Title

Treat-to-target recommendations in giant cell arteritis and polymyalgia rheumatica.

Journal

Annals of the Rheumatic Diseases, 83(1)

Authors

Dejaco, Christian
Kerschbaumer, Andreas
Aletaha, Daniel
et al.

Publication Date

2024-01-02

DOI

10.1136/ard-2022-223429

Peer reviewed

OPEN ACCESS

Treat-to-target recommendations in giant cell arteritis and polymyalgia rheumatica

Christian Dejaco [1,2] Andreas Kerschbaumer [3] Daniel Aletaha [4] Milena Bond [2] Elvis Hysa,[5] Dario Camellino [6] Lisa Ehlers [7] Andy Abril,[8] Simone Appenzeller,[9] Maria C Cid [10] Bhaskar Dasgupta [11] Christina Duftner [12] Peter C Grayson [13] Bernhard Hellmich [14] Alojzija Hočevar [15,16] Tanaz A Kermani [17] Eric L Matteson [18] Susan P Mollan,[19,20] Lorna Neill,[21] Cristina Ponte [22,23] Carlo Salvarani [24,25] Sebastian Eduardo Sattui [26] Wolfgang A Schmidt [27] Philip Seo,[28] Josef S Smolen [29] Jens Thiel,[1,30] Carlos Enrique Toro-Gutiérrez [31] Madeline Whitlock,[32] Frank Buttgereit [33]

Handling editor Mary K Crow

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2022-223429).

For numbered affiliations see end of article.

Correspondence to
Dr Christian Dejaco, Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Medical University of Graz, Graz, 8036, Austria;
christian.dejaco@gmx.net

Received 3 October 2022
Accepted 11 February 2023
Published Online First
24 February 2023

ABSTRACT

Objectives To develop treat-to-target (T2T) recommendations in giant cell arteritis (GCA) and polymyalgia rheumatica (PMR).

Methods A systematic literature review was conducted to retrieve data on treatment targets and outcomes in GCA/PMR as well as to identify the evidence for the effectiveness of a T2T-based management approach in these diseases. Based on evidence and expert opinion, the task force (29 participants from 10 countries consisting of physicians, a healthcare professional and a patient) developed recommendations, with consensus obtained through voting. The final level of agreement was provided anonymously.

Results Five overarching principles and six-specific recommendations were formulated. Management of GCA and PMR should be based on shared decisions between patient and physician recognising the need for urgent treatment of GCA to avoid ischaemic complications, and it should aim at maximising health-related quality of life in both diseases. The treatment targets are achievement and maintenance of remission, as well as prevention of tissue ischaemia and vascular damage. Comorbidities need to be considered when assessing disease activity and selecting treatment.

Conclusion These are the first T2T recommendations for GCA and PMR. Treatment targets, as well as strategies to assess, achieve and maintain these targets have been defined. The research agenda highlights the gaps in evidence and the need for future research.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is large heterogeneity in clinical practice related to treatment strategies in giant cell arteritis (GCA) and polymyalgia rheumatica (PMR).

⇒ The concept of treat-to-target (T2T) is widely adopted in rheumatology, but has yet not been defined for these diseases.

WHAT THIS STUDY ADDS

⇒ Here, we present consensus-based recommendations on T2T in GCA and PMR developed by an international, multidisciplinary task force.

⇒ Treatment targets, as well as strategies to assess, achieve and maintain these targets, have been provided.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These recommendations advise clinicians how to effectively implement a T2T approach for GCA and PMR in clinical practice.

⇒ Gaps in current knowledge have been identified and a research agenda frames the needs to be addressed by future studies in the field.

INTRODUCTION

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are overlapping inflammatory rheumatic conditions of older people.[1 2] For decades, GCA has been considered a predominantly cranial disease. More recently, advanced vascular imaging has demonstrated that large vessels (LV) are frequently involved, leading to the understanding that GCA represents a generalised vasculitic syndrome that includes cranial and extracranial medium/LV vasculitis (LV-GCA) and overlaps with PMR.[3]

Glucocorticoids (GC) are the standard treatment for GCA and PMR. Unfortunately, GC-related toxicity occurs in up to 85% of patients.[1 2] In addition, many patients have pre-existing comorbidities that may worsen with GC therapy. Moreover, the prevalence of symptomatic disease relapse is high: in cohort studies, 34–62% of people with GCA and/or PMR were reported to have at least one relapse.[4] In a clinical trial in GCA comparing tocilizumab (TCZ) with placebo along with a standardised GC tapering, sustained remission was achieved in only one-fifth of those who were treated with GC alone.[5] Tapering of GCs, however, was much faster in that study as compared with clinical practice. (Hysa *et al*, manuscript in preparation)

Check for updates

To cite: Dejaco C, Kerschbaumer A, Aletaha D, *et al*. *Ann Rheum Dis* 2024;**83**:48–57.

Methotrexate, in combination with GC, can be considered in the treatment of patients with GCA and PMR, even though data from clinical trials revealed conflicting results.[6–8] TCZ has been approved for treatment in GCA following the phase III study mentioned above, which demonstrated higher remission rates and better GC sparing than placebo.[5] Notably, neither drug has so far been associated with a reduction in GC-related adverse outcomes. For PMR, TCZ was also highly effective in recent phase II/III trials but has not yet been approved for this disease indication.[9 10] Another phase III trial of sarilumab in PMR was terminated early because of the COVID-19 pandemic. Preliminary results indicated a higher efficacy of sarilumab over placebo in terms of achieving sustained remission.[11] Other drugs are currently being tested in randomised controlled trials, and upcoming registries will soon collect observational data on the management of these diseases.

Along with these exciting developments, new unmet needs have emerged, including questions about the relevant treatment targets and outcomes in GCA and PMR. Other points of discussion are how the suppression of disease activity should be balanced against adverse consequences from drugs.[12]

The treat-to-target (T2T) concept includes the definition of a specific treatment target, regular monitoring of the progress of therapy with respect to the treatment target and, if necessary, adjustment of therapy to achieve the lowest possible disease activity or remission. Treatment targets have already been defined in several areas of rheumatology, including rheumatoid arthritis (RA), spondyloarthritis (SpA), gout and systemic lupus erythematosus (SLE).[13–17] Moreover, studies have demonstrated that a targeted management approach yields superior outcomes than conventional care in terms of clinical course, long-term damage and functional status.[18–21]

Up to now, T2T is not a recognised treatment approach in GCA and PMR, and to this point there has not been a systematic evaluation and consensus finding process on this topic. The development of T2T recommendations for GCA/PMR, therefore, addresses a current unmet medical need.[12]

To address this gap, an international, multidisciplinary task force was formed to develop recommendations aimed at defining treatment targets for GCA and PMR, with the goal of improving the management of these diseases in clinical practice.

METHODS

The convenors (CDe and FB) and the methodologists (AK and DA) led a task force guided by the 2014 updated EULAR standardised operating procedures for developing recommendations.[22] The 29 task force members consisted of rheumatologists, internists, a neuro-ophthalmologist, a patient representative, methodologists and a healthcare professional representing 10 countries. One face-to-face and one virtual meeting of the scientific committee (CDe, FB, ELM, MCC, PCG, AA, DA, AK, JSS, DC, LE, CDu, MW, LN, MB and EH), several virtual meetings of the steering committee (CDe, FB, DA, AK, MB and EH) and one face-to-face meeting of the entire task force took place. A nominal group technique was used for the virtual and the face-to-face meetings.

At the first (virtual) meeting, the scientific committee agreed on 11 key questions relevant to T2T in GCA and PMR (see online supplemental table 1). These key questions were transformed into the respective Population, Intervention, Comparator, Outcome question format, which served as the basis for the systematic literature review (SLR).

A single SLR was conducted by four fellows (DC, LE, MB and EH) under the guidance of the methodologists. DC and LE conducted the screening and selection of articles. Data extraction, data synthesis and quality appraisal were performed by MB and EH.

