2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative


ABSTRACT
Therapy for polymyalgia rheumatica (PMR) varies widely in clinical practice as international recommendations for PMR treatment are not currently available. In this paper, we report the 2015 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) recommendations for the management of PMR. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology as a framework for the project. Accordingly, the direction and strength of the recommendations are based on the quality of evidence, the balance between desirable and undesirable effects, patients' and clinicians' values and preferences, and resource use. Eight overarching principles and nine specific recommendations were developed covering several aspects of PMR, including basic and follow-up investigations of patients under treatment, risk factor assessment, medical access for patients and specialist referral, treatment strategies such as initial glucocorticoid (GC) doses and subsequent tapering regimens, use of intramuscular GCs and disease modifying anti-rheumatic drugs (DMARDs), as well as the roles of non-steroidal anti-rheumatic drugs and non-pharmacological interventions. These recommendations will inform primary, secondary and tertiary care physicians about an international consensus on the management of PMR. These recommendations should serve to inform clinicians about best practices in the care of patients with PMR.

INTRODUCTION
There are wide variations in the treatment of polymyalgia rheumatica (PMR) with respect to glucocorticoid (GC) dosages, tapering strategies, use of disease modifying anti-rheumatic drugs (DMARDs) and duration of treatment. Up to 29–45% of patients with PMR do not adequately respond to GCs within 3–4 weeks. Relapses and long-term GC dependency are common.1–4 GC side effects are frequently observed, occurring in around 50% of patients, and present a further challenge.5 Well considered, international recommendations can serve to standardise practice and improve patient care.

Primary objective of the recommendations
These recommendations are intended for the management of patients with PMR in various settings and are based on clinical evidence and expert opinion including informed patient decision-making.

Target population
The target population are patients with PMR based on clinician diagnosis which may be supported by

Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient’s individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. The American College of Rheumatology is an independent, professional, medical and scientific society which does not guarantee, warrant, or endorse any commercial product or service.
currently available diagnostic or classification criteria. Management of PMR with concomitant giant cell arteritis (GCA), rheumatoid arthritis (RA) or other conditions that present with PMR features or mimic PMR is not addressed by these recommendations.

Target users
The target users of these recommendations are primary, secondary and tertiary care physicians (that is, general practitioners (GPs), specialists in general (internal) medicine and rheumatologists).

METHODS
For a detailed description of methods, see online supplementary file S1.

In brief, we used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology as a framework.12–15 We formulated 12 PICO (problem/ population, intervention, comparison, and outcome) questions on interventions and 10 questions on prognostic factors (see online supplementary box S1A and S1B, or the accompanying paper by Dejaco et al16). The systematic literature review (SLR) was conducted by two investigators (CD and YPS) using Ovid MEDLINE, Embase, PubMed, CINAHL, Web of Science and the Cochrane Library databases (from January 1970 until April 2014), and applying the thesauri of PMR, text words, abbreviations and truncated text words. Outcome parameters used in the SLR may be found in supplementary box S2. Quality appraisal of interventional and prognostic studies was performed using GRADE17–18 and the Quality in Prognostic Studies (QUIPS) tool,19 respectively. According to GRADE methodology, a guideline panel should consider the following aspects when formulating recommendations: (1) overall quality of evidence; (2) balance between desirable and undesirable effects; (3) patients’ and clinicians’ values and preferences; and (4) resource use. External evidence (from other American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) recommendations; see online supplementary table S1 for details) on safety aspects related to the use of non-steroidal anti-inflammatory drugs (NSAIDs), GCs and methotrexate (MTX) was taken into account as indirect evidence, in order to identify the optimal trade-off between the benefit and harm of interventions. Prognostic factors were used to build subgroups and to adapt the recommendations based on the presence or absence of unfavourable prognostic factors. Final recommendations were either ‘in favour’ or ‘against’ an intervention, and were graded as ‘conditional’ or ‘strong’. A strong recommendation in favour (against) was considered when the panel was certain that benefits did (did not) outweigh risks and burdens, the preferences/values of patients were met (not met) and resource use was reasonable (unreasonably high). If uncertainty existed, a conditional recommendation was made.

RESULTS
The results of the SLR are reported in a separate manuscript.16 See online supplementary file S2 for a summary of the SLR and external evidence considered by the guideline panel.

General aspects
These recommendations should be understood as clinical advice and do not dictate the care of a particular patient. The EULAR and ACR consider adherence to these recommendations to be voluntary, with the physician making the ultimate decision to apply them in light of each patient’s individual circumstances.

Overarching principles for the management of PMR
The group agreed upon several principles deemed to be fundamental aspects of clinical care in PMR as detailed in box 1. These principles have not directly resulted from the SLR, but are consensus based. They are intended as a framework for the implementation of the specific treatment recommendations and are of a general ‘overarching’ nature, a concept adapted from earlier EULAR recommendations.20–22

Specific recommendations
See box 1 for a summary of the recommendations. A flow-chart for the management of PMR patients is depicted in figure 1.

Recommendation 1: (PICO 1) The panel strongly recommends using GCs instead of NSAIDs in patients with PMR, with the exception of possible short-term use of NSAIDs and/or analgesics in PMR patients with pain related to other conditions (eg, co-existing osteoarthritis). No specific recommendation can be made for analgesics.

Explanation: The group recommends strongly against the use of NSAIDs compared to GCs in the treatment of PMR since the relative harm of long-term NSAID use (as mainly indicated by external evidence) outweighs the possible small benefits in PMR. No specific recommendation can be made for analgesics. On a basis of consensus, the panel recognised that the short-term use of NSAIDs and/or analgesics may be necessary in the setting of pain related to conditions other than PMR.

Recommendation 2: (PICO 2) The panel strongly recommends using the minimum effective individualised duration of GC therapy in PMR patients.

A more specific recommendation is not possible due to the lack of published evidence on this issue. On a basis of consensus and in accordance with the overarching principles, the group unanimously agreed to choose the minimum effective individualised duration and dose of GCs to balance benefit versus harm after assessing risk factors for GC-related adverse events, comorbidities, concomitant medications, relapses and prolonged therapy. Our recommended GC tapering schedule (see Recommendation 4) assumes a minimum of 12 months of treatment. A more specific statement is not possible because of the lack of PMR studies on this particular topic and because of the multiple subgroups and factors that need to be taken into account.

Recommendation 3: (PICO 3–5) The panel conditionally recommends using the minimum effective GC dose within a range of 12.5–25 mg prednisone equivalent daily as the initial treatment of PMR. A higher initial prednisone dose within this range may be considered in patients with a high risk of relapse and low risk of adverse events, whereas in patients with relevant comorbidities (eg, diabetes, osteoporosis, glaucoma, etc) and other risk factors for GC-related side effects, a lower dose may be preferred. The panel discourages conditionally the use of initial doses ≤7.5 mg/day and strongly recommends against the use of initial doses ≥30 mg/day.

According to the SLR on prognostic factors and based on clinical experience, the group agreed upon the existence of various PMR subgroups that are characterised by different risks of relapse, prolonged GC therapy and/or GC-related adverse events as well as by various comorbidities and co-medications. As there are insufficient data to make evidence-based recommendations for all conceivable subgroups, and taking current clinical practice into account,28–30 the panel agreed upon the use of the minimum effective GC dose out of a range of 12.5–25 mg prednisone equivalent daily balancing benefits versus...
Box 1  Summary of the 2015 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) recommendations for the management of polymyalgia rheumatica (PMR)

Target population:
Patients with PMR based on clinician diagnosis which may be supported by currently available diagnostic or classification criteria.\(^3\)\(^4\)\(^7\)–\(^11\)

Overarching principles for the management of PMR:

A. Adoption of a safe and specific approach to ascertain the PMR case definition. The clinical evaluation should be directed towards exclusion of relevant mimicking (eg, non-inflammatory, inflammatory such as giant cell arteritis or rheumatoid arthritis), drug-induced, endocrine, infective and neoplastic) conditions.

B. Every case of PMR should have the following assessments prior to the prescription of therapy (primary or secondary care):

- Documentation of a basic laboratory dataset. This will help to exclude mimicking conditions and establish a baseline for monitoring of therapy. This should include rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies (ACPA), C-reactive protein and/or erythrocyte sedimentation rate (ESR), blood count, glucose, creatinine, liver function tests, bone profile (including calcium, alkaline phosphatase) and dipstick urinalysis. Additional investigations to consider are protein electrophoresis, thyroid stimulating hormone (TSH), creatine kinase and vitamin D.

- Depending on clinical signs and symptoms and the likelihood of the alternative diagnoses, additional more extensive serological tests such as anti-nuclear antibodies (ANA), anti-cytoplasmic neutrophil antibodies (ANCA) or tuberculosis tests may be performed to exclude mimicking conditions. Additional investigations such as chest radiographs may be considered at the discretion of the physician in order to exclude other diagnoses.

- Determination of comorbidities (particularly hypertension, diabetes, glucose intolerance, cardiovascular disease, dyslipidaemia, peptic ulcer, osteoporosis (and particularly recent fractures), presence of cataract or (risk factors for) glaucoma, presence of chronic or recurrent infections, and co-medication with non-steroidal anti-inflammatory drugs (NSAIDs) as outlined in Smolen et al\(^13\) and Gossec et al\(^22\) other relevant medications and risk factors for steroid-related side effects. Female sex was associated with a higher risk of glucocorticoid (GC) side effects in low to moderate quality studies.\(^23\)–\(^25\)

- The role of risk factors for relapse/prolonged therapy is not clear yet. Baseline factors that were associated in low to moderate quality studies with a higher relapse rate and/or prolonged therapy in PMR studies were: female sex,\(^24\)\(^26\) high ESR (>40 mm/1st hour)\(^26\)–\(^28\) and peripheral inflammatory arthritis.\(^32\) A number of equally low to moderate quality studies, however, failed to demonstrate an association between these factors and relapse/prolonged therapy.

