Guidelines for PMR Favor Lowest Effective Dose of GCs as Initial Therapy

Written by Wayne Kuznar

The 2014 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) guidelines proposal for the treatment and management of polymyalgia rheumatica (PMR) and the process to develop them were discussed in a special session.

Bhaskar Dasgupta, MD, Southend University Hospital, Anglia Ruskin University, Westcliff-on-Sea, United Kingdom, started by enumerating the significant health care burden of PMR, including that patients with PMR are nearly twice as likely to have a history of myocardial infarction and have approximately double the incidence of peripheral vascular diseases and cerebrovascular diseases compared with the general population. These comorbid conditions are mainly responsible for the increased health care costs associated with PMR.

Of the rheumatologic conditions, the one with the most uncertain diagnosis is PMR, because the polymyalgic syndrome is found in most late-onset rheumatologic conditions, said Prof Dasgupta. Late-onset spondyloarthropathy, constitutional symptoms, and a high erythrocyte sedimentation rate (ESR) may mimic PMR. Distinguishing isolated PMR from giant cell arteritis with polymyalgia is an important challenge.

Evaluation of the patient with PMR starts with ruling out mimics and assessing the overlap with inflammatory arthritis and large vessel vasculitis. Severity should be assessed in terms of pain, stiffness, and disability. The choice of steroid dose must be individualized, and advice on range of motion exercises for the shoulder and pelvic girdle muscles should be provided.

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The core inclusion criteria for PMR, based on the 2012 EULAR/ACR Provisional Classification Criteria Study, are new-onset bilateral shoulder pain, with or without hip pain, associated with an abrupt onset; morning stiffness >45 minutes; patient age >50 years; duration of pain >2 weeks; and a raised ESR or C-reactive protein (CRP) level [Dasgupta B et al. *Ann Rheum Dis.* 2012]. After certainty of diagnosis following appropriate laboratory tests, treatment is initiated with low-dose steroids, with assessment for response at 4 weeks. A poor response to low-dose steroids is an indication to reevaluate the diagnosis. The steroid response needs to be complete and sustained (>70% global response and normalization of inflammatory markers); doses should not be increased to normalize levels of acute phase markers.

Imaging (ultrasonography, magnetic resonance imaging [MRI], and positron emission tomography) has an important role in PMR in diagnosis, in disease monitoring, and in assessing large artery involvement. All new PMR patients should have ultrasound imaging of the shoulders, hips, and other involved structures. Imaging should also be used to exclude suspected cancer, infection, and giant cell arteritis. When the likelihood of late-onset spondyloarthropathy is high, MRI of the spine plus sacroiliac joints is indicated.

Christian Dejaco, MD, PhD, Medical University Graz, Graz, Austria, spoke about the grading of evidence used in the development of the new guidelines. Following a literature search of almost 11 000 articles, the evidence examined included the effect of 12 interventions vs comparators and the effect of 10 prognostic factors (including age, sex, high ESR, rapid response to steroids, presence of peripheral arthritis, high disease activity at time of diagnosis, long symptom duration, and presence of comorbidities) on outcomes.

Relevant outcomes were determined by patient interviews, literature search, and surveys of general practitioners, rheumatologists, and patients. The most important outcomes were determined to be disease remission, disease relapse, duration of glucocorticoid (GC) therapy, discontinuation of GC therapy, cumulative GC dose, development of giant cell arteritis during follow-up, and GC-related side effects.

For the prognostic factors, strict criteria were used that included only original data with follow-up >6 months available; a systematic literature search yielded 16 articles on intervention, 30 on prognostic factors, and 6 that reported data on both interventions and prognostic factors. For the interventions, trials with a shorter follow-up were also included. Prof Dejaco discussed the results with the highest levels of evidence.

On the question of the effect of an initial low dose (10 to 20 mg) of prednisone (vs 20 to 30 mg), only the outcome of relapse rate at 2 months had a level of evidence rated as moderate, from a single randomized controlled trial. In this study, the relapse rate was lower at 2 months in the higher initial dose group. All trials of methotrexate (MTX) with moderate- or high-quality evidence found a benefit to MTX in PMR, including higher remission rate, lower relapse rate, higher discontinuation of prednisone, and a lower cumulative GC dose.

With respect to prognostic factors, females have a higher rate of GC-related side effects than males. Conflicting results were obtained with ESR at the time of diagnosis and peripheral arthritis as prognostic factors.

The working group's recommendations contained in the 2014 ACR/EULAR guidelines for treatment of PMR, and the next steps, were discussed by Eric L. Matteson, MD, MPH, Mayo Clinic, Rochester, Minnesota, USA.

The target population for the guidelines are patients with PMR meeting the 2012 EULAR/ACR provisional classification criteria [Dasgupta B et al. *Ann Rheum Dis.* 2012], as described by Prof Dasgupta. Dr Matteson discussed several principles of PMR management, the first being documentation of a basic laboratory data set that includes rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies, CRP and/or ESR, and bone profile—including calcium and alkaline phosphatase. The second management principle is determination of comorbidities such as hypertension, diabetes, glucose intolerance, and cardiovascular disease. Risk factors for relapse or prolonged therapy need to be assessed.

The working group recommended consideration of referral to a specialist, especially with atypical presentation. It also recommended an individualized PMR management plan and shared decision making between the patient and treating physician. Follow-up and monitoring for disease activity and assessment of risk factors should be routine.

Specific, evidence-based guideline recommendations were as follows:

- A strong recommendation against nonsteroidal anti-inflammatory drugs vs GCs
- A conditional recommendation in favor of medium-dose over low-dose GCs, with a strong recommendation against high doses
- Use of the minimum effective dose within a range of 12.5 to 25 mg of prednisone equivalent as the initial dose
- A conditional recommendation in favor of considering intramuscular methylprednisolone as an alternative to oral GCs
- A conditional recommendation in favor of early addition of MTX to GCs
- A strong recommendation against the use of tumor necrosis factor-α inhibitors, either alone or with GCs
- A general recommendation against Chinese herbal preparations, as the only nonpharmacologic interventions for which there was any evidence

No evidence-based recommendations were possible for the following:

- Short vs long duration of GC therapy
- Rapid vs slow taper of GCs
- Divided dose of GCs vs single daily dose
- The use of nonpharmacologic interventions other than the Chinese herbal preparations

The working group agreed that future studies in PMR should be multicenter, and use a validated core outcome set and a robust trial design that would maximize the power of the studies. These proposed PMR treatment guidelines are now under review by the ACR.