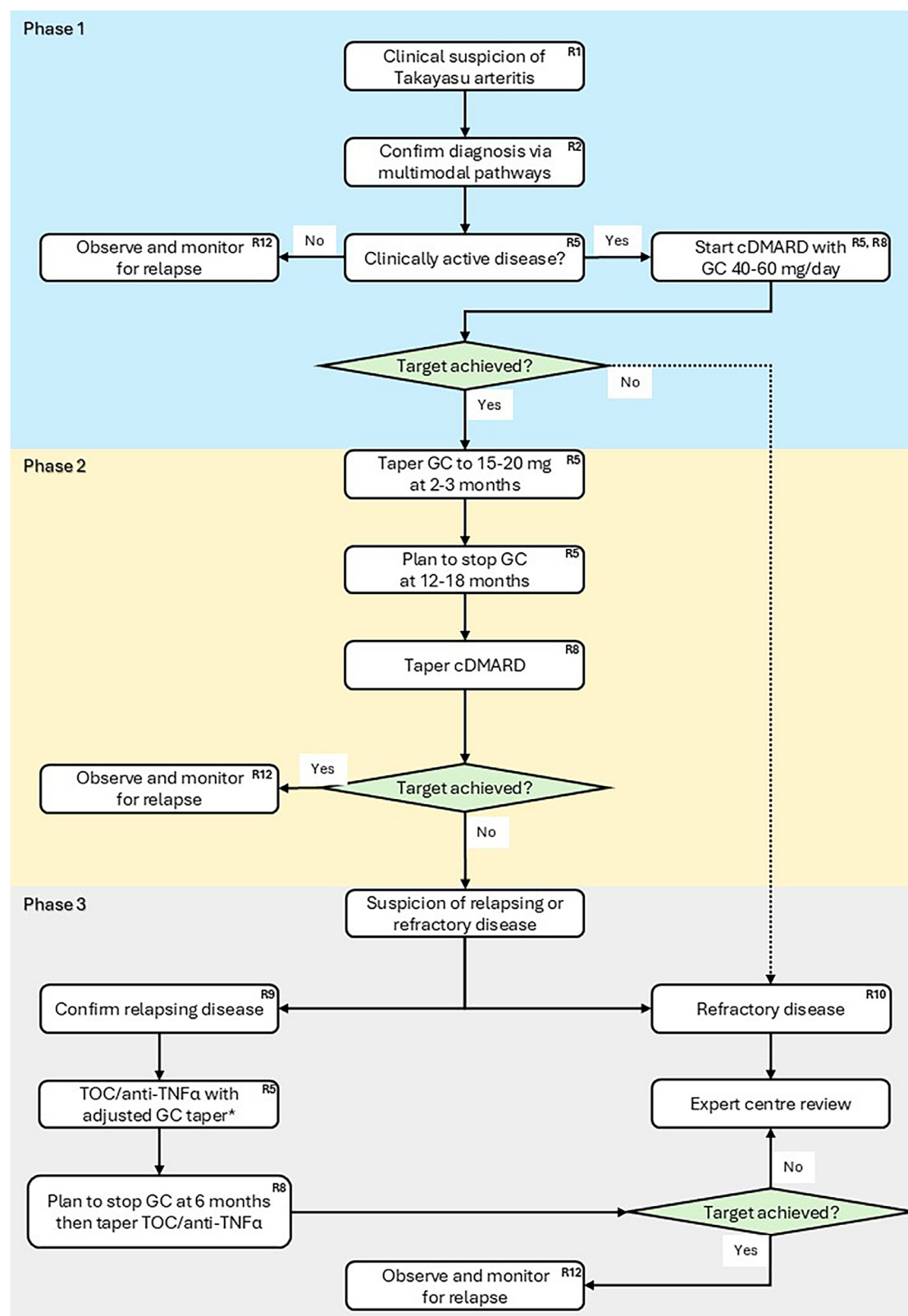


Figure 3. Management of Takayasu arteritis. The target is remission induction or maintenance. R, Recommendation Statement; GC, glucocorticoid therapy (dosages given in prednisolone or prednisone equivalents); cDMARD, methotrexate, azathioprine, mycophenolate mofetil, leflunomide; TOC, tocilizumab 162 mg/week subcutaneously or 8 mg/kg/month intravenously; anti-TNFα, infliximab 5 mg/kg/8 weeks intravenously after initial loading, adalimumab 40 mg every 2 weeks subcutaneously, etanercept 50 mg every week subcutaneously.