The search strategies were developed by an experienced librarian (LF) and a systematic search was conducted in MEDLINE, EMBASE and the Cochrane Library (initial search to March 2021, updated search through May 2022). Full research articles, short reports and letters of randomised controlled trials as well as prospective and retrospective studies including an intervention and control group were retrieved. Further inclusion criteria were sample size of >20 patients, publication in English or qualitative studies without a limit of participants and addressing any of the aspects raised by the key questions. Risk of bias (RoB) was assessed using the Cochrane RoB tool for randomised trials version 2, the RoB tool for non-randomised studies of Interventions and the appraisal tool for cross-sectional studies (AXIS).[23–25]

The evidence was presented during the second (face-to-face) meeting of the scientific committee and the task force in June 2022. The data presented at this meeting were synthesised in a separate manuscript, describing the SLR in detail, providing the scientific evidence base for the present manuscript. (Hysa *et al*, manuscript in preparation)

At this second meeting of the scientific committee, the evidence was discussed, and based on the initial clinical key questions and the evidence, four proposals for overarching principles and five specific recommendations were prepared. Subsequently, the entire task force discussed the evidence again and refined and complemented the statements. This was followed by voting on the individual statements. Consensus was accepted if ≥75% of the members voted in favour of the statement at the first round of discussion, ≥67% at the second round, and at a third round >50% was accepted.[26] The Oxford Centre for Evidence-based Medicine 2011 levels of evidence (LoE) derived from the SLR were added to each recommendation.[27]

After the task force meeting, each member anonymously indicated their level of agreement (LoA) via Survey Monkey. (LoA, 0–10 numeric rating scale ranging from 0= 'completely disagree' to 10= 'completely agree'). The mean and SD of the LoA, as well as the percentage of task force members with an agreement ≥8 are presented. Based on the gaps in evidence and controversial points, a research agenda was formulated.

RESULTS

General aspects

These T2T recommendations are intended to advise primary, secondary and tertiary care physicians (including general practitioners, rheumatologists, ophthalmologists, neurologists, geriatricians as well as specialists in internal or vascular medicine, radiology and vascular surgery), health professionals in rheumatology, pharmacists, patient organisations, payers, hospital managers and trial investigators.

The target population are people with GCA, PMR and GCA/PMR.

These recommendations provide a strategic management concept for GCA and PMR, but are not intended to cover all management aspects of these diseases. They should be understood as complementary to the current international treatment recommendations.[6–8]

A total of five overarching principles and six specific recommendations were formulated. These are summarised in table 1 (including the LoE and LoA) and are discussed in detail below.

Table 1 Treat-to-Target (T2T) recommendations in giant cell arteritis (GCA) and polymyalgia rheumatica (PMR)

Overarching principles	LoE	LoA
A. Clinical management of GCA and PMR should be driven by the awareness that they are closely interrelated conditions in a common spectrum of inflammatory diseases and can occur separately, simultaneously or in temporal sequence to each other.	n.a.	9.8 (0.6) 96.3% >8
B. GCA is a medical emergency because of the imminent risk of sight loss and other ischaemic events, and therefore, requires immediate treatment; management usually requires multidisciplinary collaboration.	n.a.	9.9 (0.3) 100% >8
C. Patients should be offered access to information about GCA and PMR, including clinical disease features, patient-reported outcomes, potential complications, treatment-related benefits and risks, as well as relevant comorbidities.	n.a.	9.7 (1.0) 96.3% >8
D. Management of GCA and PMR should be based on shared decision making between the informed patient and the physician.	n.a.	9.8 (0.5) 100% >8
E. Treatment of GCA and PMR should aim at maximising health-related quality of life through control of symptoms, preventing disease-related damage and minimising treatment-related adverse consequences, taking relevant comorbidities into account.	n.a.	9.9 (0.4) 100% >8
Recommendations		
1. The treatment target of GCA and PMR should be remission; remission is the absence of clinical symptoms and systemic inflammation.	5*	9.6 (0.9) 96.3% >8
2. Treatment of GCA should also aim to prevent tissue ischaemia and vascular damage.	5	9.9 (0.4) 100% >8
3. Treatment selection in GCA and PMR should be based on disease severity and activity, presence of relevant comorbidities and potential predictors of outcome; treatment should be modified as needed during follow-up.	5	9.9 (0.3) 100% >8
4. Comorbidities may influence the assessment of the treatment target and should be considered before modifying treatment.	5	9.8 (0.5) 100% >8
5. Once remission is reached, it should be maintained with the minimal effective dose of medication[#]; drug-free remission may be achieved in a proportion of patients[##].	5[#] - 2[##]	9.9 (0.3) 100% >8
6. Disease activity in GCA and PMR should be monitored regularly, as frequently as every 1–4 weeks until remission has been achieved, and at longer monitoring intervals (eg, between 3 and 6 months) in patients in stable remission on therapy; monitoring of patients off therapy should be discussed on an individual basis.	5	9.8 (0.6) 100% >8

Numbers in column 'LoE' indicate the LoE supporting the respective recommendation according to the Oxford Centre for Evidence-based Medicine 2011 levels of evidence (LoE).[27] Accordingly, LoE 2=randomised trial or observational study with dramatic effect; LoE 5=mechanism-based reasoning.
Numbers in column 'LoA' indicate the mean and SD (in parenthesis) of the LoA (range 0–10 with 0= 'completely disagree' to 10= 'completely agree'), as well as the percentage of task force members with an agreement ≥8; 27/29 (93.1%) task force members expressed their level or agreement.
*While 'remission' has been an outcome in several trials in GCA and PMR, (Hysa *et al*, manuscript in preparation) there is no comparison of the performance of remission with another treatment target.
LoA, level of agreement; LoE, level of evidence; n.a., not applicable.

Overarching principles

These statements refer to principles of a generic and self-evident nature. They are, therefore, not necessarily based on specific LoE but reflect issues of good clinical practice. The task force considered them as a framework for the subsequent, specific recommendations.

A. Clinical management of GCA and PMR should be driven by the awareness that they are closely interrelated conditions in a common spectrum of inflammatory diseases and can occur separately, simultaneously or in temporal sequence to each other.

GCA and PMR are interlinked conditions that frequently overlap.[3] PMR often occurs as a symptom of relapse in GCA[28]; therefore, it is possible that people with PMR who have recurrent relapses, as well as those who are unable to taper GCs, have underlying GCA that was 'masked' at the time of diagnosis. Moreover, there is evidence of subclinical vasculitis in some people with PMR, however, the significance of this observation for clinical outcomes is still unclear.[29–31]

In current practice, PMR is mainly treated by primary care physicians, whereas people with GCA are commonly referred to secondary/tertiary care specialists.[32 33] Shared care between specialists and primary care physicians for both diseases is desirable, with regular evaluation of patients by an expert, particularly in case of difficult to treat PMR. This should ensure the early recognition of a possible GCA/PMR overlap and the management of both diseases according to a T2T strategy.

B. GCA is a medical emergency because of the imminent risk of sight loss and other ischaemic events and, therefore, requires immediate treatment; management usually requires multidisciplinary collaboration.

This statement emphasises the need for early treatment of GCA, particularly in case of cranial manifestations (such as headache, jaw claudication and visual symptoms), given that sight loss occurs in 15%–35% of patients.[4 34 35] This complication has a dramatic impact on the quality of life of patients and their caregivers.[36] If one eye is affected, the risk for losing the second eye is as high as 50%.[37 38] Sight loss almost exclusively occurs before the initiation of GC therapy; the risk for visual impairment is reduced dramatically once patients are on treatment.[34 35]

Immediate treatment of GCA implies that the diagnosis is also confirmed rapidly. Treatment of a person with high suspicion for GCA should not be delayed because of pending diagnostic procedures.[39] 'Fast-track' GCA clinics have facilitated rapid diagnosis and specialist care,[34 35 40–43] and have helped to increase the awareness about the disease among referrers, thus further reducing the symptom to therapy lag.[33]

People with GCA may present with different symptoms. This is the leading reason why they are often seen by a variety of specialists, and explains why a multidisciplinary collaboration is needed for a T2T strategy in this disease. Further, GCA may cause damage in different vascular territories potentially leading to sight loss, strokes, tongue or scalp necrosis, as well as peripheral limb ischaemia, requiring multidisciplinary management including ophthalmologists, neurologists and plastic and vascular surgeons.[3]

C. Patients should be offered access to information about GCA and PMR, including clinical disease features, patient-

reported outcomes, potential complications, treatment-related benefits and risks, as well as relevant comorbidities.