C. Consideration of specialist referral, particularly in case of atypical presentation (such as peripheral inflammatory arthritis, systemic symptoms, low inflammatory markers, age <60 years), experience of or high risk of therapy-related side effects, PMR refractory to GC therapy, and/or relapses/prolonged therapy.

D. Treatment of PMR patients should aim at the best care and must be based on a shared decision between the patient and the treating physician.

E. Patients should have an individualised PMR management plan. Patient perspective and preferences should be considered in the individualised choice of initial GC dose and subsequent tapering of GCs in PMR.

F. Patients should have access to education focusing on the impact of PMR and treatment (including comorbidities and disease predictors) and advice on individually tailored exercise programmes.

G. Every patient treated for PMR in primary or secondary care should be monitored with the following assessments: risk factors and evidence for steroid-related side effects, comorbidities, other relevant medications, evidence and risk factors for relapse/prolonged therapy. Continuous documentation of a minimal clinical and laboratory dataset should be conducted while prescribing GCs.

Follow-up visits are suggested every 4–8 weeks in the first year, every 8–12 weeks in the second year, and as indicated in case of relapse or as prednisone is tapered and discontinued.

H. It is important for patients to have rapid and direct access to advice from doctors, nurses or trained allied healthcare staff to report any changes in their condition such as flares and adverse events.

Specific recommendations for the management of PMR patients:

1. The panel strongly recommends using GC instead of NSAIDs in patients with PMR, with the exception of possible short-term use of NSAIDs and/or analgesics in PMR patients with pain related to other conditions. No specific recommendation can be made for analgesics.

2. The panel strongly recommends using the minimum effective individualised duration of GC therapy in PMR patients.

3. The panel conditionally recommends using the minimum effective GC dose within a range of 12.5–25 mg prednisone equivalent daily as the initial treatment of PMR. A higher initial prednisone dose within this range may be considered in patients with a high risk of relapse and low risk of adverse events, whereas in patients with relevant comorbidities (eg, diabetes, osteoporosis, glaucoma, etc) and other risk factors for GC-related side effects, a lower dose may be preferred. The panel discourages conditionally the use of initial doses ≤7.5 mg/day and strongly recommends against the use of initial doses >30 mg/day.

4. The panel strongly recommends individualising dose tapering schedules, predicated to regular monitoring of patient disease activity, laboratory markers and adverse events. The following principles of GC dose tapering are suggested:

   A. Initial tapering: Taper dose to an oral dose of 10 mg/day prednisone equivalent within 4–8 weeks.

   B. Relapse therapy: Increase oral prednisone to the pre-relapse dose and decrease it gradually (within 4–8 weeks) to the dose at which the relapse occurred.

   C. Tapering once remission is achieved (following initial and relapse therapies): Taper daily oral prednisone by 1 mg every 4 weeks (or by 1.25 mg decrements using schedules such as 10/7.5 mg alternate days, etc) until discontinuation given that remission is maintained.
5. The panel conditionally recommends considering intramuscular (i.m.) methylprednisolone as an alternative to oral GCs. The choice between oral GCs and i.m. methylprednisolone remains at the discretion of the treating physician. In one clinical trial, a starting dose of 120 mg methylprednisolone i.m. injection every 3 weeks was applied.22

6. The panel conditionally recommends using a single rather than divided daily doses of oral GCs for the treatment of PMR, except for special situations such as prominent night pain while tapering GCs below the low-dose range (prednisone or equivalent <5 mg daily).

7. The panel conditionally recommends considering early introduction of methotrexate (MTX) in addition to GCs, particularly in patients at a high risk for relapse and/or prolonged therapy as well as in cases with risk factors, comorbidities and/or concomitant medications where GC-related adverse events are more likely to occur. MTX may also be considered during follow-up of patients with a relapse, without significant response to GC or experiencing GC-related adverse events. MTX has been used at oral doses of 7.5–10 mg/week in clinical trials.24–27

8. The panel strongly recommends against the use of TNFα blocking agents for treatment of PMR.

9. The panel conditionally recommends considering an individualised exercise programme for PMR patients aimed at the maintenance of muscle mass and function, and reducing risk of falls especially in older persons on long-term GCs as well as in frail patients.

10. The panel strongly recommends against the use of the Chinese herbal preparations Yanghe and Biqi capsules in PMR patients.

The group discouraged low (<7.5 mg/day) and strongly recommended against high (>30 mg/day prednisone equivalent) initial GC doses. For this statement the group extrapolated the data from randomised controlled trials,29 31 and took clinical experience, national PMR guidelines,28–30 as well as current ACR and/or EULAR recommendations on the use of GCs in rheumatic diseases into account.22–33 In addition, there is incontrovertible external evidence of harm from long-term large doses of GCs32–35 and lack of evidence for any benefit of a high-dose regimen in PMR. It was unanimously agreed among the group that patients requiring high doses of GCs should be evaluated for alternate diagnoses and an alternate management plan.

Recommendation 4: (PICO 6) The panel strongly recommends individualising dose-tapering schedules, based on regular monitoring of patient disease activity, laboratory markers and adverse events.

The following principles of GC dose tapering are suggested:

A. Initial tapering: Taper dose to an oral dose of 10 mg/day prednisone equivalent within 4–8 weeks

B. Relapse therapy: Increase oral prednisone to the pre-relapse dose and decrease it gradually (within 4–8 weeks) to the dose at which the relapse occurred.

C. Tapering once remission is achieved (following initial and relapse therapies): Taper daily oral prednisone by 1 mg every 4 weeks (or by 1.25 mg decrements using schedules such as 10/7.5 mg on alternate days, etc) until discontinuation as long as remission is maintained.

In accordance with the overarching principles, the panel agreed upon a strong recommendation to individualise dose tapering and to regularly monitor PMR patients. Further, the panel proposed general principles for initial and post-relapse tapering of GCs (based on consensus and current clinical practice) but did not fix a schedule as in other guidelines.28–30 The panel agreed that equivalent objectives may be achieved by alternative tapering schedules. For example, a patient with a high initial prednisone dose (eg, 25 mg/day) may have a fast initial taper followed by a more gradual decrease in the GC dose, whereas in a patient starting at a lower initial dose (eg, 12.5 mg/day), the initial dose may be kept constant for longer and then eventually reduced.

The group suggested prednisone should be tapered by 1 mg/4 weeks or similar once remission is achieved. Again, the panel emphasised the important overall principle of gradual GC reduction without the need to prescribe a fixed schedule. The group further recognised that 1 mg prednisone tablets are not available in all countries (making a reduction of 1 mg/4 weeks unfeasible) and that other regimens such as alternate day reductions (eg, 10/7.5 mg on alternate days, etc) are common clinical practice.28

Recommendation 5: (PICO 7) The panel conditionally recommends considering intramuscular (i.m.) methylprednisolone as an alternative to oral GCs. The choice between oral GCs and i.m. methylprednisolone remains at the discretion of the treating physician.

In one clinical trial, i.m. methylprednisolone was applied at a dose of 120 mg every 3 weeks until week 9. At week 12, 100 mg were used and subsequently, injections were continued at monthly intervals and the dose was reduced by 20 mg every 12 weeks until week 48. Thereafter, the dose was reduced by 20 mg every 16 weeks until discontinuation.23 36

The panel did not specify a clinical phenotype where i.m. GCs would be appropriate or adequate therapy; however, the panel agreed that in clinical practice this preparation may be considered in cases where a lower cumulative GC dose is desirable, for example in female patients with difficult to control hypertension, diabetes, osteoporosis and/or glaucoma.37–39 Nonetheless, the panel acknowledged that there is a lack of convincing evidence showing significantly fewer side effects with i.m. methylprednisolone than with oral GC therapy.

The reasons why the panel did not endorse a strong recommendation for the use of i.m. methylprednisolone are the following: (1) the efficacy of i.m. methylprednisolone is supported by a single randomised controlled trial and confirmation of these data is still necessary;23 36 (2) this trial was neither designed nor powered as a non-inferiority trial and therefore, a difference between the efficacy of i.m. and oral GC cannot be excluded; (3) the trial failed to demonstrate a reduction in GC-related adverse events except for weight gain; (4) the long-term benefit of this preparation is unknown (particularly with respect to a possible reduction in GC side effects); and (5) i.m. methylprednisolone is not available in all countries.

Recommendation 6: (PICO 8) The panel conditionally recommends using a single rather than divided daily doses of oral GCs for the treatment of PMR, except for special situations such as prominent night pain while tapering GCs below the low-dose range (prednisone or equivalent <5 mg daily).

There are no studies available addressing this issue specifically in PMR. Based on clinical experience and because of the
Concern that adverse events (including disturbance of the hypothalamic–pituitary–adrenal axis) may be higher with divided doses, the group agreed against the general use of divided GC doses in PMR. The effectiveness and acceptability of a single daily GC dose has been standard clinical practice in PMR and other inflammatory conditions and evening doses can cause circadian rhythm and sleep disturbances.