^aMinor relapse: increase GCs to last effective dose; major relapse: treat as new disease.

Recommendation 4

In patients with new-onset GCA, GC should be used for induction of remission, at an initial dose of 40 to 60 mg/day, tapered to 15 to 20 mg/day within 2 to 3 months, with the

aim of stopping therapy with GC within 12 to 18 months. In case of major relapse, therapy with GC should be reinsti-tuted or the dose escalated as for new-onset disease. For minor relapses, the dose of GC should be increased to at

Table 2
Top quality indicators with suggested audit measures

Recommendation	What to Measure	Suggested Timing for Measure	Suggested Measurement Method
4. In patients with new-onset GCA, GC should be used for induction of remission, at an initial dose of 40 to 60 mg/day, tapered to 15 to 20 mg/day within 2 to 3 months, with the aim of stopping therapy with GC within 12 to 18 months. In case of major relapse, therapy with GC should be reinstituted or the dose escalated as for new-onset disease. For minor relapses, the dose of GC should be increased to at least the last effective dose. Subsequent tapering should be individualised.	Dose of GC Dose of GC Individualised GC taper plan	At diagnosis At 3 months At diagnosis and relapse	Audit
8. Adjunctive therapy with nonbiologic disease-modifying agents should be given to all patients with TAK. Tocilizumab or TNF inhibitors can be considered in case of relapsing or refractory disease despite therapy with conventional disease-modifying antirheumatic drug.	Use of adjunctive immunosuppression	At diagnosis	Audit

GCA, giant cell arteritis; TAK, Takayasu arteritis; GC, glucocorticoid therapy.

least the last effective dose. Subsequent tapering should be individualised.

Clinical trials in GCA have used different regimens of GC [41]. There are no new data to revise the previous advice on the starting dose [8]. There remains consensus that patients with new-onset active GCA should commence oral GCs at a starting dose between 40 and 60 mg/day. This dose needs to be maintained until the symptoms remit with or without normalisation of acute phase response. Variations in practice include the selection of cases for use of intravenous GC, the exact starting dose of oral GC, and the time to commencing taper. Pulsed intravenous methylprednisolone 0.25 to 1.0 g daily for up to 3 days could be considered in select cases with acute vision loss attributable to active GCA. The benefit of this strategy remains unclear.

Longer GC therapy usually results in a lower relapse rate [41], but there is growing evidence and mounting concern about the risks of continuous low dose GC [42–45]. It is now recommended to aim for achieving GC-free remission of disease, recognising that this may be accompanied with a higher risk of relapse. As an example, a 52-week GC taper was superior to a 26-week GC taper for preventing relapse [46].

The 2018 recommendation defined major relapse as a recurrence of disease activity with either clinical features of ischaemia, or evidence of large vessel inflammation resulting in structural change [8]. Those situations necessitate increasing the dose of GC as for new disease. Minor relapses are those that do not meet the definition of a major relapse. They need a pragmatic assessment of the clinical situation and increasing the GC dose to at least the last effective dose. Both of these approaches acknowledge that patients with GCA should be cared for in services that have availability for timely assessment of patients suspected to have relapses, and access to imaging of large vessels [36]. Relapses may occur in an arterial territory different from that involved at disease onset and, therefore, need a broader search for inflamed arteries [47]. Patients with GCA who present with new symptoms of PMR considered to be related to active disease, but without evidence of active vasculitis, can be treated as ‘minor relapse’ with a specialist review as outlined in Statement 1. Adrenal insufficiency may present with constitutional symptoms, and myalgia which could be mistaken for PMR or a minor relapse [48].

Subsequent tapering of GC after relapse is similar to the approach in new-onset disease but needs individualisation,

considering the cumulative dose of GC already given, the status of comorbidities, the nature and severity of the relapse, and the use of adjuvant immunosuppression (see Recommendation 7). The aim in most cases would still be to achieve GC-free remission. In some instances, low-dose GC (≤ 5 mg/day) may be the most pragmatic long-term plan.

