Turkish Society for Rheumatology recommendations for the diagnosis, follow-up and management of giant cell arteritis

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Abstract

Objective

To integrate evidence-based data with expert opinion to provide guidance for the diagnosis, follow-up and treatment of giant cell arteritis (GCA).

Methods

A systematic literature review (SLR) was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. To structure the key clinical questions, the task force employed the Population, Intervention, Comparison Outcome (PICO) format. The Oxford system was subsequently applied to grade the quality of the evidence and determine the strength of each recommendation.

Results

This guideline provides 16 recommendations. We recommend the use of methotrexate in addition to glucocorticoids as first-line treatment in all patients with GCA without ischaemic symptoms. We recommend leflunomide, azathioprine and mycophenolate mofetil as alternatives in these patients if methotrexate is not tolerated. We recommend tocilizumab in GCA patients with ischaemic symptoms or with refractoriness to at least one conventional immunosuppressive. We also recommend upadacitinib as an alternative to tocilizumab in patients with low cardiovascular risk. To our knowledge, our recommendations are the first recommending upadacitinib as an alternative treatment option for the treatment of GCA.

Conclusion

The large RCTs assessing and comparing new effective options are still required in GCA. Assessment of the value of conventional immunosuppressives, which are more cost-effective options compared to biologic agents, is another research area in GCA treatment especially for developing countries. Upadacitinib seems to be a promising option in GCA. However, more real-life experience is needed to assess the safety of upadacitinib in the elderly population with especially high cardiovascular risk.

Key words

giant cell arteritis, recommendations

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Introduction

Giant cell arteritis (GCA) is a granulomatous large-vessel vasculitis (LVV) characterised by the presence of ischaemic manifestations, including headache, visual manifestations, scalp tenderness, jaw claudication and stroke along with systemic symptoms such as weight loss, anorexia, fatigue and fever. GCA is the most common primary systemic vasculitis in patients over the age of 50. The incidence peaks in the seventh and eighth decades of life. The global pooled prevalence is 51 cases per 100,000 persons older than 50 years of age (1). The European and North American populations have the highest incidence of GCA (2). Diagnosis is based on clinical presentation, abnormalities in temporal artery biopsy (TAB) and vascular imaging. Ultrasonography (USG) of temporal and axillary arteries was suggested as the first imaging modality to investigate mural inflammatory changes in patients with suspected GCA by the European Alliance of Associations for Rheumatology (EULAR) recommendations for the use of imaging in LVV. Other vascular imaging modalities can also be used for the detection of both cranial and extracranial involvement in GCA (3).

Glucocorticoids (GCs) are the mainstay of treatment in GCA. EULAR recommendations for the management of LVV suggest starting with 40–60 mg/day prednisone equivalent for induction of remission and tapering the GC dose to a target dose of 15–20 mg/day within 2–3 months and to ≤5 mg/day after 1 year. Withdrawal of GCs is suggested between 18 and 24 months (4). The American College of Rheumatology (ACR) 2021 guideline for GCA also recommends initiating treatment with high-dose oral GCs over moderate-dose oral GCs (5). While conventional immunosuppressives (ISs) are suggested for selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC-related adverse effects or complications) by EULAR (4), ACR guideline conditionally recommends the use of tocilizumab (TCZ) or methotrexate (MTX) as GC-sparing agents; however routine use of ISs remains controversial (5). Although LVV has been reported in 22–85% of newly diagnosed patients with GCA, screening for LVV is another controversial issue in patients with GCA (6-10).

Despite a lack of clear epidemiological data, GCA is not a frequent form of LVV in Turkey. The aim of these recommendations that were developed under the auspices of the Turkish Society for Rheumatology (TSR), is to bring together evidence from the literature review with expert opinion to provide guidance on the diagnosis, follow-up and treatment of GCA for rheumatologists and other stakeholders involved in the management of patients with GCA.

Methods

This guideline was developed within a multidisciplinary, evidence-based, and consensus-driven framework, in accordance with the standardised procedures recommended by EULAR (11). A systematic literature review (SLR) was conducted in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (12). Key clinical questions were formulated using the PICO (Population, Intervention, Comparator, Outcome) format. The Oxford Centre for Evidence-Based Medicine system was used to assess the quality of evidence and grade the strength of recommendations, as outlined in EULAR's methodological guidance (13, 14).

Task force

The task force included 23 rheumatologists with expertise in vasculitis (including one methodologist (GH) and 14 junior researchers) and one ophthalmologist (VD). Each subgroup was led by a senior expert, and junior researchers worked in pairs under the supervision of the methodologist to ensure reproducibility and minimise individual bias.

Selection of clinical questions

During the initial meeting, the expert panel defined the scope of the guideline and identified four main domains: the role of imaging in diagnosis and follow-up, TAB, diagnosis and monitoring of patients, pharmacologic treatment (including GCs, conventional ISs, biologic DMARDs, and adjunctive

therapies). Based on these domains, a set of structured research questions was developed to guide the literature review (Supplementary Table S1).

Systematic literature review

An SLR was conducted in PubMed and SCOPUS databases, covering the period from January 1, 2017, to October 15, 2024. While the review was restricted to publications from 2017 onwards, several seminal earlier studies were included if they contributed substantial foundational knowledge or were frequently cited in recent literature. Eligible studies included meta-analyses, systematic reviews, randomised controlled trials (RCTs), and cohort studies. The search terms and strategy were predefined and piloted before implementation.

Titles and abstracts were screened for relevance to each clinical question by two independent reviewers. Reference lists of selected meta-analyses and systematic reviews were also reviewed to identify additional eligible publications. Full-text articles were then evaluated by junior and senior task force members. Any discrepancies in study selection or data extraction were resolved by consensus. Further details on the search strategy and study selection process are available in the Supplementary material.

Development of recommendations

Findings from the SLR were presented to the task force during 5 online meetings for structured discussion. Draft recommendations were prepared by integrating the available evidence with expert opinion. Where evidence was lacking, consensus statements were formulated based on expert opinion. Each statement was debated, refined where necessary, and submitted to an online vote. A predefined consensus threshold of 70% agreement was required for approval. Task force members also rated their level of agreement with each recommendation on a numeric scale from 0 (complete disagreement) to 10 (complete agreement).

Ethical considerations

These recommendations were developed based solely on published literature and expert opinion. No direct patient or public involvement occurred.

Results

All recommendations, levels of evidence and levels of agreement are summarised in Table I.

Recommendation 1. *In patients with suspected GCA, TAB or USG can be preferred according to the experience of the unit/centre performing the evaluation*.

While TAB has traditionally been considered the gold standard for the diagnosis of GCA, a growing body of evidence now supports the use of temporal artery USG, a non-invasive tool, in evaluating patients with suspected GCA (15).

