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.
REFERENCES