Figure 1  Algorithm based on the 2015 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) recommendations for the management of polymyalgia rheumatica (PMR). The algorithm is applied to patients with PMR based on clinician diagnosis which may be supported by currently available diagnostic or classification criteria. The algorithm assumes the consideration of overarching principles emphasising the importance of assessing comorbidities, other relevant medications and possible risk factors for steroid-related side effects and relapse/prolonged therapy. In addition, patients diagnosed in primary care should be considered for specialist referral, particularly in case of atypical presentation (such as peripheral inflammatory arthritis, systemic symptoms, low inflammatory markers, age <60 years), experience or high risk of therapy-related side effects and/or relapse/prolonged therapy. A minimal clinical and laboratory dataset should be documented in each patient before prescribing therapy. Examples for comorbidities associated with an increased risk of glucocorticoid (GC)-related side effects (according to Duru et al and Hoes et al): hypertension, diabetes, glucose intolerance, cardiovascular disease, dyslipidaemia, peptic ulcer, osteoporosis (and particularly recent fractures), presence of cataract or (risk factors for) glaucoma, presence of chronic or recurrent infections, and co-medication with NSAIDs. A baseline factor that was associated with a higher risk of GC-related adverse events in PMR studies was: female sex. The role of risk factors for relapse/prolonged therapy is not yet clear. Baseline factors that were associated with a higher relapse rate and/or prolonged therapy in PMR studies were: female sex, high erythrocyte sedimentation rate (ESR) (>40 mm/1st hour) and peripheral inflammatory arthritis. A number of studies, however, failed to demonstrate an association between these factors and relapse. Use the minimum effective dose out of a range of 12.5–25 mg prednisone equivalent daily; a high risk of relapse/prolonged therapy favours a higher dose, while a high risk of side effects favours a lower dose. In one randomised controlled trial, 120 mg methylprednisolone intramuscular (i.m.) injection was used every 3 weeks as a starting dose. I.m. methylprednisolone may not be available in all countries and the possible long-term benefit in terms of efficacy and GC-sparing effects of this preparation is unknown. Methotrexate (MTX) has been used at oral doses of 7.5–10 mg/week in clinical trials. Clinical improvement should be noted after 2 weeks, and almost complete response can be expected after 4 weeks. The definition of response criteria was beyond the scope of this project; however, a definition of response was proposed in Dasgupta et al. For initial GC tapering, we recommend reducing the oral dose gradually to a dose of 10 mg/day prednisone equivalent within 4–8 weeks; after relapse therapy the dose should be decreased gradually (within 4–8 weeks) to the dose at which the relapse occurred. For i.m. methylprednisolone, a dose of 120 mg every 3 weeks was used for the first 9 weeks in Dasgupta et al. No recommendation about dose adjustments of MTX can be made. The definition of criteria for remission and relapse was beyond the scope of this project. Definitions of remission and relapse used in clinical studies are summarised in Dejaco et al. Once remission is achieved (following initial and relapse therapies), taper oral prednisone by 1 mg/4 weeks (or similar, eg, 2.5 mg/10 weeks) until discontinuation given that remission is maintained. In case i.m. methylprednisolone is used, the following tapering regimen was previously applied: 100 mg methylprednisolone i.m. at week 12, then continuation of the injections at monthly intervals with the dose reduced by 20 mg every 12 weeks until week 48. Thereafter, the dose was reduced by 20 mg every 16 weeks until discontinuation. The group suggests that PMR patients be followed up every 4–8 weeks in the first year, every 8–12 weeks in the second year and as indicated in case of relapse or as prednisone is tapered off. No recommendation can be made for minimal/optimal duration of therapy. In case patients are treated with a combination of GCs plus MTX and GCs have been withdrawn already, discontinuation of MTX may be considered. Initial lack of response (eg, insufficient improvement of symptoms within 2 weeks): increase oral dose to the previously effective (ie, pre-relapse) dose.
In special situations such as in case of night pain while tapering below the low-dose range (prednisone or equivalent <5 mg daily), split doses may be considered. However, persistent breakthrough symptoms should prompt re-consideration of the diagnosis.

**Recommendation 7:** (PICO 9) The panel conditionally recommends considering early introduction of MTX in addition to GCs, particularly in patients at high risk of relapse and/or prolonged therapy as well as in cases with risk factors, comorbidities and/or concomitant medications where GC-related adverse events are more likely to occur. MTX may also be considered during follow-up in patients with a relapse, without a significant response to GC or experiencing GC-related adverse events.

In clinical trials, MTX has been used at oral doses of 7.5–10 mg/week.24–27 Similar to the explanation of Recommendation 5, the panel felt that there is no clinical prototype unconditionally warranting treatment with MTX, rather the use of this drug should be discussed on an individual basis. In clinical practice, MTX may be considered for example in female patients6–19 47 with high initial erythrocyte sedimentation rate (ESR) (>40 mm/1st hour),48–53 peripheral inflammatory arthritides54 and/or comorbidities that may be exacerbated by GC therapy.

The panel also reached a consensus that MTX should be considered in patients who have relapsed (either on or off GCs), cases without significant response to GC or patients experiencing GC-related adverse events. The group further agreed that MTX may be used with oral or i.m. GC preparations even if the concomitant use of MTX and i.m. methylprednisolone has not been tested formally.

The efficacy of MTX was addressed in four randomised controlled trials and one retrospective study testing the use of MTX plus oral GCs (initial predniione doses ranging from 15 to 25 mg/day).54–57 Evidence from studies indicating a benefit of MTX regarding remission (1 study),25 relapse rate (1 study),24 discontinuation of GC (1 study)24 and cumulative GC doses (3 studies).24 26 27 Evidence from one to four studies (1 related to remission, 4 to relapse, 1 to discontinuation of GC) indicating no benefit regarding these outcomes was of very low quality.25–27 51

The reasons why the panel did not support a stronger recommendation for the use of MTX in PMR are the following: (1) the total number of patients investigated in randomised trials was small (n=194).24–27 hence further confirmation of the present data is necessary; (2) results were contradictory in part, although trials with a negative result had a very low QoE; (3) a reduction in GC-related adverse events with the use of MTX has not been tested formally. The power of the prospective studies to address this outcome, however, was insufficient. The panel nevertheless felt that earlier discontinuation of GC24 and a lower cumulative GC dose in MTX users26 27 decreases the likelihood of GC-related side effects; and (4) the cost-effectiveness of MTX use in PMR is not clear. More frequent prescriptions of MTX may lead to higher utilisation of healthcare resources in the short term (e.g., because of specialist referral, monitoring visits, blood tests, etc) but may in the long term save costs by reducing GC-related side effects. Future studies are necessary to clarify this issue.

The group recognised that no recommendation can be made for the use of other non-biologic (i.e., conventional synthetic and conventional targeted) DMARDs in PMR because of the lack of good evidence from PMR studies. Hydroxychloroquine was investigated by a single very low QoE retrospective study reporting no benefit regarding relapse rate.51

**Recommendation 8:** (PICOs 10–11) The panel strongly recommends against the use of TNFα blocking agents for the treatment of PMR.

The group agreed strongly against the use of TNFα blocking agents in PMR at this time since there is no evidence for benefit, but there is a considerable risk of potential harm and high resource use.55 No recommendation can be made for other biologic agents as no prospective trials have been published so far. There is one ongoing randomised study on the use of tocilizumab (clinicaltrials.gov NCT01396317) and another three-arm trial comparing secukinumab, canakinumab and GCs (clinicaltrials.gov NCT013664389) in PMR. The results of these studies may lead to a modification of this recommendation.

**Recommendation 9:** (PICO 12) The panel conditionally recommends considering an individualised exercise programme for PMR patients aimed at the maintenance of muscle mass and function, and reducing risk of falls.

There are no studies investigating the value of non-pharmacological therapies (e.g., physiotherapy, relaxation techniques, diets, etc) in PMR and there is insufficient clinical experience on this issue to agree on a specific recommendation. Nevertheless, the panel agreed on recommending an individualised exercise programme (see overarching principles) in view of its benefit for maintaining muscle mass and function and reducing risk of falls, especially in older persons on long-term GCs as well as in frail patients.

**Use of herbal preparations in PMR**

The panel strongly recommends against the use of the Chinese herbal preparations Yanghe and Biqi capsules in PMR patients.

There were some discussions about whether herbal preparations could be considered non-pharmacological interventions (and were therefore within the scope of PICO 12); however, the panel felt the need for comment on this issue because several preparations are available which may be popular with PMR patients.

The SLR identified two studies testing Chinese Yanghe herb decoction and Chinese Biqi capsules in PMR patients.56 57 For Chinese Yanghe there is moderate QoE for a lower ESR at week 8 (mean difference 6.0 mm/h) and 12 (6.4 mm/h) and very low QoE indicating a lower rate of GC-related adverse events (with borderline significance of the effect estimate) as well as reduced morning stiffness at week 12.56 For Biqi capsules there is low QoE indicating a higher response rate at week 12.57

The group nevertheless agreed (after balancing evidence, benefit/harm, availability and resource use) to recommend strongly against the regular use of these preparations at this time for the following reasons: (1) the relevance of the small effect of Chinese Yanghe herb decoction on ESR is minimal for patients and good evidence for a clinical benefit of the substance is not available; (2) neither of the two substances is approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA); (3) the generalisability of the evidence for benefit is unclear; (4) these preparations may have unforeseeable adverse effects; (5) the availability of high quality preparations is unclear; and (6) resource impact (i.e., costs) is unknown.

**Release and implementation of the recommendations**

See online supplementary file S2.

**Cost implications and conflicts of interest**

Cost implications are outside the scope of these recommendations.

None of the panel members disclosed any conflict of interest associated with the development of these recommendations.
Box 2 Research agenda

The group agreed that future studies in polymyalgia rheumatica (PMR) should be multicentre and properly powered using an agreed, validated core outcome set and a robust trial design that would maximise the power of studies, facilitate regulatory approvals and allow future meta-analysis.