Zarka *et al*. found that the diagnostic accuracy of temporal artery USG was superior to that of TAB in a retrospective cohort study of 198 patients (93.3% sensitivity and 98.5% specificity *vs*. 69.2% sensitivity and 100% specificity) (16). A prospective validation study of 25 patients also demonstrated better agreement of between temporal artery USG and TAB long-term compared with TAB (kappa: 0.8 *vs*. 0.4) (17). An international observational cohort study of 941 patients identified 4 distinct clinical subsets based on a temporal artery abnormality (positive biopsy or halo sign on USG and/or evidence on imaging of large-vessel involvement), and found that diagnostic yield of temporal artery USG was superior to that of TAB and large-vessel imaging (79% for USG, 66% for TAB, and 40% for large-vessel imaging) (15). Sommer *et al*. (18) and El-Jade *et al*. (19) demonstrated 100% specificity of a positive temporal artery USG for a positive biopsy in retrospective cohort studies of 68 and 38 patients, respectively, when TAB was used as the reference standard. These excellent specificities also support a high positive predictive value for temporal artery USG. On the other hand, there are studies suggesting a lower diagnostic accuracy with USG compared to TAB. In two prospective studies, Conway *et al*. (20) found USG performance of 52.8% sensitivity and 71.8% specificity in 162 patients while González Porto *et al*. (21) reported lower USG performance of 47.6% sensitivity and 65.7% specificity in 53 patients. He *et al*. (22) showed that USG had 55% sensitivity and 95.3% specificity compared with TAB in a single-centre 10-year experience including 63 patients. Hansen *et al*. (23) found similar sensitivity of USG and TAB (63% *vs*. 69%); however lower specificity with USG (79% *vs*. 100%), yielding a lower overall diagnostic accuracy with USG compared to TAB. Finally, in a prospective study of 242 patients USG demonstrated 60% sensitivity and 94% specificity, compared with 66% sensitivity and 100% specificity for TAB (24).

Recommendation 2. *TAB should preferably be performed before treatment initiation, or at the latest within two weeks if treatment has already been started. The biopsy should be planned unilaterally from the symptomatic side, and the specimen length should be at least 1.5 cm*.

TAB remains the gold standard for diagnosing GCA, with a specificity of up to 100% and a pooled sensitivity of 77.3% in a recent meta-analysis. The variability in the reported false-negative rates that range from 9% to 61% seems to be associated with the segmental arterial involvement characteristic of the disease (25). This limitation has prompted ongoing discussion regarding whether TAB should be performed unilaterally or bilaterally. Mehta *et al*. (26) found a 12.1% discordance rate between specimens in 310 patients who underwent bilateral TAB. This finding suggests that approximately 1 in 8 patients with biopsy-proven GCA would be missed with a unilateral approach. Interestingly, pre-operative temporal artery USG added little value in identifying patients with biopsy-proven GCA. Similarly, Butendieck *et al*. (27) reported that 7% of 603 patients who underwent bilateral TAB had a negative result on the initial side followed by a positive result on the contralateral side. Although previous studies have reported discordance rates between 4.4% and 13% in bilaterally performed biopsies (28), unilateral approach is generally preferred, considering proce-

Table I. Recommendations for management of patients with giant cell arteritis.

n.	Recommendation	Level of evidence	Level of agreement (mean)
1.	In patients with suspected giant cell arteritis (GCA), temporal artery biopsy (TAB) or ultrasonography (USG) can be preferred according to the experience of the unit/centre performing the evaluation.	1	9.58
2.	TAB should preferably be performed before treatment initiation, or at the latest within 2 weeks if treatment has already been started[a]. The biopsy should be planned unilaterally from the symptomatic side and the specimen length should be at least 1.5 cm[b].	[a]2 [b]3	9.88
3.	If USG is preferred for diagnosis, bilateral temporal and axillary artery, USG should be the first choice imaging method. Demonstration of halo sign and/or increased intima-media complex thickness by USG should be accepted as diagnostic for GCA.	1	9.58
4.	In patients where diagnosis cannot be established by ultrasound or biopsy, magnetic resonance (MR)-angiography can be used for imaging of cranial vascular structures. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) or computed tomography (CT)-angiography if FDG-PET is unavailable can be used for extracranial vascular structures.	2	9.52
5.	Screening for large-vessel involvement in patients with GCA should preferably be done with FDG-PET, or if unavailable, with CT angiography. Patients with high baseline PET scores should be closely monitored for relapse and vascular damage (stenosis/aneurysm/occlusion) that may develop during follow-up.	3	9.53
6.	Patients with GCA are monitored using clinical findings and acute-phase reactants. There is no evidence to support routine imaging during follow-up. Patients with large-vessel involvement at diagnosis, especially those with aneurysms, may be monitored with CT angiography.	3	9.17
7.	Treatment of newly diagnosed active GCA patients should be initiated with high-dose oral glucocorticoids (GC) (0.5-1 mg/kg/day prednisolone or equivalent)[a]. Patients with ischaemic symptoms should receive intravenous methylprednisolone (500-1000 mg/day) for 3 days followed by continuation with high-dose oral GC[b].	[a]3 [b]2	9.76
8.	All patients should receive immunosuppressive therapy together with GC.	3	8.82
9.	In patients without ischaemic symptoms, methotrexate (MTX) is preferred[a]; if MTX cannot be used, leflunomide[b], azathioprine, or mycophenolate mofetil can be selected.	[a]2 [b]3	9.41
10.	Tocilizumab (TCZ) should be used in patients with ischaemic symptoms or those refractory to at least one conventional immunosuppressive agent[a]. Upadacitinib[b] (UPA) may be an alternative to tocilizumab (TCZ) in patients with low risk for cardiovascular disease. Abatacept[c] (ABA) may be considered in patients refractory or intolerant to these two agents.	[a]1 [b]2 [c]3	9.11
11.	Glucocorticoid dose reduction should be initiated after disease control is achieved (2-4 weeks)[a]. A 6-month glucocorticoid tapering regimen can be applied in patients starting treatment with TCZ[b] or UPA[c] and a 12-month glucocorticoid tapering regimen in patients starting with MTX or another conventional immunosuppressive agent[d].	[a]5 [b]2 [c]3 [d]4	9.17
12.	In patients who have been receiving immunosuppressive therapy for at least 1 year and have been in GC-free remission for at least 6 months, gradual discontinuation of immunosuppressive therapy may be considered. In patients with ischaemic symptoms, immunosuppressive therapy should be continued for a longer period.	3	9.35
13.	In the management of relapses, the medications the patient is currently using and the presence of ischaemic symptoms are determining factors. In patients with relapse, glucocorticoid dose and tapering strategy can be applied as recommended for newly diagnosed patients.	2	9.64
14.	In patients who relapse with non-ischaemic symptoms while on immunosuppressive therapy, GC should be initiated or the dose should be increased if already using GC and immunosuppressive therapy should be intensified.	2	9.35
15.	In patients who relapse while on optimal doses of TCZ or UPA, GC should be initiated or the dose increased if already taking them, and immunosuppressive agent switching is recommended. In patients who relapse despite these two agents, addition of conventional immunosuppressive therapy or switching to ABA may be considered.	3	9.17
16.	Cardiovascular risk assessment should be performed in patients diagnosed with GCA and their treatments should be managed according to current guidelines. Although routine initiation of anticoagulants, antiplatelets, or statins is not recommended, their use should be evaluated individually on a patient basis.	3	9.70

Superscript letters (**a**-**d**) indicate the level of evidence assigned to individual treatment options within the same recommendation.

dural cost, potential complications and overall healthcare burden. To overcome the limitations of a unilateral approach, Cohen *et al*. (29) suggested that, when feasible, intraoperative frozen section analysis may be performed; if the result is negative, a contralateral biopsy can be considered. Agostino *et al*. (30) recommended sectioning the entire tissue block to improve diagnostic yield. Shimohama *et al*. (31) showed a strong correlation between transmural inflammation and temporal artery tenderness (odds ratio (OR) 11.0) in a retrospective study of 26 TAB-positive GCA patients, supporting the performance of the biopsy on the symptomatic side. The use of GC at the time of TAB has been considered a potential cause of negative biopsy results. Similarly, Sachdev *et al*. (32) found that TAB sensitivity was similar in the first week (60%) and between 8-14 days (52%) after GC initiation; however, sensitivity decreased to 38% when GC had been administered for more than 15 days. While some studies suggest that diagnostic yield may remain adequate over a longer period, the general opinion is that the biopsy should be performed within two weeks of starting GC treatment. Nevertheless, two studies reported that, in cases of high clinical suspicion, patients with negative TAB often continue GC therapy and negative TAB frequently fails to decisively alter clinical management (33, 34).