Recommendation 5

In patients with newly diagnosed active TAK, GC should be used for induction of remission, at an initial dose of 40 to 60 mg/day, tapered to 15 to 20 mg/day within 2 to 3 months, with the aim of stopping therapy with GC within 12 to 18 months. In case of major relapse, therapy with GC should be reinstituted or the dose escalated as for new-onset disease. For minor relapses, the dose of GC should be increased to at least the last effective dose. Subsequent tapering should be individualised.

The previously recommended target of GC dose was ≤ 10 mg/day at 12 months [8]. Recent long-term follow-up data from a phase 3 trial of tocilizumab in TAK show that $>40\%$ of patients treated with tocilizumab can achieve a GC dose of <0.1 mg/kg/day at 18 months, suggesting that lower GC doses than previously recommended can be achieved in a substantial number of patients [49]. Although recognising the ambitious nature of this target, it is now recommended to aim for complete withdrawal of GC at 12 to 18 months.

Patients with TAK can present with damage [50] and may not have active disease at diagnosis [51]. This recommendation refers to patients with clinically active disease. In those patients where it is deemed that the disease is inactive, it is reasonable to not immediately start GC. The differentiation of relapses into major and minor is difficult because most patients will already have structural damage to the aorta or its immediate branches. In all instances, an attempt must be made to investigate for, and demonstrate active disease, rather than treat emerging symptoms with increasing immunosuppression. Damage related to GC can also cause manifestations similar to active disease (eg, stroke, myocardial infarction) [52]. The GC taper needs to be individualised considering patient factors, such as body habitus, comorbidities, and adjuvant immunosuppression, and disease factors, including the nature of relapse, amount of damage, and patient preference.

Recommendation 6

Adjunctive therapy with an IL-6R inhibitor (tocilizumab) may be considered in selected patients with new-onset PMR. Adjunctive therapy with an IL-6R inhibitor (preferably sarilumab, or tocilizumab as an alternative) should be considered in selected patients with relapsing or refractory PMR. Methotrexate may be used as an alternative to IL-6R inhibitors in both groups of patients.

Most patients with PMR will initially respond to GC as outlined in recommendation 3. However, relapses are frequent, leading to chronic GC use in 40% to 50% of patients at 5 to 7 years [53,54]. Patients with contraindications or intolerance to GC may be considered for primary GC-sparing therapy. In 2 small prospective studies of patients with new-onset PMR, the use of tocilizumab 8 mg/kg every 4 weeks as monotherapy led to GC-free remission in most patients [55,56]. A subsequent RCT demonstrated that tocilizumab 162 mg every week subcutaneously with an 11-week GC taper was superior to a placebo controlled 14-week GC taper in achieving GC-free remission at 16 weeks [38]. This recommendation is based on available evidence, cognisant of the absence of medical licence of tocilizumab in this indication. The SLR did not retrieve high-quality evidence on the use of other adjunctive therapies for patients with new-onset PMR.

Sarilumab 200 mg every 2 weeks subcutaneously has been approved for use in relapsing or refractory PMR on the basis of a single RCT where sustained remission was demonstrated in 28% of 60 patients with relapsing PMR treated with sarilumab plus a 14-week GC taper compared with 10% of 58 patients treated with a placebo plus a 52-week GC taper [40]. There is also evidence for the GC-sparing efficacy of tocilizumab (currently not formally approved for this indication) in patients with relapsing PMR [39]. At present there are no long-term pharmacovigilance studies of IL-6 inhibition in PMR. In the RCT, neutropenia and diarrhoea were more common in patients receiving sarilumab than placebo, whereas other adverse events were similar to placebo [39]. The clinical trial for sarilumab included patients who relapsed on doses ≥ 7.5 mg/day GC. Patients who are relapsing or dependent on a lower dose of GC may not be automatic candidates for escalation to IL-6 inhibition. There is evidence for the GC-sparing effect of methotrexate 15 mg/week orally [57,58]. This can be used when sarilumab and/or tocilizumab are not available or unlikely to be tolerated, and there is need for GC-sparing agents.

