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 provides 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.

REFERENCES

1 Gilbert K. *Polymyalgia Rheumatica and Giant Cell Arteritis: a survival guide*. Amazon Digital Services 2014. http://www.amazon.com/Polymyalgia-Rheumatica-Giant-Cell-Arteritis-ebook/dp/B00IJJBXS2/ref=sr_1_3?ie=UTF8&qid=1397063656&sr=8-3&keywords=gilbert+kate (accessed 9 Apr2014).

2 Mackie SL, Arat S, Silva J da, *et al.* Polymyalgia Rheumatica (PMR) Special Interest Group at OMERACT 11: Outcomes of Importance for Patients with PMR. *J Rheumatol* 2014;**41**:819–23.

3 American College of Rheumatology. Policy and Procedure Manual for Clinical Practice Guidelines. 2012.http://www.rheumatology.org/practice/clinical/guidelines/ACR_Guideline_Manual.pdf

4 Brozek JL, Akl EA, Jaeschke R, *et al.* Grading quality of evidence and strength of recommendations in clinical practice guidelines: Part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies. *Allergy* 2009;**64**:1109–16.

5 Brożek JL, Akl EA, Compalati E, *et al.* Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. *Allergy* 2011;**66**:588–95.

6 Brożek JL, Akl EA, Alonso-Coello P, *et al.* Grading quality of evidence and strength of recommendations in clinical practice guidelines. *Allergy* 2009;**64**:669–77.

7 Grossman JM, Gordon R, Ranganath VK, *et al.* American College of Rheumatology 2010 recommendations for the prevention and treatment of

glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)* 2010;**62**:1515–26.

8 Van Assen S, Agmon-Levin N, Elkayam O, *et al.* EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2011;**70**:414–22.

9 Hernandez-Rodriguez J, Cid MC, Lopez-Soto A, *et al.* Treatment of polymyalgia rheumatica: a systematic review. *Arch Intern Med* 2009;**169**:1839–50.

10 Diamantopoulos AP, Hetland H, Myklebust G. Leflunomide as a corticosteroid-sparing agent in giant cell arteritis and polymyalgia rheumatica: a case series. *Biomed Res Int* 2013;**2013**:120638.

11 Adizie T, Christidis D, Dharmapaliah C, *et al.* Efficacy and tolerability of leflunomide in difficult-to-treat polymyalgia rheumatica and giant cell arteritis: a case series. *Int J Clin Pract* 2012;**66**:906–9.

12 Al Rashidi A, Hegazi MO, Mohammad SA, *et al.* Effective control of polymyalgia rheumatica with tocilizumab. *J Clin Rheumatol* 2013;**19**:400–1.

13 Macchioni P, Boiardi L, Catanoso M, *et al.* Tocilizumab for polymyalgia rheumatica: report of two cases and review of the literature. *Semin Arthritis Rheum* 2013;**43**:113–8.

14 Hagihara K, Kawase I, Tanaka T, *et al.* Tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica. *J Rheumatol* 2010;**37**:1075–6.

15 De Silva M, Hazleman BL. Azathioprine in giant cell arteritis/polymyalgia rheumatica: a double-blind study. *Ann Rheum Dis* 1986;**45**:136–8.

16 Smolen JS, Landewé R, Breedveld FC, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-

modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;**73**:492–509.

17 Gossec L, Smolen JS, Gaujoux-Viala C, *et al.* European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis* 2012;**71**:4–12.

18 Duru N, van der Goes MC, Jacobs JWG, *et al.* EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2013;**72**:1905–13.

19 Van der Goes MC, Jacobs JWG, Boers M, *et al.* Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. *Ann Rheum Dis* 2010;**69**:1913–9.

20 Hoes JN, Jacobs JWG, Boers M, *et al.* EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2007;**66**:1560–7.

21 Dasgupta B, Cimmino MA, Kremers HM, *et al.* 2012 Provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Arthritis Rheum* 2012;**64**:943–54.

22 Dasgupta B, Cimmino MA, Maradit-Kremers H, *et al.* 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis* 2012;**71**:484–92.

23 Dejaco C, Duftner C, Cimmino MA, *et al.* Definition of remission and relapse in polymyalgia rheumatica: data from a literature search compared with a Delphi-based expert consensus. *Ann Rheum Dis* 2011;**70**:447–53.

24 Smolen JS, Aletaha D, Bijlsma JW, *et al.* Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;**69**:631–7.