Recommendation 3. *If USG is preferred for diagnosis, bilateral temporal and axillary artery USG should be the first-choice imaging method. Demonstration of halo sign and/or increased intima-media complex thickness by USG should be accepted as diagnostic for GCA.*

Temporal artery USG is an increasingly used non-invasive imaging method in the diagnosis of GCA. Bilateral evaluation of temporal and axillary arteries increases diagnostic sensitivity considering the segmental arterial involvement characteristic of the disease. In the EUREKA study, a prospective, multicentre, non-interventional cohort study of 106 patients, USG of cranial and large vessels demonstrated 94% sensitivity and 84% specificity, compared with 74% sensitivity and 100% specificity for TAB and all TAB-positive patients also had at least one positive USG findings related to vasculitis in the facial arteries, common carotid arteries, axillary arteries, or the three branches of the temporal arteries (35). This study highlights the benefit of assessing extracranial vessels in addition to the temporal arteries by USG. In a prospective study, the authors examined the relationship between 'halo score' and TAB findings. Interestingly, a higher halo score was associated with intimal hyperplasia, but not with transmural inflammation on biopsy. The authors proposed that the halo score may be an additional tool to predict patients who carry a higher risk of ischaemic vision loss since patients with a positive TAB and intimal hyperplasia present with ocular ischaemia more frequently (36).

Recommendation 4. *In patients where diagnosis cannot be established by ultrasound or biopsy, magnetic resonance (MR)-angiography can be used for imaging of cranial vascular structures. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) or computed tomography (CT)-angiography if FDG-PET is unavailable and can be used for extracranial vascular structures.*

The role of alternative imaging methods was evaluated in patients with suspected GCA when diagnosis could not be confirmed with USG or TAB. A large study published in 2024 showed that among 127 patients with suspected diagnosis of GCA and a negative TAB, GCA was diagnosed in 73 patients and FDG-PET was positive in 83.5% of these patients (37). Sammel *et al*. (38) demonstrated the of FDG-PET diagnostic accuracy in a prospective, double-blind, cross-sectional study of 64 patients (92% sensitivity, 85% specificity compared to TAB; 71% sensitivity, 91% specificity compared to clinical diagnosis). FDG-PET had an excellent negative predictive value of 98%. Emamifar *et al*. (39) reported low sensitivity (25%) but high specificity (88.9%) for FDG-PET in a prospective study of 80 patients with suspected polymyalgia rheumatica (PMR) and GCA. Although FDG-PET had low sensitivity for cranial disease, it showed high specificity. Other recent studies published within the last three years have reported FDG-PET sensitivity for GCA between 61.1% and 92.0% and specificity between 41.0–97.2% (40-43). It has been shown that performing FDG-PET before initiation of GC therapy increases diagnostic sensitivity by preserving inflammatory metabolic signals (40, 41). MR angiography plays an important role in the non-invasive evaluation of cranial arteries. A validation study by Lecler *et al*. (44) demonstrated that when MR imaging (MRI) is used as first-line imaging together with USG or retinal angiography, it provides 100% sensitivity and 100% specificity for GCA diagnosis. Studies published after 2023 have shown that contrast-enhanced vessel wall MRI has sensitivity exceeding 80% in patients with cranial symptoms and findings (44, 45). Additionally, there is evidence that diffusion-weighted MRI using 'scrolling artery sign' pattern recognition approach may assist in diagnosis (46, 47). In a retrospective study of 268 patients, Junek *et al*. (48) evaluated the role of temporal artery MR angiography in GCA diagnosis. Temporal artery-MR angiography showed 64.7% sensitivity and 91.5% specificity, while TAB showed 38.9% sensitivity and 100% specificity. CT angiography provides high-resolution analysis of the aortic wall, and regular circumferential thickening "≥2.2 mm" in the absence of atherosclerosis is considered highly suggestive for aortitis (49).

Recommendation 5. *Screening for large-vessel involvement in patients with GCA should preferably be done with FDG-PET, or if unavailable, with CT angiography. Patients with high baseline PET scores should be closely monitored for relapse and vascular damage (stenosis/aneurysm/occlusion) that may develop during follow-up.*

There are limited data in the literature regarding the role of imaging modalities in outcome prediction. In a prospective study the target-to-background ratio on FDG-PET decreased significantly in patients with a clinical response during follow-up, whereas

no significant change was found in patients without a clinical response (50). When angiographic progression during follow-up was compared with CT angiography or MR angiography in vessels with and without baseline PET activity, new or worsening stenosis, occlusion and aneurysm were significantly more common in vessels with baseline PET activity (OR 19.49 [95%CI 2.44–156.02]; $p<0.01$) (51). The overall relapse rate was similar between the patients with total vascular score (TVS) >10 and those with TVS <10 (58% *vs*. 56%) in another prospective study. However, patients with higher scores were numerically more likely to have an ischaemic relapse (33% *vs*. 11%, $p=0.34$) (52). In LVV patients in clinical remission, the risk of relapse was higher in patients with a PETVAS score >20 compared with those who had PETVAS score <20 (55% *vs*. 11%, $p=0.03$) (53). It has also been reported that PETVAS score during the early follow-up after discontinuation of TCZ can be used to predict subsequent relapse. The age and sex-adjusted hazard ratio (HR) (95% CI) for relapse was 1.36 (0.92–2.00) for each unit increase in the PETVAS score (54). The decrease in TVS was similar between patients who experienced relapse and those who did not. Involvement of extremity arteries (HR: 2.7 (1.3–5.5)) (55) and baseline LVV involvement (56, 57) were also found to be risk factors for the development of future relapse. Overall, high baseline PET scores may predict poor outcomes, including relapse and vascular damage during follow-up.

USG, although commonly employed in the diagnosis of GCA, does not seem to predict future relapses. In a prospective study, improvement in wall thickening did not translate to fewer relapses or a reduced cumulative GC dose (58). Similarly, a retrospective study examined OMERACT GCA USG score (OGUS) changes over six months (59). Patients who did not have a relapse had higher change in OGUS at 6 months. However, changes at 3 months were not different in relapsing and non-relapsing patients. Therefore, an early change in OGUS could not predict relapses at six months. Another prospective study compared patients with and without axillary artery involvement (60). The number of relapses and time to first relapse were similar in both groups. In retrospective studies, it was reported that halo count did not predict future relapses or severity of relapses (61, 62).