Specific research questions:
1. Which outcome measures including patient-related outcomes, and response, remission and relapse criteria should be used in PMR?
2. What is the efficacy and safety of different routes of glucocorticoid (GC) administration (oral, intramuscular, intra-articular), different initial GC doses, various GC tapering regimens, and different GC flare doses?
3. What is the efficacy and safety of DMARDs (non-TNFα biologic, conventional synthetic and conventional targeted) in PMR? What is the optimal strategy for using DMARDs in PMR: monotherapy versus combination therapy, early versus late introduction, and (particularly for biologics) use with or without GCs?
4. What is the minimal/optimal duration of therapy and which strategies for withdrawing GCs and/or DMARDs yield the best efficacy/safety profile?
5. What is the optimal strategy for shared primary and specialty care including recommendations for specialist referral? How can patients be better involved in treatment decisions, and are there any decision aids? What is the role of self-management?
6. What is the value of tight control (ie, treat to target) versus conventional management strategies in PMR?
7. How should patients with long-standing disease and long-term low-dose GC therapy be managed?
8. What is the cost utility and effectiveness of DMARD use in PMR (versus GC use alone)?
9. What is the value of non-pharmacological therapies in PMR? Particularly, it is assumed but not yet demonstrated that physiotherapy may support preservation of function and reduce the risk of adverse events related to GC use. Patients may benefit from exercise by maintaining muscle mass and function as well as by fall prevention especially in the frail. What is the role of diet in PMR and nutrition supplements (eg, fish oil) related to outcomes?
10. What is the efficacy and safety of herbal preparations in PMR?
11. What is the role of imaging (particularly ultrasound) for the assessment and monitoring of PMR, identification of overlap with other diseases (eg, large vessel vasculitis or inflammatory arthritis) alongside clinical and patient reported outcomes?
12. Which biomarkers may be useful in PMR? Why do some patients do better than others? How can we identify these groups and what is the biological mechanism behind it? Should different drugs be applied to different PMR subgroups?
13. What is the morbidity and mortality of PMR patients (with a particular focus on cardiovascular risk) in long-term observational studies?
14. What is the aetiology/pathogenesis of PMR? Which targeted therapies could be developed based on new knowledge of disease mechanisms?

Bolded points indicate the top 5 items of the research agenda according to the opinion of the guideline panel.

DISCUSSION

See online supplementary file S3 for a full-length discussion. The 2015 EULAR/ACR recommendations for the management of PMR is the first collaborative project between EULAR and ACR to endorse treatment recommendations in rheumatology.

We recognise that our recommendations are only partially supported by evidence, and that they do not cover all aspects important for the management of PMR. The group therefore unanimously agreed that the research agenda (covering the evidence gaps related to PMR management) is an important result of this project (Box 2).

Due to our rigorous SLR approach to select high quality papers, we did not include other reviews, case reports or case series indicating possible treatment options in treatment-resistant PMR patients. For example, we found one earlier SLR reporting similar conclusions regarding the value of MTX in PMR.58 In addition, two case series were recently published on the use of leflunomide59 60 and a few case reports are available on tocilizumab.61–63 Azathioprine has been tested in a double-blind randomised controlled trial in patients with PMR and GCs; however, as PMR patients were not analysed separately, we did not include this study in the SLR.64

It was beyond the scope of this recommendation project to define treatment targets in PMR. ‘Clinical improvement’ was considered as the first treatment goal after the initiation of GCs, and the response criteria used in the 2012 classification criteria study may be considered.3 4 Remission and relapse have been heterogeneously defined in the literature, as we pointed out previously.65 Future prospective studies aimed at the validation of new definitions of response, remission and relapse are, therefore, required to enable a targeted treatment approach in PMR.66

The most important limitations of this project are the paucity of high quality trials (as mentioned above) and the fact that GRADE is less well developed for the assessment of rare outcomes. Consequently, the QoE for adverse events is usually lower than for efficacy data. This necessitated the use of relevant external evidence to strengthen this aspect of our recommendations.

These recommendations should support clinicians to achieve the best patient outcomes. Further research on existing drugs is necessary to offer additional, evidence-based treatment options to our patients. We anticipate an update of these recommendations 3 years after their publication; however, an earlier revision may be necessary if new data emerge that would modify the current recommendations.

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Contributors
All authors contributed to conception and design of the study, acquisition and/or interpretation of data, drafting the article or revising it critically for important intellectual content, and approved the final version of the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests
All the participants of this project made a disclosure of possible conflicts of interest. The individual declarations are available on demand at the American College of Rheumatology secretariat and are summarised below as remuneration for consultation and/or speaking engagements (the American College of Rheumatology secretariat and are summarised below as research funding (possible conflicts of interest).

REFERENCES

METHODS

For this project, we followed the policy and procedure manual for clinical practice guidelines by the American College of Rheumatology (ACR).[1] Accordingly, we used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology as a framework to develop these recommendations involving 2 expert panels:[2–5] a) a Core Expert Panel (CEP) of clinicians and methodologists (BD, ELM, CD, YS, AH, PP, DC, SM) who drafted the protocol, coordinated the survey on outcome parameters, conducted the systematic literature review (SLR) and the evidence synthesis; and b) a voting panel consisting of 42 members, including rheumatologists (n=25), specialists in internal medicine (n=2), general practitioners (n=4), allied health care professionals (n=4) and patient representatives (n=7) from Europe, USA, South America, Africa, India, Japan, Australia and New Zealand. The voting panel formulated the PICO (=Population, Intervention, Comparator, Outcome) questions, interpreted the evidence and drafted the final recommendations.

Involvement of patients in the development of the recommendations

GRADE encourages the involvement of patients in the development of management recommendations and supports a shared clinical decision of treatment between physicians and patients.[3,4] For this project, patients’ representatives were involved in each step, from the formulation of the key questions and outcomes, to the formulation and approval of the final recommendations. A challenge in this regard is the selection of adequate patients’ representatives given that thoughts, values and preferences should be considered from as many patients’ subgroups as possible. We invited the chairs and other members of Polymyalgia rheumatic giant cell arteritis UK (PMRGCAuk) as well as patient’s representatives from USA to participate in this
exercise. PMRCAuk is a patient charity for people with Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) and has recently conducted a survey within UK to identify the thoughts and concerns of people living with PMR.[6,7] We recognized that these people (and their experience from the survey) may not reflect the feelings of all PMR patients; however, their close contact with other PMR patients, their interest in patients’ values and preference as well as their experience with research studies qualified them as representative members of the recommendation development group. For other, non-English patients, language restrictions were an insuperable barrier to participate in this project.

**Formulation of the key questions and outcomes**

The key questions were framed in the PICO format, taking patient experiences and preferences into account.[8] We formulated 12 PICO questions on therapeutic interventions and 10 questions on prognostic factors as detailed in the Supplementary Box S1 (a+b) below.
Supplementary Box S1a. PICO questions on interventions

1. In Polymyalgia rheumatica (PMR) (P), what is the effect of Non-steroidal Anti-inflammatory drugs (NSAIDs) and/or analgesics (I) on outcome (O) compared with glucocorticoids (C).

2. In PMR (P), what is the effect of short duration of glucocorticoid therapy (I) on outcome (O) compared with long duration of glucocorticoid therapy (C).

3. In PMR (P), what is the effect of low dose oral glucocorticoids (≤ 7.5mg/day of prednisone equivalent) (I) on outcome (O) compared with medium dose of glucocorticoids (> 7.5mg/day but ≤ 30mg/day of prednisone equivalent) (C).

4. In PMR (P), what is the effect of medium dose oral glucocorticoids (>7.5mg/day but ≤ 30mg/day of prednisone equivalent) (I) on outcome (O) compared with high dose of glucocorticoids (> 30mg/day but ≤ 100mg/day of prednisone equivalent) (C).

5. In PMR (P), what is the effect of an oral glucocorticoid dose of ≥10mg/day but ≤20mg/day prednisone equivalent (I) on outcome (O) compared with a dose of >20mg but ≤30mg/day of prednisone equivalent (C).

6. In PMR (P), what is the effect of rapid taper of glucocorticoids (I) on outcome (O) compared with slow taper of glucocorticoids (C).

7. In PMR (P), what is the effect of intramuscular injection of glucocorticoids (I) on outcome (O) compared with oral glucocorticoids (C).

8. In PMR (P), what is the effect of administration of oral glucocorticoid therapy at divided doses (morning plus evening) (I) on outcome (O) compared with single dose (morning only) (C).

9. In PMR (P), what is the effect of glucocorticoids plus Non-biological disease modifying anti-rheumatic drugs (I) on outcome (O) compared with glucocorticoids alone (C).

10. In PMR (P), what is the effect of glucocorticoids plus biological agents (I) on outcome (O) compared with glucocorticoids alone (C).