Information about GCA and PMR needs to be accessible to all patients and caregivers. Because GCA and PMR commonly overlap, all patients should receive information on both diseases. Most people with GCA and PMR respond quickly to GC therapy and, therefore, some of them may prematurely stop treatment in the assumption that they are cured. This results not only in a rapid return of symptoms, but also bears the risk of tissue ischaemia.[44 45] Patients also need to be informed that up to 60% of them will have one or more relapses during GC tapering, and that a relapse might lead to ischaemic complications.[46 47]

Patient awareness should also be directed to understand the distinctions between disease-related and disease-unrelated symptoms. For example, shoulder pain in PMR might be due to a relapse or unrelated to PMR, such as osteoarthritis, adhesive capsulitis or rotator cuff disease. Fatigue can be either a symptom of GCA and PMR, caused by other conditions or due to treatment.[48] Likewise, increment of acute phase reactants does not always reflect active GCA/PMR but can be related to infections or other inflammatory conditions. Relapses may also be present despite normal erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), particularly, but not only, in people who are treated with interleukin-6 receptor (IL-6R) blocking agents.[49] People with GCA should further be informed that certain manifestations such as vision loss can be related to active disease (when new or worsened, occurring in one-fifth of cases with a major relapse),[50] to damage (when persistent in spite of treatment and with no other sign of active disease) or to other conditions (eg, age-related macular degeneration, glaucoma or cataracts). Patients should also be educated about possible adverse consequences of therapy and taught to recognise them.[51]

Patients should receive information about comorbidities. The term 'relevant' was chosen to express that rheumatologists are trained to focus on those that are relevant to the disease and/or to its treatment, such as osteoporosis, diabetes mellitus or cardiovascular disease, while general medical concerns are addressed by their primary and other specialty care physicians as appropriate.[52 53]

The best method of providing information and the amount of information that should be delivered to patients is likely dependent on patient-specific preferences. The foundation for disease education is the medical consultation, and may be complemented by specific training programmes of healthcare professionals, patient charities, online, print or video material, as well as via telemedicine.[54]

D. Management of GCA and PMR should be based on shared decision making between the informed patient and the physician.

The vast majority of patients with GCA and PMR accept initial treatment given the sudden onset of symptoms and their significant impact on quality of life and daily activities. Once remission is achieved, 'coming off glucocorticoids' and 'living with glucocorticoids' become important aspects of the ongoing care for patients.[55] The maintenance of the target must, therefore, be discussed in light of emerging adverse consequences of treatment, particularly in the long term. Similarly, the possible advantages and disadvantages of different drugs and routes of administration need to be discussed with patients on an individual basis.

E. Treatment of GCA and PMR should aim at maximising health-related quality of life through control of symptoms, preventing disease-related damage and minimising treatment-related adverse consequences, taking relevant comorbidities into account.

The goal of maintaining health-related quality of life is common to several T2T recommendations, an outcome regarded as the highest value for patients.[13–15] Mortality is not increased in PMR,[56 57] whereas in GCA, patients have higher mortality, particularly at disease onset, most likely as a consequence of disease manifestations and adverse effects of intensive treatment.[58]

Among disease-related symptoms, patients pay particular attention to pain, stiffness, disability and fatigue.[48 59] In GCA, preservation of sight and integrity of other tissues potentially affected by vascular compromise are other fundamental aspects of maintaining a high quality of life.[36] Side effects from treatment, such as weight gain, bruising, skin atrophy, diabetes, infections, mood changes and muscle weakness, might gradually reduce the gains of quality of life achieved in early stages of disease management through suppression of inflammation.[51 60] Negative adverse consequences from treatment unfortunately cannot always be avoided, but should be minimised. Preventing overtreatment of GCA and PMR with GC, due to starting or maintenance dosages that are excessively high or for a period of time that is too long or by not considering GC sparing agents is an important additional goal. Even though several drugs may help to reduce the cumulative GC dose in both GCA and PMR, so far none have been proven to reduce GC-related adverse outcomes.[5 9 10 61 62] Common comorbidities such as osteoporosis, diabetes or cardiovascular disease also need to be considered, especially those that may be worsened by treatment and negatively impact health-related quality of life.[52 53]

Specific recommendations

Recommendation 1

The treatment target of GCA and PMR should be remission; remission is the absence of clinical symptoms and systemic inflammation.

This treatment target is similar to that of other T2T recommendations in rheumatology,[13–15] and frequently serves as an outcome in clinical trials and observational studies of GCA and PMR.[12 63] (Hysa *et al*, manuscript in preparation) The LoA was high, even though there was no evidence that remission performed better than any other treatment target (eg, absence of relapse, cumulative GC dose). (Hysa *et al*, manuscript in preparation) Remission is normally achieved rapidly with GC therapy, although a proportion of patients may be refractory and achieve only incomplete disease control.[64 65] The definition of an instrument to determine remission in GCA and PMR was beyond the scope of this project and is the subject of ongoing research. Several proposals to define remission have been made by international study groups and investigators of clinical trials. They most commonly include the absence of clinical symptoms related to GCA and/or PMR and the normalisation of acute phase reactants, particularly ESR and CRP.[12 63] The task force stipulated the term 'absence of systemic inflammation' to potentially also include other markers of disease activity such as imaging. While the role of imaging as an outcome variable or component of remission is still unclear, there is the increasing evidence that, at least in GCA, imaging-determined signs of activity might have an impact on future relapses and vascular damage.[66–68] The present statement, however, should not be understood as a recommendation to reach imaging remission and/or negative acute phase reactants at all costs, rather the achievement of the target should

be balanced against the potential burden from treatment-related adverse events.

Alternative treatment targets (such as low-disease activity in RA) need to be investigated further in PMR and GCA,[10 12] hence, this topic has been added to the research agenda.

Recommendation 2

Treatment of GCA should also aim to prevent tissue ischemia and vascular damage.

The prevention of tissue ischaemia and vascular damage was added as a specific treatment target even though this topic has been included in the overarching principles. There was some discussion among the task force whether the 'maintenance of tissue and vascular integrity' would be the more adequate target. However, the group ultimately came to the conclusion that this might be a too ambitious goal, given that, in an older patient population there might be several other factors not directly related to GCA such as atherosclerosis threatening the 'integrity' of organs and vessels. The clear objective in the management of GCA is the prevention of the sequelae from disease and long-term treatment.[36]

Prevention of vascular damage should, therefore, not only be understood as prevention of damage from GCA (eg, aortic aneurysms) but also as a prevention of macrovascular and microvascular damage associated with long-term GC therapy.[69–71] In this context, it is important to understand that progression of vascular damage, particularly aortic aneurysms, may also occur in patients in persistent clinical remission.[72] The pathogenic mechanisms triggering the progression of vessel wall destruction, as well as the possibilities to prevent, or at least halt these changes, require further study.

Recommendation 3

Treatment selection in GCA and PMR should be based on disease severity and activity, presence of relevant comorbidities and potential predictors of outcome; treatment should be modified as needed during follow-up.