The use of adjuvant immunosuppression should influence the GC taper but still needs individualisation after considering all patient and disease factors. The GC taper could be as rapid as within 14 weeks in patients receiving sarilumab [40]. If methotrexate is used, the data are less clear but the general principle of aiming for GC-free state by 12 months remains valid. There are no data to guide the length of continuation of the adjuvant immunosuppression, but it would be reasonable to not consider withdrawal until at least after achieving GC-free remission of symptoms [59].

Recommendation 7

Adjunctive therapy with tocilizumab or upadacitinib should be considered in patients with GCA, especially those with refractory or relapsing disease, or at an increased risk of GC-related adverse effects. Current guidance on safety of both agents must be considered. Methotrexate may be used as an alternative.

GCA is characterised by a relapsing course with relapse rates at 1, 2, and 5 years of 32%, 44%, and 47%, respectively [60].

Ongoing use of GC is associated with a high burden of adverse effects, affecting >85% of patients [61]. Adjunctive therapy should be considered in patients relapsing on GC monotherapy, as well in patients with new-onset disease where there is significant concern about the use of GC.

Compared with the 2018 iteration, the major change is the recommendation to use upadacitinib as an alternative to tocilizumab for adjunctive therapy in GCA [8]. Upadacitinib is a Janus Kinase (JAK) inhibitor with a greater affinity to inhibit JAK1 enzyme compared with other JAK subtypes. In a single phase 3 RCT, upadacitinib 15 mg orally daily plus a 26-week GC, resulted in sustained remission at 52 weeks in 46.4% vs 29.0% in patients with a 52-week GC taper plus placebo [62]. The use of upadacitinib was also associated with significantly lower cumulative exposure to GC, lower relapse rates, and greater improvement of patient-reported outcomes, whereas its safety profile was similar to that observed in other indications. Since the last update, no high-quality data were published on the use of methotrexate in GCA. Positive phase-2 RCTs have been reported for abatacept [63], mavrilimumab [64], and secukinumab [65]. Mavrilimumab is not commercially available. The results of the phase-3 RCT for secukinumab (Clinicaltrials.gov id: NCT04930094) were not available for the SLR informing this project, and the phase-3 RCT for abatacept is ongoing (Clinicaltrials.gov id: NCT04474847).

Both tocilizumab and upadacitinib are now valid options for use in GCA. The evidence for the use of methotrexate remains based on an individual patient meta-analysis of RCTs that informed the previous iterations of treatment recommendations [66]. However, the heterogeneity of the individual RCTs included in that meta-analysis lowers confidence in the use of methotrexate when compared with the quality of the RCTs for upadacitinib or tocilizumab. Results from head-to-head trials comparing the 3 drugs were lacking when these recommendations were developed. The choice of the optimal drug should consider the adverse effect profile and long-term efficacy and safety data. There is little high-quality evidence on the use of upadacitinib beyond the single phase 3 RCTs. In the absence of long-term data in larger populations and in view of safety concerns related to the use of JAK inhibitors in defined high-risk populations, tocilizumab may be preferentially used in patients with known cardiovascular diseases, risk factors for venous thromboembolism, or a history of malignancy. Where there is a preference for oral therapy, upadacitinib may be favoured. The use of both upadacitinib and tocilizumab requires caution in patients with previous history of diverticulitis or other conditions predisposing to intestinal perforation. Methotrexate may be an option in those patients, as well as when access to the newer drugs is limited. The dose used in clinical trials has been 7.5 to 15 mg every week orally and reflects the era when these trials were conducted [67–69]. It would now be reasonable to use methotrexate 15 to 20 mg subcutaneously every week [70].

The use of adjunctive immunosuppression should be an important factor for adjusting the length of GC taper in patients with GCA. RCTs for adjunctive therapy with tocilizumab or upadacitinib support the use of a 26-week taper [46,62]. There is interest in ultrashort GC. Tocilizumab with an 8-week GC taper resulted in 72% of patients achieving sustained GC-free remission at 12 months in a small proof of concept trial [71]. Sustained remission was possible with tocilizumab plus 3 daily doses of methylprednisolone 500 mg intravenously without oral GC [72]. However, this came at the cost of prolongation of time to achieve remission and potential early damage [72]. The development of ultrashort GC regimens in conjunction with

adjunctive immunosuppression remains on the research agenda (Box 1).