11. In PMR (P), what is the effect of biological agents (I) on outcome (O) compared with glucocorticoids alone (C).

12. In PMR (P), what is the effect of glucocorticoids plus non-pharmacological interventions (I) on outcome (O) compared with glucocorticoids alone (C).
### Supplementary Box S1b. PICO questions on prognostic factors

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>13.</td>
<td>In PMR (P), what is the effect of older age at diagnosis (I) on outcome (O) compared with younger age (C).</td>
</tr>
<tr>
<td>14.</td>
<td>In PMR (P), what is the effect of female sex (I) on outcome (O) compared with male sex (C).</td>
</tr>
<tr>
<td>15.</td>
<td>In PMR (P), what is the effect of high levels of inflammatory markers [i.e. erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)] at diagnosis (I) on outcome (O) compared with low levels of inflammatory markers (C).</td>
</tr>
<tr>
<td>16.</td>
<td>In PMR (P), what is the effect of more active/severe disease at diagnosis (I) on outcome (O) compared with lower disease activity/severity (C).</td>
</tr>
<tr>
<td>17.</td>
<td>In PMR (P), what is the effect of the presence of peripheral arthritis at diagnosis (I) on outcome (O) compared with absence of peripheral arthritis (C).</td>
</tr>
<tr>
<td>18.</td>
<td>In PMR (P), what is the effect of longer symptom duration at diagnosis (I) on outcome (O) compared with shorter symptom duration (C).</td>
</tr>
<tr>
<td>19.</td>
<td>In PMR (P), what is the effect of concomitant conditions (including cardiovascular disease, cerebrovascular disease, peripheral vascular disease, osteoporosis, hyperlipidaemia, diabetes, hypertension, infection, cataract, glaucoma, peptic ulcer, skin disorders, adiposity, mood disturbances, cognitive disorder) at diagnosis that could be exaggerated by PMR and/or glucocorticoid therapy (I) on outcome (O) compared with absence of these conditions (C).</td>
</tr>
<tr>
<td>20.</td>
<td>In PMR (P), what is the effect of rapid response to glucocorticoids (I) on outcome (O) compared with delayed response.</td>
</tr>
<tr>
<td>21.</td>
<td>In PMR (P), what is the effect of shared patients' management by primary and secondary care (I) on outcome (O) compared to management in primary care only.</td>
</tr>
<tr>
<td>22.</td>
<td>In PMR (P), what is the effect of optimal control management of patients (I) on outcome (O) compared to conventional management (C).</td>
</tr>
</tbody>
</table>

All questions were framed in the PICO (=Population, Intervention, Comparator, Outcome) format.
As per GRADE methodology, the list of outcomes was supposed to be comprehensive including all parameters potentially relevant to patients. We, therefore, conducted a survey among 43 rheumatologists (most of them were members of the voting panel), 87 General Practitioners (GP, all from UK) and 43 patients (all from PMRGCAuk).[6] An international survey was unfortunately not feasible within the short time-period available given the necessity for translation of the questionnaire for non-English countries and the lack of a pre-existing research network between GPs, patients and rheumatologists in non-UK countries.

A candidate item list was generated by literature review and additional input from the voting panel (including contribution from patients), containing 119 outcome measures including symptoms, physical examination findings, laboratory parameters, imaging, composite outcome measures, drug related adverse effects, functional status, quality of life and PMR-related complications. Survey participants were asked to rate each parameter based on its relative importance for clinical decision-making according to a 1-9 point scale (1-3 not important, 4-6 important, but not critical and 7-9 critical). All parameters with a grading of ≥7 by ≥50% of responders in at least 1 of the 3 groups (i.e., rheumatologists, GPs or patients) were presented to the voting panel, which refined and agreed upon the final list of critical outcome measures as detailed in Supplementary Box S2.
Supplementary Box S2. Outcome parameters used for the systematic literature review

- Disease remission
- Disease relapse
- Duration of glucocorticoid therapy
- Discontinuation of glucocorticoid therapy
- Development of giant cell arteritis
- Glucocorticoid side effects (diabetes mellitus/glucose intolerance, osteoporosis, cardiovascular disease, dyslipidemia, impaired wound healing, infections, osteonecrosis, myopathy, cataract, glaucoma, atherosclerosis, hypertension, peptic ulcer, weight gain, moon face, dyspnea, palpitations, fatigue, skin atrophy, bruising, mood disorders)
- Response to glucocorticoid therapy
- Cumulative glucocorticoid dose
- Acute phase reactants
- Patients assessment of global wellbeing
- Severity / duration of morning stiffness
- Lowest possible glucocorticoid dose (prednisone equivalent less than 5mg/day)
- Functional status (Health Assessment Questionnaire or other measures)
- Quality of life (Short Form-36, EQ5D etc.)
- Mortality
- Hospitalization (due to disease, its complications, co-morbidity and/or treatment related complications)
- Impact on patients' social environment
- Fatigue
- Imaging of shoulder/hip
- Healthcare resource use (health economics)
- Disease activity score
The panel decided not to include PICO questions on the prevention of GC-induced osteoporosis and immunization in PMR because there are published recommendations by the ACR [9] and European League Against Rheumatism (EULAR) [10], respectively on these issues. Also, the group decided not to specify cut-offs for most PICO items (such as long and short duration of GC therapy, rapid and slow taper of GCs, older and younger age, high and low levels of inflammatory markers, more and less active/severe disease, longer and shorter symptom duration, rapid and delayed response to GCs, optimal and conventional control management) because there are no uniformly accepted definitions for these parameters. The group further argued that literature review might reveal relevant cut-offs (i.e. the cut-offs that were used to segregate groups in clinical studies) for these items.

**Systematic Literature Review**

Details concerning the SLR are presented in a separate manuscript.[Dejaco et al., ARD 2015 (in press)] In brief, 2 members of the CEP (CD, Rheumatologist, Graz, Austria and YS, Rheumatologist, Southend, UK, counselled by PP, clinical epidemiologist, London, UK) performed a literature search aimed at retrieval of all published articles in PMR, without limitation on the languages of the publications. We used Ovid MEDLINE®, Embase, PubMed, CINAHL, Web of Science and the Cochrane Library databases and applied the thesauri of PMR for each database, text words in title or abstract, abbreviations and truncated text words as key words. The grey literature (e.g., reports by the Agency for Healthcare Research and Quality, conference abstracts) was reviewed to identify additional peer-reviewed articles not tracked by the search described above. We reviewed trial registries to identify ongoing and completed trials and contacted sponsors/investigators to request any
available results. Additional papers were retrieved by searching the reference list of full and review articles and by contacting experts in the field. The literature search was limited to articles published from January 1970 through June 2013. An update search was performed in April 2014. New data were presented to the voting panel in order to discuss a possible modification of the recommendations based on this new information.

We excluded all articles that did not report original data, did not study patients with PMR, or that considered PMR and GCA patients as a single group. For PICOs on prognostic factors, we excluded all studies investigating factors that were not routinely available [e.g. cytokines other than interleukin (IL)-6, adhesion molecules etc. [11,12] ] and/or trials with a follow-up of fewer than 6 months. The panel argued that studies with a shorter time frame were not helpful to predict outcomes of PMR patients given the usual duration of PMR of >6-12 months.[13,14]

Two members of the CEP (CD, YS) independently reviewed all articles identified by the literature search, performed data extraction and quality appraisal. Two additional members of the CEP (SM, Rheumatologist, Leeds, UK and DC, Rheumatologist, Genova, Italy) helped with review and data extraction of non-English articles. References and abstracts identified by the search were imported into bibliographic management software (Zotero Version 4.0.20, Fairfax, VA, USA) and duplicates were removed. Titles and abstracts were screened to remove editorials, commentaries and letters without patient data. The full text of each remaining article was then tested against the inclusion and exclusion criteria. The CEP also made every effort to identify multiple publications from a single trial. Study details and results were extracted using a pre-specified data extraction sheet. Appraisal of studies was
performed according to GRADE methodology and using the Quality in Prognostic Studies (QUIPS) tool as detailed below.

Any disagreement was resolved by discussion. In case a consensus was not achieved (15.6% of articles), a third member of the CEP (AH, clinical epidemiologist, London, UK) was consulted and made the final decision.