Specific recommendations on the selection of individual medications or drug dosages have been made elsewhere and are not subject of the present work.[6–8] The task force acknowledged that several factors in addition to disease activity need to be considered in balancing treatment benefits against risks. A person with GCA suffering from visual symptoms, jaw claudication or other ischaemic manifestations may be considered to have more 'severe' disease than a patient with predominantly systemic symptoms without evidence of tissue or vascular damage (eg, PMR or constitutional symptoms only). Consequently, the former patient may require more intensive initial treatment than the latter. In patients without organ threatening manifestations, balanced decision making should take into account comorbidities, as well as predictors of disease outcomes that may influence the choice of therapy. The ACR/EULAR recommendations for PMR management list female sex, high acute phase reactants and peripheral arthritis as associated with an increased risk of relapse, and patients with these features warrant more intensive and longer treatment.[7 62] In GCA, patients with a high level of systemic inflammation at baseline, persistently increased inflammatory markers or imaging signs of inflammation, as well as those with predominant extracranial disease, tend to relapse more frequently than patients without these factors.[67 73] Hence, these patients may benefit in particular from early administration of GC sparing agents.

Assessing benefit versus risks of treatments should be performed continuously during the follow-up. While disease activity and severity might be the main drivers of treatment choice at disease outset, therapy-related side effects, comorbidities and predictors of outcome may play a more important role later in the disease course.[51]

Recommendation 4

Comorbidities may influence the assessment of the treatment target and should be considered before modifying treatment.

Both rheumatic (eg, rotator cuff disease, osteoarthritis of the shoulder or cervical spine, fibromyalgia) and non-rheumatic (eg, Parkinson's disease) causes of pain and stiffness influence the assessment of disease activity in PMR, particularly when clinical composite scores are used that may also be affected by these conditions.[74] In GCA, other causes of headache (eg, migraine, trigeminal neuralgia, tension headache) or visual disturbances need to be distinguished from GCA-related symptoms. Acute phase reactants are certainly helpful in these situations, but when patients are treated with IL-6 blocking agents, other markers of systemic inflammation need to be identified that help to better interpret patients' symptoms.[4 12] This aspect has been added to the research agenda.

Recommendation 5

Once remission is reached, it should be maintained with the minimal effective dose of medication; drug-free remission may be achieved in a proportion of patients.

The task force discussed whether the maintenance of remission, or rather, the prevention of a relapse should be the preferred treatment target. A relapse is often defined as reappearance of clinical symptoms and systemic inflammation that requires intensification of therapy.[12 63] However, patients with non-specific symptoms or increased inflammatory markers without another explanation than GCA or PMR are in a disease state that is neither remission nor relapse. The task force voted for the maintenance of remission as a relevant target in T2T assuming that patients would benefit in the long term by a better quality of life and prevention of vascular damage. The SLR, however, retrieved no evidence on this aspect of disease management, and therefore, this topic has been added to the research agenda. (Hysa *et al*, manuscript in preparation)

The task force further emphasised that patients should not be pushed to taper-off medication too quickly, a strategy that often results in relapse of disease. At the same time, the task force recognised that overtreatment should also be avoided. Achieving the minimal effective dose of medication is an important goal, and tapering-off GCs may have a higher priority than discontinuing disease modifying antirheumatic drugs (DMARDs), if both drugs are used in combination. However, no study has yet compared the benefits and risks of low-dose GCs (≤7.5 mg prednisone equivalent per day)[75] without DMARDs against DMARDs without GCs.

In a proportion of patients, drug-free remission may be achieved. In a trial of TCZ in GCA (GIACTA), for example, 22% of patients initially randomised to TCZ reached sustained drug-free remission after 156 weeks,[76] whereas in PMR, observational studies suggest that long-term drug-free remission can be achieved in 30%–60% of patients.[77–79] Tapering off treatment should always be balanced against the risk of worsening disease activity.[5 46 47]

Recommendation 6

Disease activity in GCA and PMR should be monitored regularly, as frequently as every 1–4 weeks until remission has been achieved, and at longer monitoring intervals (eg, between 3 and 6 months) in patients in stable remission on therapy; monitoring of patients off therapy should be discussed on an individual basis.

This recommendation is fully based on expert opinion given that evidence regarding monitoring intervals is absent. The monitoring timepoints recommended by the task force are more frequent than those suggested by the 2018 EULAR management recommendations for GCA and the 2015 ACR/EULAR management recommendations for PMR.[6 7] The task force was of the opinion that both new patients and patients with relapse should be monitored very closely to document therapeutic response, exclude disease mimics and to identify those with refractory disease in order to discuss possible treatment alternatives. The task force members made the experience that lack of resources is an important obstacle for a close follow-up of patients; however, this might be overcome by shared care between general practitioners and rheumatologists.

Once stable remission has been achieved, monitoring intervals may become longer; however, disease activity and particularly adverse consequences of treatment should be checked regularly. Whether all follow-up visits need to be face to face or can be replaced by telemedicine visits are issues that future research needs to clarify.

On successful discontinuation of therapy, people with PMR may be followed up in primary care only (on demand). In GCA, regular specialist visits (even at longer intervals) are advised since aortic aneurysms may occur even years after quiescent disease.[80 81] No consensus was found for monitoring the progression of vascular damage, therefore, this topic has been included in the research agenda.

Based on the discussions and the areas of uncertainty, a research agenda has been proposed, delineated in box 1.

Box 1 Research agenda

- ⇒ To develop evidence-based definitions of response, remission and relapse for GCA and PMR.
- ⇒ To develop a definition of refractory disease.
- ⇒ To develop a definition of vascular damage.
- ⇒ To work-out tools to adequately assess disease activity, disease activity states, patient-reported outcomes (including fatigue, health-related quality of life) and a health assessment questionnaire specific for GCA and PMR.
- ⇒ To conduct a study to compare a T2T strategy in GCA and PMR with conventional care.
- ⇒ To study whether the maintenance of remission is an equivalent treatment target to the prevention of relapse(s).
- ⇒ To assess the role of imaging as a treatment target and to investigate the significance of ongoing imaging signs of inflammation in patients in clinical remission.
- ⇒ To study the phenotype and outcome of people with PMR presenting with subclinical vasculitis.
- ⇒ To identify predictors of treatment response, damage, prognosis and course of disease, including the identification of genomic/proteomic predictors from blood and tissue.
- ⇒ To collect data on long-term follow-up, including imaging and laboratory data of people with GCA and/or PMR.
- ⇒ To study the best imaging modality for early detection and monitoring of vascular damage.
- ⇒ To define low disease activity in PMR and GCA and assess its value as an alternative treatment target.
- ⇒ To study the outcome of patients with persistently low disease activity (eg, low-grade vascular inflammation or slight elevation of acute phase reactants without another explanation) concerning long-term outcomes (damage and comorbidities).
- ⇒ To compare the outcomes of patients with low disease activity without treatment versus patients in remission on long-term low-dose therapy.
- ⇒ To study whether use of glucocorticoid (GC) sparing agents leads to a reduction in GC-related adverse outcomes.
- ⇒ To assess when and in whom treatments can be stopped once remission is achieved.
- ⇒ To investigate the relationship between patient-reported outcomes and disease activity in GCA and PMR.
- ⇒ To investigate the progression of structural damage using different treatments.
- ⇒ To define intervals and methods to monitor structural damage in GCA.
- ⇒ To study the temporal evolution of vascular damage in GCA: how quickly does damage occur; what are the effects of aortic involvement early in the disease as compared with (new) involvement in later stages?
- ⇒ To investigate the role of telemedicine as a tool for T2T in PMR/GCA.
- ⇒ To study different treatment strategies and their effect on mortality in GCA.
- ⇒ To investigate the difference between long-term remission and cure of disease.
- ⇒ To test the cost-effectiveness of a T2T strategy in GCA and PMR.

DISCUSSION

These are the first T2T recommendations in GCA and PMR developed by an international multidisciplinary task force complementing current management recommendations in the field. They provide guidance to clinicians on how to implement the T2T approach for GCA and PMR in clinical practice and emphasise the importance of balancing disease burden with unwanted effects of therapy and comorbidities. Furthermore, current gaps in evidence have been identified, and a research agenda has been formulated to provide guidance on how the gaps can be filled by future research.