Two prospective studies (63, 64) assessed the value of USG for prediction of visual loss. Monti *et al*. (63) developed clinical and USG models to predict a composite outcome of visual loss, ocular vasculitis damage index item, GC >10 mg/day or the need for adjunct immunosuppressives. None of the models predicted this outcome. Similarly, another study (64) found that although temporal artery halo sign was associated with ischaemic findings, its presence failed to predict future ischaemic events. A study by van der Geest *et al*. (65) showed that quantitative halo counts and scores of temporal and axillary arteries quantify the reflect of vessel wall thickening and are strongly associated with intimal hyperplasia on biopsy. Higher counts and scores were also linked to higher rates of ocular ischaemia. Two retrospective studies (66, 67) showed an association between vertebral artery halo signs and stroke. However, these studies show associations between USG findings and disease involvement rather than predictions of future outcomes.

For imaging-based recommendations, particularly those addressing screening for extracranial large-vessel involvement in GCA, diagnostic performance data from four key studies (total n=640 patients) (50-53) were systematically reviewed as part of the SLR. Even if a standalone formal meta-analysis was not done, expert consensus agreed on that screening for large-vessel involvement in patients with GCA should preferably be done with FDG-PET, or if unavailable, with CT angiography.

Recommendation 6. *Patients with GCA are monitored using clinical findings and acute-phase reactants. There is no evidence to support routine imaging during follow-up. Patients with large-vessel involvement at diagnosis, especially those with aneurysms, may be monitored with CT angiography.*

Presence of baseline aortic FDG uptake on PET was identified as a risk factor for the development of complications including aortic aneurysm and dissection detected by CT angiography (68-70) and for predicting vascular damage (71) during follow-up in large retrospective studies. Although FDG-PET is a good predictor of incident vascular damage, as highlighted in the previous recommendation, the task force agreed to recommend monitoring large-vessel involvement, particularly aneurysms, using CT angiography.

Recommendation 7. *Treatment of newly diagnosed active GCA patients should be initiated with high-dose oral GC (0.5–1 mg/kg/day prednisolone or equivalent). Patients with ischaemic symptoms should receive intravenous (IV) methylprednisolone (500–1000 mg/day) for 3 days followed by continuation with high-dose oral GC.*

The current SLR did not identify new studies addressing optimal initial GC dose or route of administration; the proposed treatment algorithm is summarised in Figure 1. The GIACTA study provided important evidence supporting structured GC protocols (72). TCZ groups receiving a 26-week GC regimen achieved superior sustained GC-free remission rates (56% and 53% for weekly and every other week tocilizumab, respectively) compared to placebo groups with extended GC protocols (14% and 18% for 26-week and 52-week placebo groups, respectively, $p<0.001$) (72).

Studies evaluating IV pulse GC use in patients with GCA have shown some potential benefits with its use. In a randomised, double-blind, placebo-controlled study involving 27 patients, remission rates were higher in patients receiving IV pulse GCs, but the risk of GC-related side effects also increased (73).

Chevalet *et al*. (74) conducted a randomised study involving 164 patients investigated the effect of IV pulse GC therapy and suggested that it may be associated with reduced relapse rates and increased remission rates, but it remained unclear whether the benefits of routine use outweighed the risks due

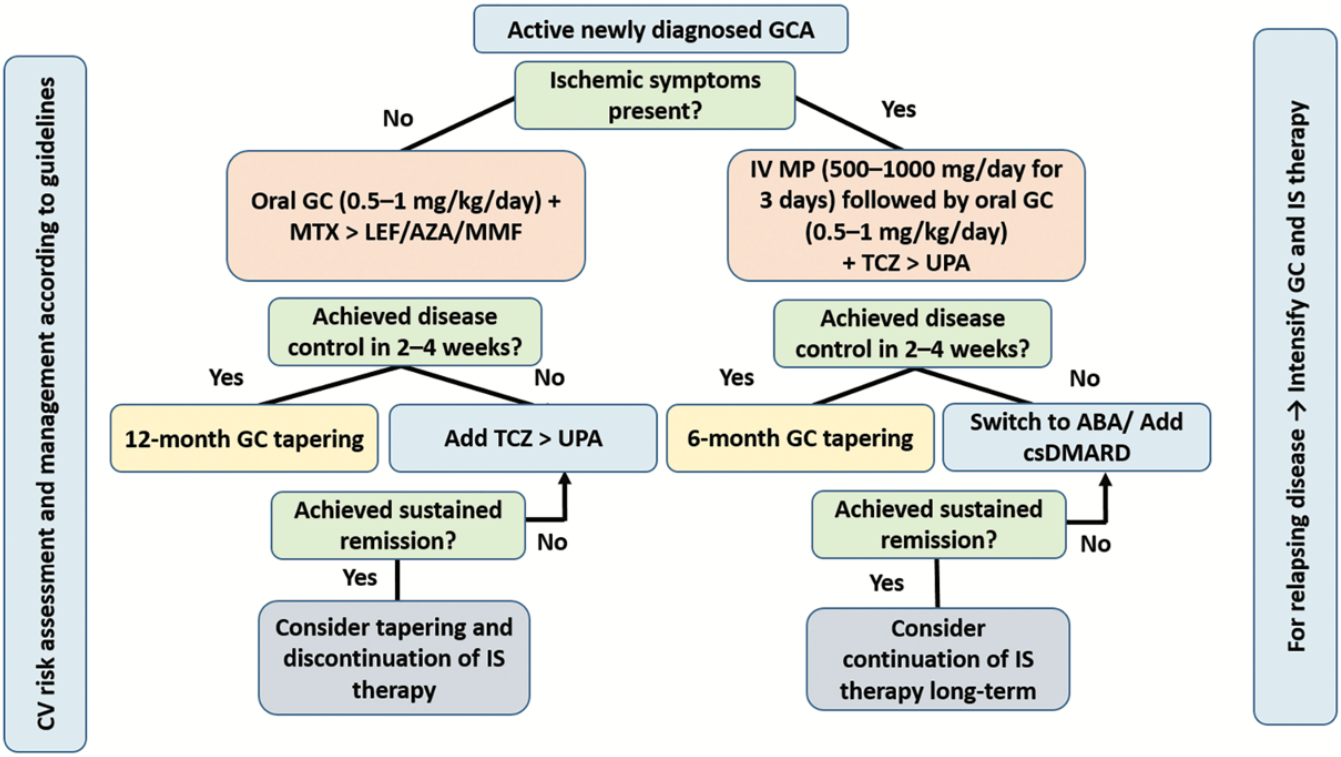

Fig. 1. Treatment algorithm of the Turkish Society for Rheumatology recommendations.
ABA: abatacept; AZA: azathioprine; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; GC: glucocorticoid; GCA: giant cell arteritis; IS: immunosuppressive; IV MP: intravenous methylprednisolone; MMF: mycophenolate mofetil; MTX: methotrexate; SECU: secukinumab; TCZ: tocilizumab; UPA: upadacitinib.

to increased adverse events such as infections, especially in the elderly (74). Nevertheless, due to their rapid anti-inflammatory effect, IV pulse GC therapy may still be considered in patients presenting with ischaemic symptoms.