External evidence: After the results of the SLR became available, the panel recognized that there is a paucity of data regarding safety aspects of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) (no prospective data), GCs (39 prospectively studied patients) and methotrexate (MTX, 97 prospectively investigated patients) in PMR. The panel found it difficult to balance benefits versus harms of these substances in PMR, given that the available studies had an insufficient sensitivity to detect rare and long-term side effects. On the other hand, all these drugs have been the standard of care for other conditions such as RA or osteoarthritis (OA) and thousands of patients have been followed-up in (non PMR) clinical studies already.[15–17] In order to inform the voting panel about important safety aspects, the panel decided to revise the protocol toward the presentation of other ACR and EULAR recommendations related to the use of NSAIDs, GCs and MTX in populations with a similar demography [i.e. RA, OA, gout, calcium pyrophosphate disease (CPPD) and giant cell arteritis] to the guideline group. The panel strongly felt that it would be unethical not to take such information into account. The information retrieved from these papers was ultimately used as indirect, supporting evidence. Supplementary Table S1 details the recommendations and the information that was presented to the panel in addition to the data from the SLR in PMR. The rationale for the consideration of ACR and EULAR recommendations (and supporting references) rather than any other source of data was the assumption that ACR and EULAR
recommendations are supported by high-quality SLRs and that the recommendations made in these papers can be accepted as the current standard of clinical care. We retrieved the recommendation papers from ACR and EULAR homepages and focused on recommendations published after January 1st, 2000.
### Supplementary Table S1. ACR and/or EULAR recommendations used to inform the voting panel about safety aspects of Non-Steroidal Anti-inflammatory Drugs (NSAIDs), Glucocorticoids (GCs) and methotrexate (MTX)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Year</th>
<th>Substances</th>
<th>Statements presented to the guideline panel*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EULAR evidence based recommendations for gout. Part II: Management. Report of a</td>
<td>2006</td>
<td>NSAIDs</td>
<td>• In acute gout, NSAID use is associated with an increased risk of gastrointestinal bleeding and may have cardiovascular toxicity.</td>
</tr>
<tr>
<td>task force of the EULAR Standing Committee For International Clinical Studies</td>
<td></td>
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<tr>
<td>Including Therapeutics (ESCISIT) [18]</td>
<td></td>
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<tr>
<td>EULAR evidence based recommendations for the management of hand osteoarthritis:</td>
<td>2007</td>
<td>NSAIDs</td>
<td>• Major concern over NSAIDs is GI toxicity (dose dependent and increases with age)</td>
</tr>
<tr>
<td>Report of a Task Force of the EULAR Standing Committee for International Clinical</td>
<td></td>
<td></td>
<td>• Concern exist that cardiorenal toxicity may be a class related side effect of NSAIDs rather than a specific side-effect of coxibs</td>
</tr>
<tr>
<td>Studies Including Therapeutics (ESCISIT) [19]</td>
<td></td>
<td></td>
<td><strong>Note:</strong> EULAR recommendations on hip [20] and knee [21] osteoarthritis raise the same concerns and are therefore not separately reported</td>
</tr>
<tr>
<td>Recommendations for Use of Selective and Nonselective Nonsteroidal Anti-</td>
<td>2008</td>
<td>NSAIDs</td>
<td>• If a patient and provider agree to utilize an NSAID for arthritis pain relief, then the patient should be advised of the potential toxicities and relevant monitoring should be pursued.</td>
</tr>
<tr>
<td>inflammatory Drugs: An American College of Rheumatology White Paper [17]</td>
<td></td>
<td></td>
<td>• If a patient is taking aspirin for cardioprotective benefit, then selective and nonselective NSAIDs should be avoided. This combination is associated with an elevated risk of GI bleeding. However, if a patient is educated about this risk and wants to take the drugs concomitantly, then a PPI or misoprostol should be added to the regimen.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• If a patient and provider agree to utilize an NSAID for arthritis pain relief, and the patient has risk factors for GI bleeding, then the patient should be treated concomitantly with either misoprostol or a PPI.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• If a patient has compromised liver function, then the risks of selective and nonselective NSAID use should be carefully considered. Diclofenac should be avoided in patients with liver disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• If a patient is fully anticoagulated with warfarin, heparin, or other anticoagulants or is thrombocytopenic, then use of nonselective NSAIDs should be avoided because they can increase the risk of bleeding.</td>
</tr>
<tr>
<td>EULAR recommendations for calcium pyrophosphate deposition. Part II: Management</td>
<td>2011</td>
<td>NSAIDs</td>
<td>• Because CPPD predominates in the older patient, the use of NSAIDs should be carefully considered according to the benefit and relative risk</td>
</tr>
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<tr>
<td>American College of Rheumatology 2012 Recommendations for the Use of Nonpharmac</td>
<td>2012</td>
<td>NSAIDs</td>
<td>• Health care providers should not use oral NSAIDs in patients with contraindications to these agents and should be aware of the warnings and precautions associated with the use of these agents.</td>
</tr>
<tr>
<td>ologic and Pharmacologic Therapies in Osteoarthritis of the Hand,</td>
<td></td>
<td></td>
<td>• For persons age ≥75 years, the TEP strongly recommends the use of topical rather than oral</td>
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<tr>
<td>Reference</td>
<td>Date</td>
<td>Recommendations</td>
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</table>
| Hip, and Knee [23] | | NSAIDs in patients with knee osteoarthritis who do not have a satisfactory clinical response to full-dose acetaminophen  
- Based on good clinical practice, oral NSAIDs should not be used in patients with chronic kidney disease stage IV or V  
- The decision to use an oral NSAID in patients with chronic kidney disease stage III should be made by the practitioner on an individual basis after consideration of the benefits and risks. |
- The potential drug toxicities due to comorbidities and drug–drug interactions are considerable in treatment of acute gout. Examples include underlying moderate and severe chronic kidney disease, congestive heart failure, peptic ulcer disease, diabetes mellitus, ongoing infection or high risk of infection, anticoagulation or antiplatelet aggregation therapy and hepatic disease |
| EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT) [25] | 2007 | NSAIDs, GCs  
- There are concerns over the gastrointestinal, renal and cardiovascular side effects of NSAIDs.  
- Replacement of NSAIDS by COX-2 selective drugs, or the addition of gastroprotective agents can reduce gastrointestinal complications  
- the long term use of COX-2 selective drugs has been associated with increased cardiovascular risk  
- the long term safety of low dose GCs is largely unknown |
| EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases [16] | 2007 | GCs  
- Comorbidities and risk factors for adverse effects should be evaluated and treated where indicated. These include hypertension, diabetes, peptic ulcer, recent fractures, presence of cataract or glaucoma, presence of (chronic) infections, dyslipidemia and co-medication with NSAIDS  
- The occurrence of GC-related AEs, osteoporosis in particular, is dependent on dose and duration.  
- Using the smallest dose of GCs for the shortest duration possible is recommended as an important strategy to minimize osteoporosis risk. |
| American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis [9] | 2010 | GCs  
- no definite conclusions can be drawn on the occurrence of most AEs, because there often is a lack of good quality evidence  
- Possibly increased risk for infections, peptic ulcer, mood disturbances, diabetes, Body weight and fat redistribution, osteoporosis. Increased risk for interference with hormone secretion and glaucoma |
| Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice [26] | 2010 | GCs  
- Before starting medium/high-dose GC treatment, consider comorbidities predisposing to AEs. These include diabetes, glucose intolerance, cardiovascular disease, peptic ulcer disease, recurrent infections, immunosuppression, (risk factors of) glaucoma and osteoporosis. Patients with these comorbidities require tight control to manage the risk/ benefit ratio  
- Keep the requirement for continuing GC treatment under constant review, and titrate the dose against therapeutic response, risk of under treatment and development of AE  
- All patients should have appropriate monitoring for clinically significant AEs. The treating physician should be aware of the possible occurrence of diabetes, hypertension, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems and neuropsychological AEs  
- For several AEs it has been proven that the occurrence depends on dose and duration of GC treatment |
### EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs [28]

2010  | GCs, MTX
---|---
- GCs  | Long-term use of GCs can lead to adverse events, but there may also be safety concerns in the intermediate term, although most studies on the toxicity of GCs are of low quality and short duration.  
- MTX  | MTX is considered the anchor drug in RA both on the basis of its efficacy as well as the beneficial long-term safety profile  
- References to a metaanalysis from 2009 summarizing the occurrence of AEs in 3463 patients with a mean MTX dose of 8.8mg/week and therapy duration of 36.5 months [15]: GI AE 30.8%, liver enzymes >2x upper limit of normal 12.9%; 3.7% stopped for liver toxicity; conflicting data regarding risk of liver fibrosis, cytopenia of 1 cell line 5.2% (up to 1.4% pan-cytopenia), AE concerning skin/hair 8.9%, AE regarding CNS 5.5%, AE of the lung 2.4% (pulmonary dysfunction, cough, unspecified pulmonary adverse drug reactions), MTX pneumonitis 0.4%, no increased risk for serious infections, insufficient data regarding risk of lymphoma and malignancies

### American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis [29]

2008/2012  | NSAIDs, GCs, MTX
---|---
- NSAIDs  | Reference the Guidelines for monitoring drug therapy in rheumatoid arthritis of the American College of Rheumatology Ad Hoc Committee on Clinical Guidelines [31]:  
  - The toxicities of NSAIDs include dyspepsia (common), gastric or small bowel bleeding or ulceration (uncommon), renal insufficiency (rare), confusion, depression, rash, headache (rare), and hepatic toxicity (rare). NSAIDs may also reversibly inhibit platelet function and prolong bleeding time.  
  - The toxicities of low-dose systemic glucocorticoids (≤10 mg prednisone daily or equivalent) include increased appetite, weight gain, fluid retention, acne, development of cushingoid facies, hypertension, diabetes, atherosclerosis, glaucoma and cataract formation, osteoporosis, a vascular necrosis, increased susceptibility to infection, and impaired wound healing  
  - The most serious toxicities of MTX include hepatic fibrosis (rare) and cirrhosis (rare), pneumonitis (uncommon), and myelosuppression

*References and individual studies supporting the statements in the recommendations were presented to the guideline panel on request

AE, adverse event; CNS, central nervous system; COX, cyclooxygenase; CPPD, calcium pyrophosphate disease; GCs, Glucocorticoids; GI, gastrointestinal; MTX, methotrexate; NSAID, Non-Steroidal Anti-inflammatory Drugs; PPI, proton pump inhibitor; RA, Rheumatoid Arthritis; TEP, total endoprothesis;
Literature appraisal and evidence report

We used the GRADE methodology for appraisal of primary interventional studies [32,33] and the QUIPS tool for studies on prognostic factors.[34] According to GRADE, the quality of evidence is graded from high, moderate, low to very low based on the evaluation of the following 5 domains: (1) Study limitations (limitations related to randomization, lack of allocation concealment, lack of blinding, large losses to follow-up, failure to adhere to intention to treat analysis, early termination and failure to report outcomes); (2) Inconsistency of results; (3) Indirectness of evidence; (4) Imprecision; and (5) Publication bias. Randomized control trials are initially presumed to be high level evidence, whereas observational studies are initially presumed to be low quality. Studies may be downgraded by 1-2 levels if any of the limitations mentioned above are present. Under certain circumstances upgrading is possible, as well.[32]

Forming recommendations

According to GRADE methodology, the voting panel should consider the following aspects when formulating the recommendations: 1) Overall quality of evidence; 2) balance between desirable and undesirable effects; 3) patients’ and clinicians’ values and preferences; and 4) resource use. External evidence on safety aspects was taken into account (as indirect evidence) in this project in order to identify the optimal trade-off between benefit and harm of interventions (see also above). Prognostic factors were used to build subgroups and to adapt the recommendations based on the presence or absence of unfavorable prognostic factors. Final recommendations were either “in favor” or “against” an intervention, and were graded with “conditional” or “strong”. A strong recommendation in favor (against) was considered when the
panel was very certain that benefits did (did not) outweigh risks and burdens, preferences/values of patients were met (not met) and resource use was reasonable (unreasonable high). In case some uncertainty existed, a conditional recommendation was made.