With these recommendations, we aim to convey the T2T strategy to the broad medical community given that patients with GCA and PMR are not only treated in highly specialised centres, but also by community-based rheumatologists and other medical disciplines including general practitioners. Observational studies indicate that in GCA and PMR, several principles of T2T such as the selection of treatment according to disease severity/activity, consideration of relevant comorbidities, the maintenance of remission at the lowest possible dose of medication and adequate screening and management of comorbidities are not or insufficiently implemented in current clinical practice.[82–84] The present project was independent of, and is thus not officially endorsed by a major rheumatological society, however, this was originally also not the case for the RA or psoriatic arthritis/SpA-T2T activities, which were subsequently embraced by EULAR and other organisations.[85–88] The T2T-SLE recommendations were also developed by an international group without initial endorsement by major professional organisations.[15] The SLE community with its very heterogeneous views subsequently appreciated

the concept of pursuing a treatment target, and the publication of T2T in SLE was essential to stimulate activities in the field to better define treatment targets and management strategies.[89] We envision the inclusion of the T2T principle in future management recommendations in GCA and PMR, its implementation in routine clinical practice and ultimately, an improved quality of care resulting in a better long-term quality of life of patients with these diseases.

A study formally comparing the management of people with GCA and/or PMR according to a T2T principle with a strategy based on routine clinical care is still warranted. The task force notes that an evidenced-based definition of remission is absent, which is in contrast to the situation in many other rheumatic diseases.[13–16] There is an ongoing ACR/EULAR project to develop response criteria in GCA and in addition, OMERACT projects are currently underway to develop definitions of remission in GCA and PMR. Another important uncertainty is the role of imaging. Whether imaging-based absence of inflammation should be a treatment target, which imaging methodology should be used to monitor the disease or whether imaging should be a component of clinical remission are unclear so far. The assessment of disease activity in patients receiving IL-6 receptor inhibitors is another challenge given that these drugs directly suppress ESR and CRP and thus render these acute phase reactants unreliable as measures of disease activity. Evaluation of alternative markers of systemic inflammation is urgently needed, including alternative laboratory tests, such as osteopontin or serum calprotectin, as well as imaging.[90 91]

The question of whether telemedicine should play a role in patient management in addition to face-to-face visits remains open. During the COVID-19 pandemic, many people with GCA and PMR were followed by remote consultation rather than face-to-face evaluation, however, the role of this technique is unclear, once the pandemic is over.[92 93]

The main limitation of our recommendations is the low LoE supporting the individual statements. While a broader search would have identified more papers, the task force was of the opinion that if a study did not have an adequate control arm (which was the most important inclusion criterion in our SLR), the observed effects could not be attributed to the T2T strategy and would thus be uninformative. The research agenda is, therefore, an important product of this project hopefully stimulating further research in the field.

Despite the limited evidence, we expect these T2T recommendations contribute to high-quality clinical care in GCA and PMR. Unresolved issues and areas of further study are outlined in the research agenda. We anticipate that new developments in the management and assessment of disease states and outcomes will take place in the coming years, which will affect these recommendations and necessitate amending them.

Author affiliations
[1]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Medical University, Graz, Austria
[2]Rheumatology, Hospital of Bruneck (ASAA-SABES), Teaching Hospital of the Paracelsius Medical University, Brunico, Italy
[3]Abteilung für Rheumatologie, Medizinische Universitat Wien Universitatsklinik fur Innere Medizin III, Wien, Austria
[4]Department of Rheumatology, Medizinische Universität Wien, Wien, Austria
[5]Laboratory of Experimental Rheumatology and Academic Division of Clinical Rheumatology, University of Genoa, Genova, Italy
[6]Division of Rheumatology, Department of Medical Specialties, Azienda Sanitaria Locale 3 Genovese, Arenzano, Italy
[7]Department of Rheumatology and Clinical Immunology, Charite Medical Faculty Berlin, Berlin, Germany
[8]Rheumatology, Mayo Clinic, Jacksonville, Florida, USA
[9]Departamento de Clínica Médica. Facultade de Ciências Medicas da UNICAMP, Universidade Estadual de Campinas, Campinas, Brazil
[10]Department of Autoimmune Diseases, Hospital Clinic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain
[11]Rheumatology, Southend Hospital NHS Trust, Westcliff-on-sea, UK
[12]Department of Internal Medicine, Clinical Division of Internal Medicine II, Medical University Innsbruck, Innsbruck, Austria
[13]National Institutes of Health/NIAMS, Bethesda, Maryland, USA
[14]Klinik für Innere Medizin, Rheumatolgie und Immunologie, Medius Kliniken Kirchheim/Teck, University Tübingen, Kirchheim-Teck, Germany
[15]Department of Rheumatology, Universitiy Medical Centre, Ljubljana, Slovenia
[16]Medical Faculty, University of Ljubljana, Ljubljana, Slovenia
[17]Rheumatology, David Geffen School of Medicine, University of California, Los Angeles, California, USA
[18]Division of Rheumatology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA
[19]Ophthalmology, University Hospitals Birmingham, Birmingham, UK
[20]Neurometabolism, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK
[21]Patient Charity Polymyalgia Rheumatica and Giant Cell Arteritis Scotland, Nethy Bridge, UK
[22]Rheumatology, Centro Hospitalar Universitario Lisboa Norte EPE, Lisboa, Portugal
[23]Rheumatology Research Unit, Instituto de Medicina Molecular, Lisboa, Portugal
[24]Unit of Rheumatology, Azienda Unità Sanitaria Locale-IRCCS, Reggio Emilia, Italy
[25]Department of Surgery, Medicine, Dentistry and Morphological Sciences with Interest in Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy
[26]Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[27]Rheumatology, Immanuel Krankenhaus Berlin, Berlin-Buch, Berlin, Germany
[28]Rheumatology, Johns Hopkins University, Baltimore, Maryland, USA
[29]Rheumatology, Medical University of Vienna, Wien, Austria
[30]Clinic for Rheumatology and Clinical Immunology, University Hospital Freiburg, Faculty of Medicine, Freiburg, UK
[31]Reference Center in Osteoporosis, Rheumatology & Dermatology, Pontificia Universidad Javeriana Cali Facultad de Ciencias de la Salud, Cali, Colombia
[32]Rheumatology, Southend University Hospital, Southend, UK
[33]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany

Twitter Bhaskar Dasgupta @profbdasgupta, Cristina Ponte @cristinadbponte, Sebastian Eduardo Sattui @SattuiSEMD, Philip Seo @philseo and Carlos Enrique Toro-Gutiérrez @carlostororeuma

Acknowledgements The authors would like to thank Louise Falzon for her work in the development of the literature search strategy. We also thank Carol Maryman, Raashid Luqmani, Christian Mallen, Sara Monti, Sarah Mackie, John Stone, Ken Warrington, Mehrdad Maz, Rula Hajj-Ali, Robert Spiera, Christian Pagnoux, Elaine Yacyshyn, Catherine Hill, Alex W Hewitt and Eun-Bong Lee for critically revising the manuscript.

Contributors All authors were involved in the discussion and formulation of the recommendations. CDe wrote the first version of the manuscript. All authors reviewed it and made extensive comments and appropriate changes to it. All authors approved the final version of the manuscript.

Funding Funding was provided by AbbVie (ISM-51500).