There are still no high-quality data to inform the optimal duration of adjunctive therapy in GCA, but in most cases it would be advisable to consider this after a taper of GC [59]. For tocilizumab, it may be better to taper rather than abruptly discontinue the drug [73]. Tocilizumab 162 mg subcutaneously every week for one year continues to reduce the risk of relapse beyond 12 months [74]. However, if tocilizumab is stopped after 1 year, around 50% of patients will relapse during the subsequent 24 months [75]. Therefore, use of tocilizumab beyond 12 months may be considered in patients with high risk of relapse. Results of observational studies indicate benefit of continuing tocilizumab treatment for >12 months [76]. The effect of longer-term treatment with adjunctive therapies on the development of structural vascular lesions remains unknown. Therefore, studies informing about the optimal length of therapy remain on the research agenda (Box 1).

Recommendation 8

Adjunctive therapy with nonbiologic disease-modifying agents should be given to all patients with TAK. Tocilizumab or TNF inhibitors can be considered in case of relapsing or refractory disease despite therapy with conventional disease-modifying antirheumatic drug (DMARD).

This recommendation is unchanged from the previous iteration [8]. The introduction of adjuvant immunosuppression in all patients with TAK is based on the view that there may be greater structural damage and wider anatomical involvement as compared with GCA. There are limited retrospective data for the use of methotrexate, azathioprine, mycophenolate mofetil, and leflunomide [18]. Tocilizumab 162 mg subcutaneously every week or 8 mg/kg intravenously every 4 weeks, infliximab 5 mg/kg every 6 to 8 weeks intravenously after initial loading, adalimumab 40 mg every 2 weeks subcutaneously, and etanercept 50 mg every week subcutaneously remain options to consider [16]. The data comparing TNF inhibitors with tocilizumab in patients with TAK warrants further exploration [77,78].

The choice of adjunctive immunosuppression at diagnosis should factor into the length of GC taper but there are not any clear data to guide this. As in Recommendation 5, the task force suggests aiming for GC taper lasting 12 to 18 months before considering DMARD taper. Patients with TAK are young, with a common need for revascularisation procedures, and the paucity of high-quality data on the effect of prolonged adjunctive therapies on the development of structural arterial lesions remains on the research agenda (Box 1).

Recommendation 9

The diagnosis of relapse of PMR and GCA should be based on the assessment of clinical signs, symptoms, and laboratory markers, supported by imaging where needed. In TAK, the diagnosis of relapse is substantially based on imaging in conjunction with clinical and laboratory assessment.

This is a new recommendation. Twenty percent or more of patients with GCA relapse with a symptom that was absent at baseline [79,80]. Patients with GCA may not relapse in the same arterial territory as that involved at diagnosis [47]. GCA may relapse with symptoms of PMR, and vice versa. A thorough search for different diagnoses should also be undertaken. Adrenal insufficiency may present with constitutional symptoms that could be mistaken for relapsing disease [48].

The use of imaging is crucial to monitor TAK and for the diagnosis of relapsing disease largely due to relapses occurring with nonspecific constitutional symptoms often with a normal acute phase response [81]. The diagnosis of relapses in PMR and GCA have traditionally been physician verified [82]. We recommend that the diagnosis of relapse in PMR and GCA be made as stringently as for new disease with careful consideration for other diagnoses. It is possible for patients with PMR and GCA to relapse with normal acute phase response (especially when treated with IL-6R inhibitors), and imaging would be appropriate to confirm the clinical suspicion and exclude mimics. The choice of the imaging modality utilised may depend on local expertise. The decision to introduce or escalate the dose of GC before waiting for confirmation of relapse must be individualised. It may be appropriate to use GC as for new patients in cases of threatened ischaemic events for which active vasculitis is the most likely cause.

Recommendation 10

Patients with refractory PMR, GCA, or TAK should undergo a re-evaluation of their diagnosis and be considered for referral to a specialist centre.