Recommendation 8. *All patients should receive immunosuppressive therapy together with GC*.

GCs remain the cornerstone of the management of GCA. Their unfavourable adverse event profile when used at high doses for prolonged durations and the high relapse rates observed during tapering or withdrawal may be reduced by the addition of an immunosuppressive agent. In a multicentre retrospective study by Quartuccio *et al*. (75) 114 patients receiving immunosuppressive therapy (within 3 months of diagnosis) were compared with 51 patients receiving GC monotherapy. Immunosuppressive therapy group developed significantly less GC-related diabetes (7% *vs*. 23.5%; p=0.003) and had lower relapse rates (38.6% *vs*. 66.7%; p=0.001) (75). The RIGA study compared GC monotherapy, MTX combination therapy and TCZ combination therapy in 88 large-vessel GCA patients (76). All three regimens significantly reduced vascular inflammation on FDG-PET, but TCZ showed the fastest recovery and strongest GC-sparing effect (76). Quartuccio *et al*. (77) further confirmed that TCZ provided faster GC-free remission compared to MTX in GCA patients. Overall, these recent studies showed that the benefits of early combination therapy with immunosuppressives and GCs are not limited to the GC-sparing effects but also include improvements in long-term outcomes (75-77).

Recommendation 9. *In patients without ischaemic symptoms, MTX is preferred; if MTX cannot be used, leflunomide (LEF), azathioprine (AZA), or mycophenolate mofetil (MMF) can be selected*.

MTX is the most widely used conventional IS agent in GCA with the most comprehensive evidence. In an individual patient data meta-analysis of 3 RCTs, Mahr *et al*. (78) individual patient data meta-analysis of 3 RCTs demonstrated that MTX reduced first relapse risk by 35% and second relapse risk by 51%. Recent studies also supported these observations. In a retrospective study by Koster *et al*. evaluating 83 patients treated with MTX and 83 patients treated with only GC monotherapy, the MTX group showed a 68% reduction in relapse rate (11.8/10 person-years *vs*. 3.72/10 person-years; risk ratio: 0.32; 95% CI: 0.24–0.41) (79). Moreover, this effect was observed despite MTX initiation occurring a median of 39 weeks after diagnosis in the Mayo Clinic cohort (79).

The RIGA study showed that the MTX group achieved a 12.3-point reduction in PETVAS compared to 8.7 points with GC monotherapy (76). LEF appears to be an alternative for MTX-intolerant patients. In an open-label study by Hočevar *et al*. involving 76 patients (30 in LEF group, 46 in GC monotherapy group), 80% achieved remission with LEF and cumulative GC dose was significantly reduced (80). In 2022, the same group further confirmed LEF's the

GC-sparing effects with an acceptable safety profile in a larger patient population (81). A retrospective comparative study by Tengesdal *et al*. showed that in patients with high disease activity (prednisolone dose >7.5 mg/day), LEF provided faster remission than MTX (49.4 weeks *vs*. 104.9 weeks; p=0.02) (82). LEF has a side effect profile similar to MTX, however, monitoring for gastrointestinal intolerance and hepatotoxicity is required for both agents (80-82). AZA may also be an alternative for MTX-intolerant patients. De Silva and Hazleman had demonstrated GC-sparing effects of AZA in GCA patients in a double-blind study conducted in 1986 (83). AZA may be a safer option than MTX in patients with renal dysfunction (83). Pankow *et al*. 2023 study showed FDG-PET improvement and 75% median GC dose reduction in 7 GCA patients treated with AZA (84). Karabayas *et al*. showed similar results with decreased relapse rates in 37 large-vessel GCA patients (85). MMF represents another option especially for patients intolerant to other immunosuppressive agents (84, 85).

Recommendation 10. *TCZ should be used in patients with ischaemic symptoms or those refractory to at least one conventional immunosuppressive agent. Upadacitinib (UPA) may be an alternative to TCZ in patients with low risk for cardiovascular disease. Abatacept (ABA) may be considered in patients refractory or intolerant to these two agents*.

A meta-analysis published in 2021 including both randomised and observational studies, established that TCZ was associated with a significantly higher rate of sustained remission and a greater GC-sparing effect compared to conventional IS therapies (86). After this meta-analysis was published, recent studies have also confirmed the efficacy of TCZ. *Post-hoc* data from the GIACTA (Part 1) trial showed that TCZ could prevent relapses in patients with GCA with concomitant PMR and/or cranial symptoms (87). Even a short induction course of three months with TCZ was also reported to reduce cumulative GC exposure (88). An observational monocentric study revealed that TCZ treatment could prevent new visual complications in patients at high risk of vision loss (89). A GIACTA (Part 2) *post-hoc* analysis showed that TCZ had similar efficacy in preventing flares in both new-onset and relapsing GCA (90). In a comparative observational cohort, relapse rates at 24 months were lower with TCZ than with MTX (22.6% *vs*. 34.6%), although the difference did not reach statistical significance (77). In a prospective study that also evaluated USG remission, TCZ achieved greater GC tapering success and higher remission rates compared to MTX (91). In summary, evidence prior to 2022 established TCZ as an effective, GC-sparing option for GCA, and studies published thereafter have expanded these findings to include prevention of vision loss and similar efficacy in both new-onset and relapsing disease, with emerging data suggesting potential advantages over MTX in achieving remission and reducing cumulative GC exposure. However, there are still unmet needs for alternative biologics for patients who are intolerant, refractory, or have contraindications to TCZ. In patients with newly diagnosed or refractory GCA, RCTs have been conducted with sirukumab, sarilumab, mavrilimumab, secukinumab, and UPA (92-96). In studies with sirukumab which is a human IL-6 monoclonal antibody and sarilumab an interleukin-6-receptor inhibitor, a high proportion of patients failed to achieve the primary endpoint of sustained remission due to early termination of both studies due to sponsor decision and Coronavirus Disease 2019 (COVID-19) pandemic. No unexpected safety signals were reported with either drug (92, 93). In the phase 2, double-blind RCT mavrilimumab was superior to placebo for time to flare by week 26. The median time to flare was 25.1 weeks in the placebo group, and the median was not reached in the mavrilimumab group, HR 0.38; 95% CI 0.15 to 0.92; p=0.026. The sustained remission rate was also significantly higher in the mavrilimumab group compared to placebo (83% *vs*. 50%, p=0.0038) at week 26 of treatment. In the phase 2, double-blind RCT with secukinumab (TitAIN trial), patients in the secukinumab group had a higher sustained remission rate compared to placebo at week 28, in combination with a GC taper regimen. The sustained remission rate was 70% (95% CrI 52–85) in the secukinumab group and 20% (95% CrI 12–30) in the placebo group (risk difference (RD) 0.50 (95% CrI 0·29–0·67; RR 3·43, 95% CrI 2.10–5.87). Secukinumab was well-tolerated in this study (95). However, the more recent phase 3 RCT comparing secukinumab in combination with a 26-week GC taper and placebo in combination with a 52-week GC taper, was early terminated due to the study not meeting its primary endpoint. According to the results of a phase 3 RCT of UPA in GCA, UPA 15 mg but not 7.5 mg showed superiority over placebo with respect to the primary end point sustained remission at week 52 (46.4% [95% CI, 39.6 to 53.2] *vs*. 29.0% [95% CI, 20.6 to 37.5]; p=0.002). Also, UPA at 15 mg was also superior to placebo in the analysis of secondary endpoints of sustained complete remission, time to disease flare, cumulative GC exposure, and patient-reported outcomes. Cardiovascular risk is a potential concern with Janus kinase (JAK) inhibitors. However, no major adverse cardiovascular events were reported in the UPA groups in this study (96). In a retrospective study including 35 patients who received JAK inhibitors (15 baricitinib, 10 tofacitinib, 10 UPA), 57% of the patients had clinical remission and 46% had complete remission (97). In a prospective observational study comparing TCZ and ABA in patients with GCA, ABA demonstrated efficacy comparable to both IV and SC TCZ (98). The overall response rates were 100% for IV TCZ (57% complete and 43% partial responses), 83% for SC TCZ (67% complete and 16% partial responses), and 62% for ABA (31% complete and 31% partial responses) (98). In a prospective open-label study, ustekinumab provided a significant GC dose reduction at week 52. Median prednisolone dose decreased from 20 mg/day (IQR 15–25) at baseline to 5 mg/day (IQR 2.5–5) at week 52 (p<0.001) (99).

