The Journal of Rheumatology Volume 41, no. 4

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J Rheumatol 2014;41;819-823
http://www.jrheum.org/content/41/4/819

# Polymyalgia Rheumatica (PMR) Special Interest Group at OMERACT 11: Outcomes of Importance for Patients with PMR

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***ABSTRACT***. We worked toward developing a core outcome set for clinical research studies in polymyalgia rheumatica (PMR) by conducting (1) patient consultations using modified nominal group technique; (2) a systematic literature review of outcome measures in PMR; (3) a pilot observational study of patients presenting with untreated PMR, and further discussion with patient research partners; and (4) a qualitative focus group study of patients with PMR on the meaning of stiffness, using thematic analysis. (1) Consultations included 104 patients at 4 centers. Symptoms of PMR included pain, stiffness, fatigue, and sleep disturbance. Function, anxiety, and depression were also often mentioned. Participants expressed concerns about diagnostic delay, adverse effects of glucocorticoids, and fear of relapse. (2) In the systematic review, outcome measures previously used for PMR include pain visual analog scores (VAS), morning stiffness, blood markers, function, and quality of life; standardized effect sizes posttreatment were large. (3) Findings from the observational study indicated that asking about symptom severity at 7 AM, or "on waking," appeared more relevant to disease activity than asking about symptom severity "now" (which depended on the time of assessment). (4) Preliminary results were presented from the focus group qualitative study, encompassing broad themes of stiffness, pain, and the effect of PMR on patients' lives. It was concluded that further validation work is required before a core outcome set in PMR can be recommended. Nevertheless, the large standardized effect sizes suggest that pain VAS is likely to be satisfactory as a primary outcome measure for assessing response to initial therapy of PMR. Dissection of between-patient heterogeneity in the subsequent treatment course may require attention to comorbidity as a potential confounding factor. (First Release Feb 1 2014; J Rheumatol 2014;41:819–23; doi:10.3899/jrheum.131254)

*Key Indexing Terms:*
POLYMYALGIA RHEUMATICA OUTCOME AND PROCESS ASSESSMENT
OMERACT PAIN STIFFNESS CORE SET

Polymyalgia rheumatica (PMR) is a common inflammatory disease with a lifetime risk estimated at 2.4% for women and 1.7% for men[1]. Untreated, PMR can cause profound disability[2]. Diagnosis relies on clinical acumen and is supported by a rapid response to low- to medium-dose glucocorticoid therapy; therefore, it is essential that response to glucocorticoids is precisely defined[3]. Further, there is substantial variation in time to cessation of glucocorticoid therapy[4], only part of which can be explained by pretreatment inflammatory markers. PMR may be more heterogeneous than is commonly supposed. Work carried out by the European League Against Rheumatism

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(EULAR) working group on glucocorticoids underlines the potential morbidity incurred by patients taking these medications. In PMR, the evidence for efficacy of any treatment other than glucocorticoid remains very limited[5]; further progress in this area requires development of a consensus on important core outcomes for use in clinical trials of PMR[3].

**A Patient's Experience of Polymyalgia Rheumatica**

When I was first feeling the effects of polymyalgia rheumatica (PMR), I naively believed that I would be able to tell my doctor all about my suffering; he would prompt me with relevant questions, which would lead to either a correct diagnosis and treatment or a referral to an expert in the right field; I would be told all about the drugs I may have to take and what side effects I could expect. However, I was sadly disillusioned in a very short time. Confused, I started to see if I could find fellow sufferers to swop stories with and get advice from on what to do and where to turn. They all had a story but the differences in their experiences were huge. It turned out that I was lucky, I was diagnosed and given prednisolone within a month of the first signs, but I talked to people who were in severe pain for a year or more, were told they had a few months to live, had their homes converted with stair lifts and hoists fitted, were unnecessarily given huge amounts of prednisolone, or were hospitalized. They would list their different experiences of prednisolone: "side effects" of the drug; the amount they had been taking; the (seemingly arbitrary) changes in dose. Some had ideas about alternative therapies and diets that they believed to be beneficial.

There seems to be little evidence as to which set of criteria (if any) provides a reliable diagnosis of PMR, nor which treatment regimen is most appropriate. The devastating impact PMR might have on a person's life is not appreciated, nor is the importance of a wide range of symptoms produced by PMR. It is very important for patients to feel confident that proven methods of diagnosis and treatment are being used and that they are being listened to: Otherwise additional stress and worry further impairs recovery. I believe that what we are involved with in this group will go a long way to improving the lot of the PMR sufferer.

**1. Outcomes of Importance to Patients**

In the process of planning the formal research that would be needed to define a core set of outcome measures in PMR, we started by consulting patients. In this preliminary, "scoping" consultation exercise, we used a modified nominal group technique. We invited clinic patients, who were either currently taking or had recently stopped taking glucocorticoids, to talk to us in informal discussion groups, each facilitated by a healthcare professional with relevant knowledge of PMR. This was done at 3 centers in the UK (Bristol, Leeds, Chertsey) and 1 in Belgium. At one of the UK centers (Chertsey), an anonymous postal survey was also conducted in which patients were asked to list issues of importance in their experience of PMR.

Within each discussion group, participants were asked to consider, in turn, symptoms, diagnosis, and treatment. The statements recorded by a facilitator during the group discussion were then provided to each patient and each then selected the 10 statements most important to them personally. This was a pragmatic way of ensuring that patients had time to reflect on the points raised during the discussion, and were able to anonymously record which were important to them, without disclosing to others. It also provided an anonymous record of issues raised by the discussion groups, serving as a starting point for us to consider what had emerged and plan more formal research as part of the Outcome Measures in Rheumatology (OMERACT) process. This process started at a study group meeting at the EULAR 2011 meeting and has continued by e-mail and teleconference subsequently.