Refractoriness was previously defined as an inability to induce remission despite the use of standard care therapy [8]. There are no data about the frequency of this happening in any of the 3 diseases in question, but this would be unusual. The symptom complex of all 3 conditions of interest can be nonspecific. The differential diagnoses in those situations is wide and can include other rheumatic diseases [83], malignancies [84], or other vasculopathies [85]. Investigations for the differential diagnoses may require supervised rapid reduction of GC. Genuinely refractory disease needs strong consideration for the addition of adjunctive therapy with either conventional DMARD, small-targeted molecules, or biologic drugs. In all these situations, referral to a specialist centre should be considered.

Recommendation 11

In GCA and TAK, elective endovascular interventions or reconstructive surgery should be performed in phases of stable remission. Arterial vessel dissection or critical vascular ischaemia requires urgent referral to a vascular team.

This recommendation is unchanged from the previous iteration except for the addition of GCA to the statement. There is now greater recognition that GCA affects arterial territory beyond the cranial vasculature [86]. The nature of involvement in a cohort of patients with extracranial disease is on a spectrum, eg, TAK tends to not involve the axillary arteries, and GCA tends not to involve the renal arteries [87]. Extracranial disease is common in GCA and may require vascular intervention [88]. When the intervention is elective, it is preferable to operate on a noninflamed artery [89]. In some instances, it may even be advisable to increase the dose of GC in the perioperative period to ensure that the artery is not inflamed and/or to potentially reduce the risk of postprocedure restenosis. However, there will be situations where the need for intervention is immediate, eg, imminent fear of aneurysm rupture or critical ischaemia, and waiting until the artery is not inflamed may not be possible. It is advisable for patients with severe extracranial disease to be managed at centres with access to vascular interventions.

Interventions may be open or endovascular. There are similar success rates with both forms of revascularisations in expert hands, but the long-term patency rates appear to be better for open procedures [18,90,91]. In individual centres, the choice of procedure will depend on the availability of expertise.

Recommendation 12

In patients with PMR, GCA, and TAK, regular follow-up and monitoring of disease should be based on symptoms, clinical findings, and acute phase markers. Imaging should be used to assess for damage on an individual basis in patients with GCA and to assess for activity and damage in all patients with TAK.

This recommendation is mostly unchanged from the previous iteration [8]. There are no data to provide an evidence-based recommendation on the optimal method of following patients with these conditions. General principles of good medical practice mean monitoring for disease relapse, disease complications, and iatrogenic complications. In the early stages of the diseases, the most concerning issue maybe GC-related side effects [61,92]. In the first year of disease, the use of high-dose GC leads to a higher risk of hospitalisation due to infections compared with the background population [93]. For ongoing monitoring of GCA, ultrasonography is gradually becoming accepted as a modality that complements clinical examination [94], but its use is not mandated [27]. Residual asymptomatic ‘positive’ imaging findings cannot be taken as evidence of active disease.

Patients with PMR can relapse as GCA, and vice versa. Recognition of the former should drive towards the need for adjuvant immunosuppression; that of the latter would allow for the patient to be treated as having a ‘minor relapse’. Both situations would be facilitated using imaging as covered by separate EULAR recommendations [27]. The diagnosis of relapsing disease in TAK always needs information from imaging. Patients with GCA and TAK are at risk of structural aortic disease which may need monitoring and/or vascular intervention [95]. It is possible for patients to have uptake of radiotracers on 18-FDG-PET-CT imaging that may not necessarily reflect active disease. Long-term GC toxicity includes osteoporosis, heart disease, hypertension, glucose intolerance, and dyslipidaemia among other effects. GCA and TAK are associated with a high risk of cardiovascular disease [96,97], especially when the renal artery is involved [98]. It would be reasonable to monitor and modify cardiovascular risk factors as per EULAR recommendations [21], 10-year fracture risk [99], and specifically monitor blood pressure and glycaemic control at every outpatient review.

DISCUSSION

This is the first time that PMR, GCA, and TAK are addressed in a single set of EULAR recommendations. This was done recognising that patients with a PMR phenotype may have underlying vasculitis, and that the lines between GCA and TAK may be blurry. All 3 diseases share overlapping clinical features and approaches to management are currently similar. These recommendations were formed by a team of international experts and guided by patient partners with lived experience of these chronic diseases. These recommendations represent a distillation of the evidence as it presently exists, as interpreted by workers in the field, supported by new SLRs [17,18].