Recommendation 11. *Glucocorticoid dose reduction should be initiated after disease control is achieved (2–4 weeks). A 6-month glucocorticoid tapering regimen can be applied in patients starting treatment with TCZ or UPA, and a 12-month glucocorticoid tapering regimen in patients starting with MTX or another conventional immunosuppressive agent*.

A critical aspect of GCA treatment is tapering the GC dose. However, there are no RCTs that primarily aim to compare different tapering protocols. Furthermore, RCTs of TCZ, sirukumab, sarilumab, mavrilimumab, and UPA have included different GC tapering arms (72, 92-94, 96). Two studies examined a 26-week GC regimen without concomitant immunosuppressive therapy. Muratore *et al*. evaluated a 26-week GC protocol in a prospective, open-label single-arm study involving 22 GCA patients (100). At week 52, 45% of the patients achieved relapse-free remission, but only 23% remained in both relapse- and GC-free remission, and 68% had at least one relapse during the study period (100). Mensch *et al*. used a similar 26-week GC regimen in a retrospective single-arm study involving 47 GCA patients used a similar 26-week GC regimen and reported that 68% of patients experienced relapse, most of which were minor (28 of 32) (101). These considerably higher relapse rates with the 26-week tapering regimen suggested that a 52-week tapering regimen may be more suitable for patients receiving conventional immunosuppressive therapies. Studies investigating TCZ with the aim of achieving a faster GC-sparing effect and reducing cumulative GC exposure have shown encouraging outcomes. Christ *et al.'s* study followed 18 GCA patients with 3 days of 500 mg methylprednisolone pulse, followed by GCs discontinuation and a single dose of IV TCZ, followed by 52 weeks of SC TCZ. The remission rate was 76% at week 24, but only 25% of the patients achieved the primary outcome, defined as remission within 31 days and without relapse at week 24 (102).

Muratore *et al*. also followed 18 GCA patients with 3 pulses of 500 mg methylprednisolone, followed by 52 weeks of SC TCZ without additional GCs (103). They observed that 56% of patients remained in relapse-free remission at week 24 and 47% at week 52, and additionally 4 patients with initial aortic dilatation had increased aortic diameter at week 52 (103). Unizony *et al*. study involving 30 GCA patients investigated the combination of 8 weeks of GC and 52 weeks of SC TCZ in 30 GCA patients (104). At week 52, 77% of patients were in both relapse and GC-free remission and the mean cumulative GC dose was 1196 mg (104).

Overall, the modest remission rates and relatively high relapse rates observed with short-term GC protocols support recommending the 26-week tapering regimen used in RCTs, rather than ultra-short GC regimens.

Recommendation 12. *In patients who have been receiving immunosuppressive therapy for at least 1 year and have been in GC-free remission for at least 6 months, gradual discontinuation of immunosuppressive therapy may be considered. In patients with ischaemic symptoms, immunosuppressive therapy should be continued for a longer period*.

Eight recent studies have investigated the outcomes of TCZ tapering or discontinuation in patients with GCA. In the first prospective study by Tomelleri *et al*., 23 patients in remission on TCZ received weekly SC TCZ for 12 months, then tapered to every other week for 12 months, and finally discontinued TCZ and were followed for 6 months. All patients had to be in remission at the start of each phase. In the case of relapse, patients could initiate GC or MTX. Only minor relapses occurred, and the relapse rate was 17% (4/23) in the first phase, 9% (2/23) in the tapering phase, and 26% (6/23) in the discontinuation phase (105).

In the open-label extension phase of the GIACTA study, patients in GC-free remission at month 12 were enrolled (106). Long-term remission was achieved in 42% (25/59) in the weekly arm and 29% (8/28) in every other week arm (106). In another prospective study by Adler *et al*., all patients maintaining remission at month 12 in the phase 2 RCT of IV-TCZ discontinued the drug (107). During a mean follow-up of 28-months, 8/17 (47%) patients experienced a minor relapse (107). In a retrospective study involving 231 patients in remission for at least 6 months, the relapse rate was 10% in the continuation group *versus* 6% in the reduction group, but serious infections were less frequent in the reduction group (108). Nielsen *et al*. study compared abrupt discontinuation with gradual discontinuation (109). Relapse rates were 14% (8/57) in the reduction group *versus* 46% (27/59) in the abrupt discontinuation group, and time to relapse was significantly longer in the reduction group (109). A multicentre study by Quick *et al*. multicentre study from the UK evaluated 336 patients who discontinued TCZ due to the COVID-19 pandemic (110). Overall, 110 of 336 (32.7%) patients experienced relapses and relapse rates increased over time: 21.4% at 6 months, 35.4% at 12 months, 45.0% at 18 months, 48.6% at 24 months (110). In a retrospective observational study of 114 patients who had received TCZ for at least 3 months and been followed for at least 6 months, the relapse rate was 36% while on TCZ, and 27 patients (52%) relapsed a median of 8.4 months after TCZ cessation (111). In the fifth retrospective observational study, patients who discontinued TCZ abruptly were compared with those who tapered TCZ. Relapse rates were 14% (8/57) in the tapering group *versus* 46% (27/59) in the abrupt-discontinuation group (109). Overall, these studies showed that higher glucocorticoid doses at TCZ initiation, TCZ treatment duration of less than 12 months, and high baseline disease activity were associated with an increased risk of relapse (109, 110). There are no data assessing the immunosuppressive discontinuation time separately in GCA patients with and without ischaemic symptoms. However, the task force recommends continuing immunosuppressive treatment for a longer period in GCA patients with ischaemic symptoms.

Recommendation 13. *In the management of relapses, the medications the patient is currently using, and the presence of ischaemic symptoms are determining factors. In patients with relapse,*

glucocorticoid dose and tapering strategy can be applied as recommended for newly diagnosed patients.