Competing interests CDe has received consulting/speaker's fees from Abbvie, Eli Lilly, Janssen, Novartis, Pfizer, Sparrow, Roche, Galapagos and Sanofi, all unrelated to this manuscript. He is an editorial board member of ARD. AK has received consultancy fees, honoraria and travel expenses from AbbVie, Amgen, Bristol-Myers Squibb, Eli Lilly, Gilead, Janssen, Merck Sharp and Dohme, Novartis, UCB and Pfizer, all unrelated to this manuscript. He is an editorial board member of ARD. DA received grants, speaker fees, and/or consultancy fees from Abbvie, Amgen, Galapagos, Lilly, Janssen, Merck, Novartis, Pfizer, Sandoz and Sanofi. He is an editorial board member of ARD. MB has received consulting fees from AbbVie. DC has received speaker fees from Abiogen, BMS and GSK. MCC received consultancy and/or speaker fees from GSK, Vifor, Abbvie, Astra Zeneca and Janssen and a research grant form Kiniksa Pharmaceuticals. BD has received consultancies from Novartis, Abbvie, Roche and speaker agreements from Chugai. CDu has received consultancy or speaker fees and travel expenses from Abbvie, AOP Orphan, Astra-Zeneca, Bristol-Myers-Squibb, Eli-Lilly, Janssen, Galapagos, Merck-Sharp-Dohme, Novartis, Pfizer, Roche, Sandoz, UCB, Vifor and research support by Eli-Lilly, Pfizer, UCB, all unrelated to this manuscript. BH received speaker fees and/or consultancies from Abbvie, Amgen, Astra-Zeneca, BMS, Boehringer, Chugai, GSK, InflaRx, Janssen, MSD, Pfizer, Novartis, Phadia, Roche and Vifor. ELM has received consulting fees from Boehringer-Ingelheim, Horizon Therapeutics, Alvotech Inc; speaker fees from Boehringer-Ingelheim; royalties from UpToDate. SPM has received consultancy fees

(Invex Therapeutics); advisory board fees (Invex therapeutics; Gensight) and speaker fees (Heidelberg engineering; Chugai-Roche Ltd; Allergan; Santen; Teva UK; Chiesi; and Santhera). All unrelated to this manuscript. LN has received consulting fees from AbbVie. CP is or has been the principal investigator of studies by AbbVie, Sanofi and Novartis and has received consulting/speaker's fees from Vifor, AstraZeneca, GlaxoSmithKline and Roche, all unrelated to this manuscript. CS has received consultancy fees from Abbvie, Boehringer-Ingelheim, Eli Lilly, Galapagos, Novartis, Pfizer and Roche and royalties from UpToDate. All unrelated to this manuscript. SES has received research support by Astra-Zeneca and has done provided unpaid consultancy for Sanofi. SES is supported by the Rheumatology Research Foundation RISE pilot award and Bristol Myers Squibb Foundation Robert A Winn Diversity in Clinical Trials Career Development Award, outside of the submitted work. WAS has received consultancy fees, honoraria and travel expenses from Abbvie, Amgen, Bristol-Myers Squibb, Chugai, GlaxoSmithKline, Johnson & Johnson, Medac, Novartis, Roche, and Sanofi and is principal investigator in trials sponsored by Abbvie, Amgen, GlaxoSmithKline, Novartis, Roche and Sanofi. PS has received consultancy fees from Amgen and Janssen and royalties from UpToDate, all unrelated to this manuscript. JSS received grants to his institution from Abbvie, AstraZeneca, Lilly, Novartis and Roche and provided expert advice for, or had symposia speaking engagements with, AbbVie, Amgen, AstraZeneca, Astro, Bristol-Myers Squibb, Celltrion, Chugai, Gilead, Janssen, Lilly, Merck Sharp & Dohme, Novartis-Sandoz, Pfizer, R-Pharm, Roche, Samsung, Sanofi and UCB. He is the editor in chief of ARD. JT has received consultancy or speaker fees Bristol-Myers-Squibb, Novartis, Glaxo-Smith-Kline, Astra-Zeneca, Janssen, Abbvie, Eli-Lilly. All unrelated to this manuscript. CET-G has received consultancy fees, honoraria and travel expenses from Abbvie, BMS, Boehringer Ingelheim, Biopas, Janssen, Pfizer, Pharmalab, Roche, all unrelated to this manuscript. FB has received consultancy fees, honoraria and travel expenses from Abbvie, Novartis, Pfizer, Roche and Sanofi, all unrelated to this manuscript. He is an editorial board member of ARD. EH, LE, AA, SA, PCG, AH, TAK and MW declare no competing interests.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Christian Dejaco http://orcid.org/0000-0002-0173-0668
Andreas Kerschbaumer http://orcid.org/0000-0002-6685-8873
Daniel Aletaha http://orcid.org/0000-0003-2108-0030
Milena Bond http://orcid.org/0000-0002-5400-2955
Dario Camellino http://orcid.org/0000-0001-6384-6458
Lisa Ehlers http://orcid.org/0000-0001-8737-001X
Maria C Cid http://orcid.org/0000-0002-4730-0938
Bhaskar Dasgupta http://orcid.org/0000-0002-5523-6534
Christina Duftner http://orcid.org/0000-0003-3137-8834
Peter C Grayson http://orcid.org/0000-0002-8269-9438
Bernhard Hellmich http://orcid.org/0000-0002-8014-1801
Alojzija Hočevar http://orcid.org/0000-0002-7361-6549
Tanaz A Kermani http://orcid.org/0000-0002-7335-7321
Eric L Matteson http://orcid.org/0000-0002-9866-0124
Cristina Ponte http://orcid.org/0000-0002-3989-1192
Carlo Salvarani http://orcid.org/0000-0003-3708-3148
Sebastian Eduardo Sattui http://orcid.org/0000-0002-3945-6828
Wolfgang A Schmidt http://orcid.org/0000-0001-7831-8738
Josef S Smolen http://orcid.org/0000-0002-4302-8877
Carlos Enrique Toro-Gutiérrez http://orcid.org/0000-0002-6084-7049
Frank Buttgereit http://orcid.org/0000-0003-2534-550X

REFERENCES

1 Buttgereit F, Dejaco C, Matteson EL, *et al*. Polymyalgia rheumatica and giant cell arteritis: a systematic review. *JAMA* 2016;315:2442–58.
2 Dejaco C, Brouwer E, Mason JC, *et al*. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. *Nat Rev Rheumatol* 2017;13:578–92.
3 Dejaco C, Duftner C, Buttgereit F, *et al*. The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. *Rheumatology (Oxford)* 2017;56:506–15.
4 Camellino D, Matteson EL, Buttgereit F, *et al*. Monitoring and long-term management of giant cell arteritis and polymyalgia rheumatica. *Nat Rev Rheumatol* 2020;16:481–95.
5 Stone JH, Tuckwell K, Dimonaco S, *et al*. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017;377:317–28.
6 Hellmich B, Agueda A, Monti S, *et al*. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2020;79:19–30.
7 Dejaco C, Singh Y, Perel P, *et al*. Recommendations for the management of polymyalgia rheumatica: a European league against rheumatism/American college of rheumatology collaborative initiative. *Ann Rheum Dis* 2015;74:2569–80.
8 Maz M, Chung SA, Abril A, *et al*. 2021 American college of rheumatology/vasculitis foundation guideline for the management of giant cell arteritis and takayasu arteritis. *Arthritis Rheumatol* 2021;73:1349–65.
9 Bonelli M, Radner H, Kerschbaumer A, *et al*. Tocilizumab in patients with new onset polymyalgia rheumatica (PMR-SPARE): a phase 2/3 randomised controlled trial. *Ann Rheum Dis* 2022;81:838–44.
10 Devauchelle-Pensec V, Carvajal-Alegria G, Dernis E, *et al*. Effect of tocilizumab on disease activity in patients with active polymyalgia rheumatica receiving glucocorticoid therapy: a randomized clinical trial. *JAMA* 2022;328:1053–62.
11 Dasgupta B, Unizony S, Warrington KJ, *et al*. LB0006 SARILUMAB in patients with relapsing polymyalgia rheumatica: a phase 3, multicenter, randomized, double blind, placebo controlled trial (SAPHYR). *Ann Rheum Dis* 2022;81:210.
12 Camellino D, Dejaco C, Buttgereit F, *et al*. Treat to target: a valid concept for management of polymyalgia rheumatica and giant cell arteritis? *Rheum Dis Clin North Am* 2019;45:549–67.
13 Smolen JS, Braun J, Dougados M, *et al*. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis* 2014;73:6–16.
14 Smolen JS, Breedveld FC, Burmester GR, *et al*. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3–15.
15 van Vollenhoven RF, Mosca M, Bertsias G, *et al*. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014;73:958–67.
16 Kiltz U, Smolen J, Bardin T, *et al*. Treat-to-target (T2T) recommendations for gout. *Ann Rheum Dis* 2017;76:632–8.
17 Smolen JS, Aletaha D, Bijlsma JWJ, *et al*. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631–7.
18 Grigor C, Capell H, Stirling A, *et al*. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364:263–9.
19 Verstappen SMM, Jacobs JWG, van der Veen MJ, *et al*. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. computer assisted management in early rheumatoid arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007;66:1443–9.
20 Coates LC, Moverley AR, McParland L, *et al*. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015;386:2489–98.
21 Molto A, López-Medina C, Van den Bosch FE, *et al*. Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. *Ann Rheum Dis* 2021;80:1436–44.
22 van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
23 Downes MJ, Brennan ML, Williams HC, *et al*. Development of a critical appraisal tool to assess the quality of cross-sectional studies (axis). *BMJ Open* 2016;6:e011458.
24 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
25 Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
26 EULAR. Voting-procedures on EULAR recommendations. 2019 Available: https://www.eular.org/myUploadData/files/voting_eular_recos_approved_exc_june_2019_web.pdf
27 OCEBM Levels of Evidence Working Group. The oxford 2011 levels of evidence. 2011. Available: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence
28 Muratore F, Boiardi L, Restuccia G, *et al*. Relapses and long-term remission in large vessel giant cell arteritis in northern italy: characteristics and predictors in a long-term follow-up study. *Semin Arthritis Rheum* 2020;50:549–58.
29 Rehak Z, Vasina J, Nemec P, *et al*. Various forms of (18) F-FDG PET and PET/CT findings in patients with polymyalgia rheumatica. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2015;159:629–36.
30 Gentil AF, Lopes AC, Dougherty DD, *et al*. Hoarding symptoms and prediction of poor response to limbic system surgery for treatment-refractory obsessive-compulsive disorder. *J Neurosurg* 2014;121:123–30.