Discussions about the evidence and the possible wording of the recommendations were conducted at the Annual Meeting of the ACR in October 2013, where the group also decided to create a flow chart supporting clinical decision pathways. Further, the group discussed and finally consented about the principal direction and strength of the recommendations. Thereafter, 3 members of the voting panel (CD, BD, ELM) drafted the preliminary recommendations/flow chart that was subject to further discussion and refinement at another face-to-face meeting (before the International conference for PMR and GCA 11/2013 in Southend, UK), four online conferences and e-mail-based communications. At each of these meetings/online conferences/e-mail contacts, the project leaders summarized the comments of the participants and asked for any dissent. The final recommendations were then circulated by e-mail for formal acceptance. At this stage, we set the dateline for a response at 21st April 2014, and assumed a consent to the final paper in case no further clarifications were requested. Since no dissent was reported until this dateline, a consensus was assumed for all points. Voting and grading of the level of agreement as performed in earlier recommendations was not necessary for this project.[35]

In addition to the individual treatment recommendations based on PICO questions and supporting evidence from the SLR, the panel formulated several principles that were uniformly considered important to be conveyed to those with PMR or involved with the management of PMR. These principles were formulated with understanding that they reflect current standards of clinical care, values and preferences of
clinicians and patients and were of such a generic nature that they were considered to be ‘overarching’. [28,35]

The first draft recommendations were publicly presented at the International conference for PMR and GCA 11/2013 in Southend, UK. This conference was open to all physicians and allied health care professionals interested in PMR and/or GCA, as well as to patients. Feedback and suggestions obtained at this meeting were recorded, summarized and presented to the voting panel by the project leaders in an online conference for further discussion and incorporation into the recommendations.
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RESULTS

Detailed results of the systematic literature review (SLR) are presented in a separate manuscript.[Dejaco et al., ARD 2015 (in press)] In this file, we summarize the data of the SLR and the external evidence considered by the guideline panel to formulate the individual recommendations.

Recommendation 1:

Results from SLR: This PICO question was addressed in a single very low Quality of Evidence (QoE) study demonstrating that Non-Steroidal Anti-inflammatory Drugs (NSAID) use is associated with lower rate of vertebral fractures (but not with other fractures such as the hip) and a higher rate of infections.[1] The reason for these findings (particularly the latter result) was unclear. In addition, there was a trend (reported in 2 articles from the same cohort analysed at 2 different time points) toward a higher rate of cardiovascular events and hypertension in NSAID treated PMR patients (both outcomes with very low QoE).[1,2] Whether this observation was directly related to NSAID use (or to other factors such as the inflammatory state of PMR itself) is unclear.

External evidence: Several ACR and EULAR recommendations dealt with the issue of long-term NSAID use in patients with degenerative and inflammatory rheumatic conditions. Most of these recommendations advised caution in the use of NSAIDs because of the known gastrointestinal, cardiovascular and renal side effects.[3–9]
Recommendation 2:

*External evidence:* The advice to use the minimum effective glucocorticoid (GC) dose is supported by other recommendations in rheumatology such as the 2010 ACR Guidelines for the Prevention and Treatment of GC-Induced Osteoporosis,[10] the EULAR evidence-based recommendations on the management of systemic GC therapy in rheumatic diseases [11] and other recommendations.[8,12–14]

Recommendation 3:

*Results from SLR:* PICO question number 5 was addressed in 1 small randomized controlled trial comparing initial doses of 20mg and 10mg prednisone, and in 4 retrospective studies comparing doses above and below 15mg daily.[15–19] Thus, none of these studies met exactly the objective of this PICO aimed at the comparison of doses between ≥10mg/day and ≤20mg/day versus >20mg and ≤30mg/day of prednisone equivalent. The randomized study by Kyle demonstrated with a moderate QoE, a lower relapse rate at 2 months in the higher dose group whereas the meta-analysed effect of 3 retrospective studies revealed (with a very low QoE) no difference regarding relapse rates during a 2-10 year follow-up period. One study each indicated with a very low QoE a higher risk of GC-related adverse events and a longer duration of therapy in the higher dose group.[17,19]

Three retrospective studies directly compared GC starting doses below and above 7.5mg/day: 1 study revealed a higher relapse rate in the medium compared to the lower dose group but this study had a very low QoE.[2] The second study, published in the format of a letter, also had a very low quality and did not find an association between medium GC doses and relapse risk.[20] A third study (very low QoE)
reported no difference between medium and low doses of GCs regarding discontinuation of steroids at 1 and 2 years after diagnosis.[16]

The value of high (>30mg/day prednisone equivalent) versus medium (>7.5mg/day and ≤30mg/day) GC doses in PMR was addressed by 2 retrospective studies showing no benefit of the high dose regarding relapse rates and the discontinuation of GCs after 1 and 2 years.[16,21] Both studies had several limitations resulting in a very low QoE overall.

Concerning prognostic factors, a few studies with variable quality indicated that females,[22] patients with high initial ESR [2,18,23,24] and patients with peripheral inflammatory arthritis [25] have a higher probability of relapse and/or a higher number of relapses; however, a number of studies also failed to demonstrate an association between these factors and relapses.[2,18,21,23,26–34] Females appeared to be at an increased risk of GC-side effects [22,35,36] and females [37] as well as patients with a high ESR had a longer duration of GC therapy.[37,38]

**Recommendation 4:**

*Results from SLR:* This PICO question was addressed in 1 study revealing low QoE that rapid tapering (as determined by a “tapering constant” in regression analysis) of GCs was associated with a higher risk of relapse than slower tapering.[2] No (optimal) tapering schemes could be extracted from this study directly.
Recommendation 5:

*Results from SLR:* This PICO question was addressed in 1 randomized controlled trial including 60 PMR patients revealing moderate to low QoE for comparable remission rates at week 12, 48 and 96 to oral GC therapy.[39,40] This study also indicated a lower cumulative GC-dose and a less weight gain (moderate QoE) in the intramuscular (i.m.) group. I.m. methylprednisolone was applied at a dose of 120 mg every 3 weeks until week 9. At week 12, 100mg were used and subsequently, injections were continued at monthly intervals and the dose was reduced by 20 mg every 12 weeks until week 48. Thereafter, the dosage was reduced by 20 mg every 16 weeks until discontinuation.

Recommendation 7:

*Results from SLR:* This PICO question was addressed in 4 randomised controlled trials and 1 retrospective study testing the use of MTX plus oral GCs (initial prednisone doses ranging from 15-25mg/day).[18,41–44] There was moderate to high QoE from 1-2 studies indicating a benefit of MTX regarding remission (1 study),[42] relapse rate (1 study),[44] discontinuation of GC (1 study) [44] and cumulative GC-doses (3 studies).[41,42,44] Evidence from 1-4 studies (1 related to remission, 4 to relapse, 1 to discontinuation of GC) indicating no benefit regarding these outcomes was of very low quality.[18,41–43]

In the 4 randomised controlled trials, MTX was used at doses of 7.5mg/week (1 study) [43] and 10mg/week (3 studies).[41,42,44]
None of the studies demonstrated a reduction of GC related adverse events by the use of MTX, except for 1 trial reporting a better DEXA result in the MTX than in the control group (moderate QoE).[41]

External evidence: As there were insufficient data on the safety of MTX use in PMR the panel considered external evidence from Rheumatoid Arthritis recommendations.[14,45] Accordingly, MTX use has an overall beneficial long-term safety profile.

Recommendation 8:

Results from SLR: PICO questions 10 and 11 were addressed in 1 trial each. A single 52-weeks randomized placebo controlled trial addressed the efficacy of infliximab (3mg/kg body weight) versus placebo in 53 PMR patients revealing moderate QoE for no benefit of infliximab regarding relapse rate and discontinuation of GCs.[46] Another trial comparing etanercept with placebo in newly diagnosed PMR patients (not receiving GCs) also failed to demonstrate a benefit of the anti-TNFα agent.[47]

RELEASE AND IMPLEMENTATION OF THE RECOMMENDATIONS

Implementation of the 2015 EULAR-ACR recommendations for treatment and management of PMR in clinical practice will be a multistep procedure initiated by presentation and discussion of the recommendations at international and national meetings. The panel member will assist the national societies of rheumatology, internal medicine, primary care and health care professionals to implement the new
recommendations into daily clinical care. The panel members will also promote the adoption of the new recommendations by national institutes of clinical excellence in health and social care (e.g. NICE). Pocket recommendations and online tools (such as the Map of Medicine by the Royal College of Physicians [48]) may support the routine use of these recommendations.

There may also be some barriers: The enthusiasm to follow these new recommendations for example may differ between primary care physicians and specialists and may differ among countries. National health care systems with a high emphasis on international quality standards of care are more likely to adopt the new recommendations than systems without such a focus. Another barrier may be the fact that early use of MTX may lead to a shift of new PMR patients from primary toward specialty care (and thus to a shift of resources), as DMARDs are usually prescribed (and often also monitored) by rheumatologists or specialists in internal medicine.
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DISCUSSION

The 2015 EULAR-ACR Recommendations for Treatment and Management of Polymyalgia Rheumatica (PMR) is the first collaborative project between EULAR and ACR to endorse treatment recommendations in rheumatology. These recommendations provide current evidence and thinking in the field of PMR management with a particular emphasis on patients’ perspectives.