Relapse management in GCA should be individualised according to the patient's current therapy and the presence of ischaemic symptoms. Although specific protocols for relapse management are limited in the literature, existing studies provide guiding principles. A protocol for patients experiencing relapse was established in the GIACTA study (72). In case of relapse, patients were withdrawn from the study and open-label treatment was initiated, highlighting the importance of relapse management in real-life practice (72). Several retrospective studies have reported relapse patterns and management strategies. Koster *et al*. study observed a 68% reduction in relapse rate after MTX initiation, emphasising the importance of adding/changing immunosuppressive therapy in patients experiencing relapse (79). Gérard *et al*. reported that steroid-sparing agents like TCZ can help maintain remission while reducing glucocorticoid exposure, offering guidance in relapse management (86). Samson *et al*. found that adding TCZ within the first 3 months of treatment significantly reduced GC requirements, suggesting a similar approach could benefit relapsing cases (88). Quartuccio *et al*. found that TCZ led to a faster steroid-free remission compared to MTX in a real-life cohort, supporting its preference in relapsing cases requiring rapid control (77). Grazzini *et al*. demonstrated superior clinical and ultrasonographic response with TCZ *versus* MTX in active GCA, suggesting that switching to TCZ in relapse is clinically effective (91). A more aggressive approach may be required in patients relapsing with ischaemic symptoms. In TCZ studies, IV pulse methylprednisolone use was recommended in the presence of ischaemic symptoms (72, 79).

Recommendation 14. *In patients who relapse with non-ischaemic symptoms while on immunosuppressive therapy, GC should be initiated or the dose should be increased if already using GC, and immunosuppressive therapy should be intensified*.

Evidence for the management of patients relapsing with non-ischaemic symptoms while on immunosuppressive therapy was evaluated. These patients typically present with constitutional symptoms, headache, or laboratory changes. The GIACTA study protocol provides guiding principles for this situation (72). In case of non-ischaemic relapse, increasing GC dose and optimising immunosuppressive therapy is recommended (72). Additionally, retrospective multicentre data support that using TCZ in combination with conventional ISs may help maintain prolonged remission in relapsing patients (112). Retrospective studies suggest that non-ischaemic relapses may generally require less aggressive treatment. However, these patients should be closely monitored, and treatment response should be evaluated (72). Spiera *et al*. showed that patients with PMR symptoms benefited from TCZ compared to placebo, supporting intensification of immunosuppression in non-ischaemic relapses (87). Calderón-Goercke *et al*. found that combining TCZ with conventional immunosuppressives in real-life practice resulted in more sustained remission compared to monotherapy, suggesting an escalation strategy (112). Grazzini *et al*. also supported the use of TCZ over MTX in patients with active GCA, reinforcing its utility in non-ischaemic relapses (91).

Recommendation 15. *In patients who relapse while on optimal doses of TCZ or UPA, GC should be initiated or the dose increased if already taking them, and immunosuppressive agent switching is recommended. In patients who relapse despite these two agents, addition of conventional immunosuppressive therapy or switching to ABA may be considered*.

Evidence for the management of patients experiencing a relapse while on optimal dose TCZ or UPA therapy is limited, but recommendations based on expert consensus and small series are available. In the extension phase of the GIACTA study, it was reported that in some patients who experienced a relapse while on TCZ, additional conventional immunosuppressive therapy was added (106). This approach was successful in some patients (106). Calderón-Goercke *et al*. also suggested that patients who experienced a relapse under TCZ monotherapy may respond better to combination treatment with a conventional immunosuppressive (112). In the UPA study, although no specific protocol for patients experiencing relapse was defined, it was emphasised that alternative treatment strategies should be evaluated in these patients (96). Amsler *et al*. emphasised the importance of close monitoring, as visual complications may still occur despite biologic therapy (89). Stone *et al*. further confirmed that TCZ was effective in both new-onset and relapsing GCA patients over a 3-year period, supporting its continued use even after relapse (90). Data regarding secukinumab and ABA are limited, but these agents have potential for use in patients refractory to TCZ and UPA.

Recommendation 16. *Cardiovascular risk assessment should be performed in patients diagnosed with GCA and their treatments should be managed according to current guidelines. Although routine initiation of anticoagulants, antiplatelets, or statins is not recommended, their use should be evaluated individually on a patient basis*.

GCA patients have increased cardiovascular risk due to age and vascular inflammation. Therefore, comprehensive cardiovascular risk assessment and determination of appropriate treatment strategies are important. Cardiovascular risk assessment should be performed according to European Society of Cardiology and American Heart Association guidelines. Risk factors include age, hypertension, diabetes mellitus, hyperlipidaemia, smoking and family history. There is potential to reduce thrombotic events in high-risk individuals with ischaemic complications. In a study by Nesher *et al*. GCA patients using low-dose aspirin (75-100 mg/day) had a cranial ischaemic complication rate of 7.4% compared to 15.2% in the control group who were treated with prednisone only ($p<0.05$) (113). Berger *et al*. support the protective effect of antiplatelet therapy in the devel-

opment of serious iscaemic complications in GCA patients (114). However, concomitant proton pump inhibitor use should be evaluated due to gastrointestinal bleeding risk, and individual risk assessment should be performed (115). Retrospective studies evaluating statin use in GCA patients show that statin use may reduce inflammatory markers; however, LDL cholesterol level targets and primary/secondary prevention indications should be determined according to standard cardiology guidelines (116). Schmidt *et al*. study showed that statin use might reduce vascular inflammation (116). However, there is insufficient evidence for routine statin initiation. Anticoagulant therapy should only be considered according to standard anticoagulation guidelines in patients with specific indications such as atrial fibrillation, venous thromboembolism, or mechanical heart valve, due to the lack of evidence-based data specific for GCA patients.

Discussion

The first TSR recommendations for GCA derived from the current literature review and expert opinion, provide guidance to rheumatologists and other clinicians involved in the diagnosis and treatment of GCA patients, especially in Turkey. For the diagnosis of GCA, we suggest the use of TAB or USG according to the availability of the tools and the experience in each centre. EULAR Recommendations for the management of LVV recommend that a suspected diagnosis of LVV should be confirmed by imaging or histology (4). The EULAR Recommendations for the use of imaging of LVV suggest temporal artery and axillary artery USG should be considered as the first imaging modality to investigate mural inflammatory changes in patients with suspected GCA, and indicate that in patients with a high clinical suspicion of GCA diagnosis may be made with a positive imaging result without additional testing such as TAB (3). ACR still recommends the TAB as the first diagnostic test for GCA possibly due to limited experience with USG in the United States of America (5). However, it has been validated that in many studies, temporal artery USG is a fast, inexpensive and reliable diagnostic tool in GCA (4). With the increasing experience and availability, USG use will make the GCA diagnosis faster in daily practice.