There are new elements in these recommendations. PMR, GCA, and TAK are each associated with a substantial chronic burden of disease. The advances in diagnostics and therapeutics have made it possible to arrive at an objective diagnosis in most patients. Specifically, for PMR, there is recognition that the diagnosis and management, especially that of relapsing disease needs to happen in expert hands. The recognition of the toxicity of long-term GC, including at low doses, mandates adequate justification for GC initiation, a clear tapering schedule, and the aim of GC-free disease control. New data from clinical trials

have informed recommendations on the use of sarilumab for PMR and upadacitinib for GCA. This comes at a cost to the health economy, a requirement for monitoring blood tests, continuing follow-up in secondary care, and potential exposure to drug toxicity. The diagnosis of a relapse needs to be a full objective assessment of the clinical manifestations, laboratory markers, imaging where needed, and thorough consideration for potential differential diagnoses. A previous recommendation on confirmation of suspected LVV was not carried forward in view of another EULAR recommendation addressing this issue [27].

Lack of new data or new confirmation of previous evidence meant that some elements from previous iterations remain unchanged. The recommendations for initial GC use in all 3 diseases have not changed much. The bulk of recommendations for TAK are not changed. There is an urgent need for international collaboration to do meaningful work to advance the management of TAK.

In the absence of consistent and high-quality data supporting the use of antiplatelet or anticoagulant therapy beyond indications for other diseases, such as coronary artery, vertebral artery, or peripheral artery disease, and given the potential risks associated with its use, the 2018 task force recommended against a routine and unselected use of these medications in LVV. Since the last update, no new data to justify a change of this recommendation have been published. As the available evidence still does not provide disease-specific advice, the task force decided to remove the previous recommendation regarding the use of antiplatelet or anticoagulant therapy.

The anticipated impact and feasibility of the recommendations have been addressed in Table 1. Recommendation 4 pertaining to the use of GC in GCA and recommendation 8 pertaining to the use of adjunctive immunosuppression together were voted as those with the optimum combination of impact in practice, and feasibility to follow (Table 2). The task force has recommended auditing the dose of GC at diagnosis and at 3 months, the presence of an agreed individualised plan for GC taper at diagnosis and relapse to audit recommendation 2, and an audit of the use of adjunctive immunosuppression at diagnosis of TAK.

Empirical use of GC is no longer acceptable for treating suspected PMR, GCA, or TAK. Definitive diagnosis, systematic monitoring, objective identification of relapses, escalation to adjunctive immunosuppression, and aspiring to GC-free remission should be the new mantra of managing this group of diseases with a multidisciplinary approach where the patient is a central part of the decision-making process.

This updated guidance on the management of PMR and LVV is provided in a single set of practical recommendations and algorithms to help improve the treatment and outcomes for patients suffering from these challenging diseases.

Competing interests

Chetan B. Mukhtyar reports contracted services and expenses from Takeda UK Ltd. Elena Nikiphorou reports receiving speaker honoraria and/or participating in advisory boards for UCB, Pfizer, Gilead, Galapagos, AbbVie, Eli Lilly, Alfasigma, Fresenius, and Novartis, and receiving research grants from UCB, Pfizer, and Eli Lilly. Paul Studenic reports receiving speaker fees from BMS, CSL Vifor, and AbbVie; consulting fees from AbbVie; and travel support from J&J. Alvise Berti reports receiving speaker honoraria and/or participating in advisory boards for UCB, AbbVie, Vifor, GSK, and AstraZeneca. Daniel Blockmans