We formulated 8 overarching principles and 9 specific recommendations based on PICO questions for the management of PMR. The overarching principles were not directly part of the systemic literature review (SLR); however, there was consensus among the group that these principles reflect current standards of clinical care. The importance of patient education and the desire to have rapid access to advice from doctors or health care professionals reflect major concerns of patients, to know about the disease and its management, maintain daily function and obtain rapid support in case of disease flares or adverse events.[1]

Our specific recommendations are only partially supported by evidence, and we required expert opinion for several points. The strongest evidence was available for methotrexate (MTX), whereas basic treatment principles for PMR such as initial glucocorticoid (GC) dose and subsequent tapering regimen have not been evaluated by high quality randomized controlled trials. The group unanimously agreed that the research agenda (containing the evidence gaps related to PMR management) is an essential result of this recommendation project (Box 2). All opinion-based statements were unanimously supported by the group and thus reflect the common view of several professionals and patients from Europe, USA, South America, Africa, India, Japan, Australia and New Zealand.
A major strength of this project was the intensive input from patients and patient group representatives. Patient representatives from PMRGCAuk and PMRGCA Scotland were involved in all parts of the project, from prioritisation of critical outcomes, to the formulation of the PICO questions, to the drafting of the recommendations. The involvement of GPs and patients from non-English countries was certainly desirable but was unfortunately not feasible within this setting and time frame, given the assumed language restrictions and logistic difficulties.

The recommendations reflects efforts to identify the outcomes most relevant to patients but also acknowledges that future research on patient-related outcomes (e.g., qualitative research studies) is necessary to achieve a better understanding of which aspects of the disease and treatment are most important to patients.[2]

We used GRADE as a framework to develop the recommendations because this methodology has become the standard approach for all new ACR recommendations.[3–6] GRADE has several advantages: it is a transparent process with explicit rating of quality of evidence, it attributes a high relevance to patient preferences and values, takes into account trade-off and resource use, enables the grading of evidence across outcomes (with 1 study contributing to several outcomes with different levels of evidence) and is flexible in using external (clinically important) evidence. On the other hand, GRADE does not explicitly value the number of studies and is less well developed for prognostic factors and rare outcomes. Consequently, the quality of evidence for adverse events is usually lower than for efficacy data, as demonstrated in our SLR. This necessitated the use of relevant external evidence to strengthen this aspect of our recommendations.

We recognize that our recommendations do not cover all aspects possibly important for the management of PMR. For example, we excluded specific PICO questions on
the prevention of GC-induced osteoporosis and immunization to reduce duplication of
effort because there are published recommendations by the ACR [7] and EULAR [8],
respectively, on these issues. Other aspects that we do not cover in these
recommendations are 1) optimal duration of treatment (related to GCs and MTX),
although our recommended GC tapering schedule assumes a minimum of 12 months
treatment; 2) optimal referral pathways from primary to subspecialty care; or 3)
management of patients with long-standing disease and low-dose GC therapy. While
formulating the PICO questions, we attempted to focus on issues most relevant to
patients and physicians, as well as areas with the highest likelihood of available high
quality data. We hope, however, that future versions of these recommendations will
address these topics specifically.

Due to our rigorous SLR approach to select high quality papers, we did not include
other reviews, case reports and case series indicating possible treatment options in
treatment resistant PMR patients. For example, we found one earlier SLR reporting
similar conclusions regarding the value of MTX in PMR.[9] Besides, 2 case series
were recently published on the use of leflunomide in PMR [10,11] and a few case
reports are available on tocilizumab.[12–14] In clinical practice, tocilizumab has been
either applied in patients with GC- or DMARD-resistant disease [12] or in cases with
a contraindication to GCs where even intramuscular methylprednisolone may not be
a safe option.[13] There is also experience of the efficacy of judicious intra-articular
injections in the treatment of localised PMR symptoms.[90] Azathioprine has been
tested in a double-blind randomized controlled trial in patients with PMR and GCA;
however, as PMR patients were not analysed separately, we did not include this
study in the SLR.[15] We are aware of a few ongoing randomized controlled trials on
biological agents including tocilizumab, secukinumab and canakinumab;
nonetheless, additional studies particularly on the value of conventional (synthetic
and targeted) DMARDs are necessary to provide further treatment options in difficult to treat PMR patients.

We formulated 10 PICO questions on prognostic factors in order to identify different subgroups to whom management plans may be tailored specifically (as proposed for other diseases previously [16,17]). We found results on prognostic factors were very heterogeneous, and studies were of varying quality, challenging the proposal of tailored treatment plans. The group felt that females, patients with high erythrocyte sedimentation rate (ESR) and patients with peripheral inflammatory arthritis may have a worse prognosis than other patients and that these factors should be considered, as treatment decisions are made.

Moreover, there was robust external evidence from other ACR and EULAR recommendations suggesting an increased risk of GC-related adverse events in patients with certain co-morbidities and co-medications.[7,18–20]

It was beyond the scope of this recommendation project to define treatment targets in PMR. “Clinical improvement” was considered as the first treatment goal after the initiation of GCs, and we reference to the response criteria used in the 2012 classification criteria study.[21,22] Remission and relapse have been heterogeneously defined in the literature, as we pointed out in a previous Delphi project.[23] Future prospective studies aimed at the validation of new definitions of response, remission and relapse are, therefore, required to enable a targeted treatment approach in PMR.[24]

The question whether the adoption of these new recommendations into clinical practice will lead to a higher resource use or help to save costs is yet unclear. Direct costs of drug treatment is presumably negligible since no recommendation was made
toward the use of expensive, biological agents. A more frequent use of MTX may lead to a higher resource use/resource shift due to monitoring and referral to secondary care but on the other hand it may help to save costs in the long-term by a reduction of GC induced adverse events. These and other issues related to the cost-effectiveness of the new recommendations should be clarified by future health economic studies.

These recommendations should support clinicians to achieve the best patient outcomes. Further research on existing drugs is necessary to offer additional, evidence-based treatment options to our patients. We anticipate an update of these recommendations 3 years upon their publication; however, an earlier revision may be necessary if new data which would modify the current recommendations become available.
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Joint EULAR and ACR recommendations for best practice in polymyalgia rheumatica

Steroids are the best option for patients with polymyalgia rheumatica.

INTRODUCTION
Polymyalgia rheumatica is an inflammatory condition that causes pain and stiffness in the muscles, usually around the upper arms, shoulders, neck and hips or thighs. The stiffness is worse in the mornings and can severely limit movement and activities. The cause of polymyalgia rheumatic is not known, but it is a fairly common condition that develops most commonly in people aged 60–70 years, and more often in women than men. The condition is usually treated with painkillers or steroid medicines.

Recommendations give advice to doctors and patients about the best way to treat and manage particular diseases. They are written by a group of experts based on the most-up to date evidence.

WHY ARE RECOMMENDATIONS NEEDED?
Until now there has been wide variation in how people with polymyalgia rheumatica have been treated. These recommendations aim to help to standardise the care that people receive and support doctors in making decisions.

HOW WERE THE RECOMMENDATIONS DEVELOPED?
Two well-respected societies – EULAR (European League Against Rheumatism) and ACR (American College of Rheumatology) – worked together to develop these recommendations. The authors performed a search of all the literature published on polymyalgia rheumatica and then used a pre-defined methodology to develop each individual point to say whether they were in favour of or against a particular medicine or intervention that might be offered to a patient.

WHAT ARE THE MAIN RECOMMENDATIONS?
The recommendations are listed below. Overall, the recommendations say that it is important to assess each patient holistically, looking at their demographics, disease severity, co-morbidities and risk factors for side effects from steroids, as well as taking into account patient preference and choice. The authors emphasise that it is important to make sure that the diagnosis of polymyalgia rheumatica is confirmed properly before beginning to use steroids, starting with low doses of up to 25 mg. Steroids can cause side effects such as diabetes and osteoporosis (bone loss and fractures) so it is important not to take higher doses than are needed.

Patients should receive education on their condition and be given specific exercises to do as well as access to a helpline where they can get advice. Anti-inflammatory painkillers should not be used. Instead, a single daily dose of steroids should be given. Early use of medicines such as methotrexate may be recommended for people with very severe disease, or those who get no response from steroids or cannot use them. Biologic medicines are not recommended in polymyalgia rheumatica.

Recommendations
1. Use steroids rather than anti-inflammatory painkillers, except where short-term pain relief is needed for other conditions
2. Use the lowest possible dose of steroid
3. Higher doses of steroid may be used as needed in patients with high risk of recurring disease and a low risk of side effects from the steroids
4. The dose of steroid should be reduced once symptoms are better and patients monitored
5. Steroid injections can be considered instead of oral steroids where needed
6. Daily oral steroids should be given in a single dose
7. Methotrexate may be considered in severe disease or for patients who get no response from steroids or cannot use them
8. Biologic medicines such as TNF-inhibitors should not be used
9. An exercise programme may help to maintain muscle mass and function
10. Chinese herbal preparations should not be used

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ARE THESE RECOMMENDATIONS NEW?
In 2010 the British Society of Rheumatology (BSR) published recommendations on polymyalgia rheumatica. But this is the first time that EULAR and the ACR have worked together to give a recommendation on management of any rheumatic disease (previous joint projects have looked mainly at disease criteria). These recommendations use new evidence to build on the earlier BSR ones.

HOW RELIABLE ARE THE RECOMMENDATIONS?
The most important limitation of this project is the lack of good trials in polymyalgia rheumatica. It is also possible that the methodology used to write the recommendations is not suitable for assessing very rare outcomes and events.

WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?
These recommendations will be used by doctors to tailor treatments for their patients and help to achieve the best possible outcomes from care. The recommendations are only advice, and they may be adapted by different countries according to how local healthcare systems are set up. The authors would like to see polymyalgia rheumatica given the same standard of care as rheumatoid arthritis. More studies are being planned to investigate polymyalgia rheumatica, and these recommendations will be updated in about 3 years based on any new evidence that has emerged.

WHAT DOES THIS MEAN FOR ME?
These recommendations should ensure better treatment for patients with polymyalgia rheumatica. A more cautious use of steroids and better monitoring and assessment should help to reduce any side effects. If you are taking painkillers for your polymyalgia rheumatic, you may wish to talk to your doctor about alternative treatments that might help you.

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