We suggest performing a TAB before initiation of treatment in GCA patients, or within two weeks at the latest, if treatment has already been started. The biopsy should be performed from symptomatic side and unilaterally, and the specimen should be at least 1.5 cm. ACR conditionally recommends a TAB specimen >1 cm over a short-segment TAB specimen (<1 cm) (5). Our SLR showed that the biopsy size should ideally be a minimum of 1 cm. However, we recommend at least 1.5 cm with the understanding that the specimen will undergo a reduction following fixation. In suspected GCA patients who cannot be diagnosed with USG or TAB, we recommend that MR angiography can be used for imaging cranial vascular structures, and FDG-PET for extracranial vascular structures. CT angiography can also be an alternative imaging modality. Different from our recommendations, EULAR recommends FDG-PET for both assessment of cranial and extracranial vascular arteries in this group of patients (3). ACR conditionally recommends non-invasive vascular imaging of the large vessels in suspected or newly diagnosed GCA. ACR also conditionally recommends obtaining baseline MR or CT angiography for evaluation of large-vessel involvement for patients with newly diagnosed GCA (5). Different from other published recommendations, we recommend performing systematic large-vessel involvement screening with FDG-PET, or with CT angiography as an alternative in all newly diagnosed GCA patients. We also recommend close monitoring of patients with high baseline FDG-PET scores for potential relapse and vascular damage (stenosis/aneurysm/occlusion) during follow-up. Extracranial arterial involvement in GCA patients is seen mostly in a silent course between 30–83% and can lead to a development of complications if not detected at diagnosis. GCA patients with large-vessel involvement are also at increased risk for relapse. FDG-PET is superior in both diagnosis and relapse prediction due to its ability to vividly demonstrate vasculitis activity (117).

GC is still the mainstay of medical treatment in GCA. All GCA recommendations suggest starting with 40-60 mg/day prednisone or equivalent for induction of remission and tapering the GC dose to ≤5 mg/day at the end of 1 year. In the presence of visual manifestations, IV pulses of GC were also recommended (4, 5, 118, 119). However, despite slow tapering, 50-80% of patients with GCA relapse under GC treatment during follow-up (120). Though conventional immunosuppressives are suggested for selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC-related adverse effects or complications) by EULAR and French Study Group for Large Vessel Vasculitis (4, 121), ACR guideline conditionally recommended the use of TCZ or MTX as GC-tapering agents in GCA patients with or without extracranial involvement (5). For patients with newly diagnosed GCA, the Pan American League of Associations for Rheumatology (PANLAR) guideline recommends treatment with GCs and TCZ over GCs alone (119). Recent Norwegian Society of Rheumatology recommendations suggest initiating MTX in refractory or relapsing patients. TCZ is suggested to be considered if the patient cannot tolerate MTX or suffers a relapse while on MTX. They also mention that LEF or AZA may be considered despite the scarce evidence (118). ACR recommends adding a non-GC immunosuppressive agent (MTX or TCZ, preferably TCZ in patients with ischaemic cranial symptoms) in relapsing GCA patients together with increasing GC dose (5). Norwegian guideline recommends increasing the GC dose to the most recent effective dose in patients with minor relapse. In patients with refractory disease or major relapse, initiation of MTX is recommended. TCZ is recommended in case of intolerance to MTX or refractory/relapsing disease while on MTX (96, 118). For relapsing GCA patients, PANLAR guideline recommends both TCZ (strongly) and MTX (conditionally). They also recommend against treatment with ABA, cy-

clophosphamide and tumour necrosis factor inhibitors (119).

TSR recommendations have some differences compared to other published guidelines. We recommend the use of MTX in addition to GC as first-line treatment in all patients with GCA without ischaemic symptoms. We recommend LEF, AZA and MMF as alternative options in these patients if MTX is not tolerated. The task force felt that this approach is important especially for developing countries that have difficulty in reaching biologic agents which are more expensive options. We recommend TCZ in GCA patients with ischaemic symptoms or with refractoriness to at least one conventional immunosuppressive agent. We also recommend UPA as an alternative to TCZ in patients with low cardiovascular risk. TSR recommendations are the first recommending UPA as an alternative option for the treatment of GCA. In a recent large RCT, UPA 15 mg was found to be superior to placebo for achievement of sustained remission at week 52 (96). We also recommend that ABA may be used for the treatment of GCA if there are intolerance or refractoriness to TCZ and UPA. We did not include secukinumab among the options due to the early termination of its phase 3 trial. In relapsing patients without ischaemic symptoms, we recommend GC initiation or an increase in GC dose with intensification of I immunosuppressive treatment. In relapsing patients during TCZ or UPA treatment, we recommend addition of conventional immunosuppressives or switching to ABA. According to the French Study Group for Large Vessel Vasculitis, which is the only guideline mentioning these biologic agents; secukinumab, baricitinib, ustekinumab, ABA and mavrilimumab were not recommended based on limited phase 2 or open-label studies. However, they can be discussed with an expert in case of need (121).

Slow tapering of GCs with a withdrawal between 18 and 24 months is suggested by EULAR to avoid relapse in GCA(4). However, there is no consensus for the optimal duration of treatment and time for cessation of treatment in GCA. Recent French guideline recommends that TCZ or MTX may be discontinued after 12 months, if possible, in patients completing the GC taper (121). TSR recommends 6 months of GC tapering with TCZ or UPA and 12 months of GC tapering with MTX and other conventional immunosuppressives for the treatment of GCA patients. We also recommend that gradual cessation of immunosuppressive treatment may be considered in patients who are in remission without GC for at least 12 months. While EULAR guidelines do not recommend the routine use of antiplatelet or anticoagulant treatment in GCA unless it is indicated for other reasons, ACR (5) and PANLAR (119) guidelines recommend the use of low-dose of aspirin, not only when otherwise indicated, but also in the presence of vasculitic involvement of the common carotid, internal carotid, or vertebral arteries. We recommend that the use of antiplatelet, anticoagulant and statin treatment should be assessed individually in each GCA patient in light of current guidelines.

This guideline has some limitations. First, although the recommendations were informed by a systematic literature review, the available evidence was heterogeneous with respect to study design, patient populations, outcome imaging and treatment protocols. Second, comparative data were limited for screening strategies for large-vessel involvement, optimal tapering and discontinuation decisions, comparative effectiveness between different treatments and the management of relapse under biologic or targeted therapies. Third, the applicability of these recommendations may vary across clinical settings due to differences in local expertise, particularly in imaging modalities and access to advanced imaging and therapies, which may affect implementation, especially outside tertiary centres.

Recent comprehensive syntheses, outline important advances in imaging strategies, diagnostic pathways, and disease stratification in large-vessel vasculitis, including giant cell arteritis. The present guideline is consistent with these developments and seeks to integrate current evidence into structured, clinically applicable recommendations (122, 123).

The present guideline has clear implications for clinical practice. By synthesising current evidence and expert opinion into structured recommendations, it provides a standardised framework to support daily clinical decision-making. This approach is expected to enhance consistency of care, facilitate timely diagnosis through prioritised imaging strategies and optimise disease management with the aim of reducing glucocorticoid-related morbidity. The integration of contemporary imaging techniques and evolving therapeutic strategies, including biological agents, may contribute to improved long-term outcomes while allowing for adaptation to local clinical contexts and resource availability.

In conclusion, large RCTs assessing and comparing new effective options are still required in GCA. The optimal duration of GC and immunosuppressive agents are also insufficiently explored. Assessment of the value of conventional immunosuppressives which are more cost-effective options compared to biologic agents, is another research area in GCA treatment for especially in developing countries. UPA seems to be a promising therapeutic option in GCA. However, more real-life experience is needed to assess the safety of UPA in the elderly population with especially those with high cardiovascular risk.

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