reports receiving honoraria for consulting services from Roche and AbbVie. Elisabeth Brouwer reports that, as an employee of the UMCG, she received grants from the Dutch Arthritis Society, the EU/EFPIA/Innovative Medicines Initiative 2 Joint Undertaking Immune-Image grant no. 831514, and speaker fees for talks on GCA and PMR; all payments were made to the UMCG. Frank Buttgereit reports receiving speaker and consultancy fees from Sanofi, Novartis, AbbVie, Chugai, Fresenius Kabi, and Medac, and grants from AbbVie, Fresenius Kabi, and Chugai. Maria C. Cid reports receiving consulting and educational fees from AbbVie, Alexion, AstraZeneca, CSL Vifor, GSK, Novartis, Royalty Pharma, and Boehringer Ingelheim, and royalties from UpToDate. She was funded by the Ministerio de Ciencia, Innovación y Universidades/AEI/FEDER (EU) grant PID2023-152265OB-I00. Richard Conway reports receiving speaker fees from Janssen, Roche, Sanofi, AbbVie, Alfasigma, Fresenius Kabi, UCB, Viatrix, and Vifor; undertaking clinical trials funded by AbbVie and Novartis; and receiving grant/research support from Janssen, Novartis, Celltrion, and Nordic Pharma. Lisa Christ reports receiving research support, consulting/speaker/advisory fees, and stock ownership from AbbVie, AstraZeneca, Gilead Sciences, F. Hoffmann-La Roche, Novartis, Pfizer, Bristol Myers Squibb, Sanofi, and Vifor. Christian Dejaco reports receiving speaker and consultancy fees from Sanofi, Novartis, AbbVie, Sparrow, Janssen, and Fresenius Kabi. Kresten K. Keller reports receiving research grants from the Novo Nordisk Foundation and SynAct Pharma. Peter A. Merkel reports receiving funds for the following activities in the past 2 years: consulting from AbbVie, Alexion, Amgen, ArGenx, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Capstan, GlaxoSmithKline, iCell, Interius, Kinevant, Kyverna, Lifordi, Lilly, Melodia, Neovii, Neutrolis, Novartis, NS Pharma, Otsuka, Protalix, Q32, Quell, Regeneron, Sanofi, Sparrow, and Takeda; research support from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Electra, GlaxoSmithKline, Neutrolis, Q32, and Takeda; stock options from Kyverna, Q32, Lifordi, Neutrolis, Serpass, and Sparrow; and royalties from UpToDate. Aladdin J. Mohammad reports receiving lecture fees, consultation fees, research funds, and advisory board fees from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, CSL Vifor, Eli Lilly Sweden, GSK, Novartis, and Roche Sweden. Susan Mollan reports receiving consultancy fees from Invex Therapeutics; advisory board fees from Ocular Therapeutix and Dompé Farmaceutici S.p.A.; speaker fees from Teva and AbbVie; travel support from AbbVie and EssilorLuxottica; and research equipment from Heidelberg Engineering. Berit D. Nielsen reports receiving a grant from the Danish Central Region, speaking fees unrelated to this manuscript from Novartis and AbbVie, consulting fees from Boehringer Ingelheim, and travel expenses from Janssen. Cristina Ponte reports receiving speaker honoraria and/or participating in advisory boards for AbbVie, CSL Vifor, Celltrion, Novartis, GSK, and AstraZeneca, and receiving research grants from CSL Vifor and Roche. Wolfgang A. Schmidt reports receiving speaker fees from AbbVie, Alfasigma, Amgen, Chugai, GlaxoSmithKline, Lilly, Medac, Novartis, Pfizer, Sanofi, and UCB; advisory board fees from AbbVie, Boehringer Ingelheim, Fresenius Kabi, Novartis, and Sanofi; and participating in trials as principal investigator for AbbVie and Novartis. Kenneth Warrington reports receiving clinical trial support from BMS and consulting fees from AstraZeneca and Sanofi. Bernhard Hellmich reports receiving speaker fees from AbbVie, AstraZeneca, Boehringer, CSL Vifor, GSK, InflaRx, Janssen, MSD, Pfizer, Novartis, and Roche; honoraria for consultation services from AbbVie, AstraZeneca, Alexion, Boehringer, CSL Vifor, GSK, Pfizer, Novartis, and

Sanofi; and funding for guideline development from EULAR (AAV, LVV) and DGRh (LVV). Alice Bartoletti, Mrinalini Dey, Georgina Ducker, Durga P. Misra, Sara Monti, Kathleen Cannings, Lisa Kingham, and David Saadoun have no conflicts of interest to disclose.

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Funding

The project was funded by EULAR.

Patient consent for publication

Not applicable.

Ethics approval

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2026.06.009.

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