31 Blockmans D, De Ceuninck L, Vanderschueren S, *et al*. Repetitive 18-fluorodeoxyglucose positron emission tomography in isolated polymyalgia rheumatica: a prospective study in 35 patients. *Rheumatology (Oxford)* 2007;46:672–7.
32 Barraclough K, Liddell WG, du Toit J, *et al*. Polymyalgia rheumatica in primary care: a cohort study of the diagnostic criteria and outcome. *Fam Pract* 2008;25:328–33.
33 Helliwell T, Muller S, Hider SL, *et al*. Challenges of diagnosis and management of giant cell arteritis in general practice: a multimethods study. *BMJ Open* 2018;8:e019320.
34 Patil P, Williams M, Maw WW, *et al*. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. *Clin Exp Rheumatol* 2015;33:S103–6.
35 Diamantopoulos AP, Haugeberg G, Lindland A, *et al*. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: towards a more effective strategy to improve clinical outcome in giant cell arteritis? *Rheumatology (Oxford)* 2016;55:66–70.
36 Ní Mhéalóid Á, Conway R, O'Neill L, *et al*. Vision-related and health-related quality of life in patients with giant cell arteritis. *Eur J Ophthalmol* 2021;31:727–33.
37 González-Gay MA, Blanco R, Rodríguez-Valverde V, *et al*. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. *Arthritis Rheum* 1998;41:1497–504.
38 Cid MC, Font C, Oristrell J, *et al*. Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. *Arthritis Rheum* 1998;41:26–32.
39 Dejaco C, Ramiro S, Duftner C, *et al*. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018;77:636–43.
40 Pinnell J, Tiivas C, Mehta P, *et al*. Corticosteroids reduce vascular ultrasound sensitivity in fast- track pathways (FTP): results from coventry multi-disciplinary FTP for cranial giant cell arteritis. *Scand J Rheumatol* 2022:1–10.
41 Melville AR, Donaldson K, Dale J, *et al*. Validation of the southend giant cell arteritis probability score in a Scottish single-centre fast-track pathway. *Rheumatol Adv Pract* 2022;6:rkab102.
42 Oshinsky C, Bays AM, Sacksen I, *et al*. Vascular ultrasound for giant cell arteritis: establishing a protocol using vascular sonographers in a fast-track clinic in the United States. *ACR Open Rheumatol* 2022;4:13–8.
43 Frølund LL, Våben C, Dam M, *et al*. Fast track clinic for early diagnosis of polymyalgia rheumatica: impact on symptom duration and prednisolone initiation. *Joint Bone Spine* 2021;88:105185.
44 Narváez J, Estrada P, López-Vives L, *et al*. Prevalence of ischemic complications in patients with giant cell arteritis presenting with apparently isolated polymyalgia rheumatica. *Semin Arthritis Rheum* 2015;45:328–33.
45 Hernández-Rodríguez J, Font C, García-Martínez A, *et al*. Development of ischemic complications in patients with giant cell arteritis presenting with apparently isolated polymyalgia rheumatica. *Medicine* 2007;86:233–41.
46 Mainbourg S, Addario A, Samson M, *et al*. Prevalence of giant cell arteritis relapse in patients treated with glucocorticoids: a meta-analysis. *Arthritis Care Res (Hoboken)* 2020;72:838–49.
47 Floris A, Piga M, Chessa E, *et al*. Long-term glucocorticoid treatment and high relapse rate remain unresolved issues in the real-life management of polymyalgia rheumatica: a systematic literature review and meta-analysis. *Clin Rheumatol* 2022;41:19–31.
48 Prior JA, Muller S, Helliwell T, *et al*. The association of pain and stiffness with fatigue in incident polymyalgia rheumatica: baseline results from the polymyalgia rheumatica cohort study. *Prim Health Care Res Dev* 2019;20:e46.
49 Stone JH, Tuckwell K, Dimonaco S, *et al*. Glucocorticoid dosages and acute-phase reactant levels at giant cell arteritis flare in a randomized trial of tocilizumab. *Arthritis Rheumatol* 2019;71:1329–38.
50 Aussedat M, Lobbes H, Samson M, *et al*. Epidemiology of major relapse in giant cell arteritis: a study-level meta-analysis. *Autoimmun Rev* 2022;21:102930.
51 Hoon E, Ruediger C, Gill TK, *et al*. A qualitative study of patient perspectives related to glucocorticoid therapy in polymyalgia rheumatica and giant cell arteritis. *Open Access Rheumatol* 2019;11:189–98.
52 Partington R, Helliwell T, Muller S, *et al*. Comorbidities in polymyalgia rheumatica: a systematic review. *Arthritis Res Ther* 2018;20:258.
53 Gale S, Wilson JC, Chia J, *et al*. Risk associated with cumulative oral glucocorticoid use in patients with giant cell arteritis in real-world databases from the USA and UK. *Rheumatol Ther* 2018;5:327–40.
54 de Thurah A, Bosch P, Marques A, *et al*. 2022 EULAR points to consider for remote care in rheumatic and musculoskeletal diseases. *Ann Rheum Dis* 2022;81:1065–71.
55 Gilbert K. Polymyalgia rheumatica and giant cell arteritis: a survival guide. Amazon Digital Services; 2014. Available: http://www.amazon.com/Polymyalgia-Rheumatica-Giant-Cell-Arteritis-ebook/dp/B00IJJBXS2/ref=sr_1_3?ie=UTF8&qid=1397063656&sr=8-3&keywords=gilbert+kate [Accessed 9 Apr 2014].
56 Raheel S, Shbeeb I, Crowson CS, *et al*. Epidemiology of polymyalgia rheumatica 2000-2014 and examination of incidence and survival trends over 45 years: a population-based study. *Arthritis Care Res (Hoboken)* 2017;69:1282–5.
57 Partington R, Muller S, Mallen CD, *et al*. Mortality among patients with polymyalgia rheumatica: a retrospective cohort study. *Arthritis Care Res (Hoboken)* 2021;73:1853–7.
58 Therkildsen P, Nielsen BD, de Thurah A, *et al*. All-cause and cause-specific mortality in patients with giant cell arteritis: a nationwide, population-based cohort study. *Rheumatology (Oxford)* 2022;61:1195–203.
59 Twohig H, Mitchell C, Mallen C, *et al*. "I suddenly felt I'd aged": a qualitative study of patient experiences of polymyalgia rheumatica (PMR). *Patient Educ Couns* 2015;98:645–50.
60 de Boysson H, Barakat C, Dumont A, *et al*. Tolerance of glucocorticoids in giant cell arteritis: a study of patient-reported adverse events. *Rheumatology (Oxford)* 2022;61:3567–75.
61 Mahr AD, Jover JA, Spiera RF, *et al*. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum* 2007;56:2789–97.
62 Dejaco C, Singh YP, Perel P, *et al*. Current evidence for therapeutic interventions and prognostic factors in polymyalgia rheumatica: a systematic literature review Informing the 2015 European League against rheumatism/american college of rheumatology recommendations for the management of polymyalgia rheumatica. *Ann Rheum Dis* 2015;74:1808–17.
63 Dejaco C, Duftner C, Cimmino MA, *et al*. Definition of remission and relapse in polymyalgia rheumatica: data from a literature search compared with a delphi-based expert consensus. *Ann Rheum Dis* 2011;70:447–53.
64 Dasgupta B, Cimmino MA, Maradit-Kremers H, *et al*. 2012 provisional classification criteria for polymyalgia rheumatica: a European League against rheumatism/American college of rheumatology collaborative initiative. *Ann Rheum Dis* 2012;71:484–92.
65 Liozon E, Dumonteil S, Parreau S, *et al*. Risk profiling for a refractory course of giant cell arteritis: the importance of age and body weight: "risk profiling for GC resistance in GCA." *Semin Arthritis Rheum* 2020;50:1252–61.
66 Quinn KA, Dashora H, Novakovich E, *et al*. Use of 18F-fluorodeoxyglucose positron emission tomography to monitor tocilizumab effect on vascular inflammation in giant cell arteritis. *Rheumatology (Oxford)* 2021;60:4384–9.
67 Grayson PC, Alehashemi S, Bagheri AA, *et al*. 18 f-fluorodeoxyglucose-positron emission tomography as an imaging biomarker in a prospective, longitudinal cohort of patients with large vessel vasculitis. *Arthritis Rheumatol* 2018;70:439–49.
68 Quinn KA, Ahlman MA, Alessi HD, *et al*. Association of 18 f-fluorodeoxyglucose-positron emission tomography activity with angiographic progression of disease in large vessel vasculitis. *Arthritis Rheumatol* 2023;75:98–107.
69 Therkildsen P, de Thurah A, Nielsen BD, *et al*. Increased risk of thoracic aortic complications among patients with giant cell arteritis: a nationwide, population-based cohort study. *Rheumatology (Oxford)* 2022;61:2931–41.
70 Robson JC, Kiran A, Maskell J, *et al*. Which patients with giant cell arteritis will develop cardiovascular or cerebrovascular disease? A clinical practice research datalink study. *J Rheumatol* 2016;43:1085–92.
71 Li L, Neogi T, Jick S. Giant cell arteritis and vascular disease-risk factors and outcomes: a cohort study using UK clinical practice research Datalink. *Rheumatology (Oxford)* 2017;56:753–62.
72 García-Martínez A, Arguis P, Prieto-González S, *et al*. Prospective long term follow-up of a cohort of patients with giant cell arteritis screened for aortic structural damage (aneurysm or dilatation). *Ann Rheum Dis* 2014;73:1826–32.
73 Monti S, Águeda AF, Luqmani RA, *et al*. Systematic literature review Informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis: focus on giant cell arteritis. *RMD Open* 2019;5:e001003.
74 Halilloglu S, Carlioglu A, Akdeniz D, *et al*. Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity. *Rheumatol Int* 2014;34:1275–80.
75 van der Goes MC, Jacobs JWG, Boers M, *et al*. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. *Ann Rheum Dis* 2010;69:1913–9.
76 Stone JH, Han J, Aringer M, *et al*. Long-term effect of tocilizumab in patients with giant cell arteritis: open-label extension phase of the giant cell arteritis actemra (giacta) trial. *Lancet Rheumatol* 2021;3:e328–36.
77 Marsman DE, den Broeder N, Boers N, *et al*. Polymyalgia rheumatica patients with and without elevated baseline acute phase reactants: distinct subgroups of polymyalgia rheumatica? *Clin Exp Rheumatol* 2021;39:32–7.
78 Okazaki S, Watanabe R, Kondo H, *et al*. High relapse rate in patients with polymyalgia rheumatica despite the combination of immunosuppressants and prednisolone: a single center experience of 89 patients. *Tohoku J Exp Med* 2020;251:125–33.
79 Hattori K, Hirano Y, Kojima T. Predictors of glucocorticoid-free remission in patients with polymyalgia rheumatica treated with prednisolone. *Int J Rheum Dis* 2020;23:1581–6.
80 Gonzalez-Gay MA, Garcia-Porrua C, Piñeiro A, *et al*. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from northwestern Spain: a population-based study. *Medicine (Baltimore)* 2004;83:335–41.
81 Jud P, Verheyen N, Dejaco C, *et al*. Prevalence and prognostic factors for aortic dilatation in giant cell arteritis-a longitudinal study. *Semin Arthritis Rheum* 2021;51:911–8.
82 Albrecht K, Huscher D, Buttgereit F, *et al*. Long-term glucocorticoid treatment in patients with polymyalgia rheumatica, giant cell arteritis, or both diseases: results from a national rheumatology database. *Rheumatol Int* 2018;38:569–77.

83 Therkildsen P, de Thurah A, Hansen IT, *et al*. Giant cell arteritis: a nationwide, population-based cohort study on incidence, diagnostic imaging, and glucocorticoid treatment. *Semin Arthritis Rheum* 2021;51:360–6.
84 Sokhal BS, Hider SL, Paskins Z, *et al*. Fragility fractures and prescriptions of medications for osteoporosis in patients with polymyalgia rheumatica: results from the PMR cohort study. *Rheumatol Adv Pract* 2021;5:rkab094.
85 Fraenkel L, Bathon JM, England BR, *et al*. 2021 American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2021;73:924–39.
86 Smolen JS, Landewé RBM, Bergstra SA, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023;82:3–18.
87 Ramiro S, Nikiphorou E, Sepriano A, *et al*. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis* 2023;82:19–34.
88 Gossec L, Baraliakos X, Kerschbaumer A, *et al*. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;79:700.
89 van Vollenhoven RF, Bertsias G, Doria A, *et al*. 2021 DORIS definition of remission in SLE: final recommendations from an international task force. *Lupus Sci Med* 2021;8:e000538.
90 Prieto-González S, Terrades-García N, Corbera-Bellalta M, *et al*. Serum osteopontin: a biomarker of disease activity and predictor of relapsing course in patients with giant cell arteritis. Potential clinical usefulness in tocilizumab-treated patients. *RMD Open* 2017;3:e000570.
91 van Sleen Y, Sandovici M, Abdulahad WH, *et al*. Markers of angiogenesis and macrophage products for predicting disease course and monitoring vascular inflammation in giant cell arteritis. *Rheumatology (Oxford)* 2019;58:1383–92.
92 Dejaco C, Alunno A, Bijlsma JW, *et al*. Influence of COVID-19 pandemic on decisions for the management of people with inflammatory rheumatic and musculoskeletal diseases: a survey among EULAR countries. *Ann Rheum Dis* 2021;80:518–26.
93 Mackie SL, Brouwer E, Conway R, *et al*. Clinical pathways for patients with giant cell arteritis during the COVID-19 pandemic: an international perspective. *Lancet Rheumatol* 2021;3:e71–82.