In all, 104 patients with PMR were involved; because this was not a formal research study, we did not collect data about the participants themselves, such as age, sex, or treatment duration. However, some common issues arose across more than 1 center and these are now discussed. As a first approach to grouping them, we classified them under headings of the World Health Organization International Classification of Functioning, Disability and Health (WHO-ICF)[6].

*Impairments*. Symptoms, or "impairment" in WHO-ICF[6], were clearly important to patients. Pain, stiffness, fatigue, and sleep disturbance were very often mentioned. Some patients said, "The stiffness is so bad, it is pain," suggesting that for some the 2 words pain and stiffness may not always represent separate constructs. This idea has been suspected by others and potentially challenges many traditional assumptions about PMR[7]. We felt that formal qualitative research would be valuable to define exactly what patients with PMR mean by stiffness, which is the cardinal symptom in this disease. The concepts of "morning stiffness" and "early morning stiffness," although an essential part of the physician's diagnostic process to discriminate inflammatory from noninflammatory musculoskeletal symptoms, were rarely volunteered by patients using those words during group discussions unless specifically prompted. However, patients did have variation in their symptoms over the day.

*Activities*. Ability to perform activities of daily living, and to remain independent on all levels, appeared of great importance to patients. Indeed, many patients found it easier to describe what they could not do, than to describe the actual symptoms that prevented them from doing things. Getting out of bed and turning over in bed were frequently

mentioned, but patients also mentioned activities such as getting up from the floor, getting off the sofa or the toilet, driving, picking things up from the floor, opening doors, walking, or dressing. The Health Assessment Questionnaire (HAQ) Disability Index, a widely used measure of disability[8], may capture many of these aspects of activity.

*Participation*. Not many patients reported problems with participating in work or other social roles. This may relate to the age group of patients with PMR and the context of the discussions, and highlighted the need for further work exploring the nature of the effect of PMR symptoms, diagnosis, and treatment on patients' lives. Participation might be influenced by many factors including fatigue (reported by many patients), which is an important factor for other rheumatic conditions[9,10]. Anxiety and depression were mentioned by some patients; it may be worthwhile to use a standard instrument, such as the Hospital Anxiety and Depression Scale, in research studies and perhaps in clinical practice[11].

*Diagnosis and treatment*. Regarding diagnosis, the overwhelming message from our patients was that the time taken to reach a diagnosis was very important to them. As these patients were all self-recruited from secondary care, however, they may represent a more difficult-to-diagnose subset of patients. Conversely, glucocorticoid (steroid) treatment was frequently referred to as like "magic" or "a miracle," often with an effect within 3 days. Some patients mentioned a "steroid high" or a burst of energy that later "wore off."

Patients told us that as treatment went on they had increasing concern over known and potential side effects of glucocorticoids. Concerns expressed by patients often related to changes in physical appearance, including bruising, skin changes, change in facial shape, hirsutism, and thinning of scalp hair. Patients were also concerned about delayed wound healing, high blood sugar levels, and osteoporosis. Patients were concerned about the need to take extra tablets to reduce the risk of steroid-related complications. Fear of relapse and difficulty managing the steroid dose reduction were described as important for some patients. Patients sometimes found it hard to tell whether some of their ongoing symptoms (such as sweating) were due to the PMR or the glucocorticoid treatment, or were simply the effects of age or comorbidities.

A common theme was patients' requirement for information, and for their treating physicians to be well-informed about the disease, both in primary and secondary care. For example, patients at 1 center said that they had been worried that doing sport or physical exercise might be damaging, and that it was important to them to be reassured that physical activity was not harmful in PMR. The value of a multidisciplinary approach was emphasized; the family physician, hospital specialist, and nurse-led advice lines were all specifically mentioned and patients expressed a need for clear directions as to how to reduce their glucocorticoid dose.

In response to the messages arising from this conversation with patients, the OMERACT PMR Outcomes Working Group was formed. We feel it is worthwhile documenting these informal consultations with patients to make explicit our participatory approach, central to the OMERACT philosophy, in which patients are involved as partners at all stages of research[12,13]. We initiated 3 studies that were briefly reported at the OMERACT PMR Special Interest Group (SIG).

## 2. Literature Review of Outcome Measures Used in Studies of PMR

C. Duarte reported on a systematic literature review of outcome measures used in studies of PMR, on behalf of herself and J. da Silva. Of 623 articles screened, 8 observational studies and 13 controlled trials met the selection criteria. Pain was recorded as an outcome in 11. Of these, 6 used a visual analog scale (VAS) with no defined stem question or anchors, and the remainder used differently named grades. "Morning stiffness" was recorded in 10, but there was no consistency about how this was defined or collected. Blood markers of inflammation (erythrocyte sedimentation rate and C-reactive protein) were nearly always recorded. A few studies measured function (using the HAQ[2,14]) and 1 observational study assessed health-related quality of life using the Medical Outcome Study Short Form Health Survey 36[2]. The main conclusion was that, although standardized effect sizes following treatment were large (2.5 to 6.5), these studies used nonspecific instruments; there was a lack of consensus on definitions; and there was poor evidence of validity.

## 3. Pilot Work on Measuring Symptoms and Function in PMR

S. Mackie and C.T. Pease described pilot work on measuring symptoms and function in PMR. Ethical approval was obtained (MREC 09/H1307/98 and MREC 05/Q1108/28) and patients gave informed consent. Patients presenting to clinic with untreated PMR (n = 23) were assessed using outcome measures arbitrarily selected from the literature. Patients tended to give higher pain and stiffness VAS scores if asked specifically about pain at 7 AM or on waking, rather than referring to pain "now" at the moment of completion of the questionnaire.

Because of this finding, patients were also asked about their function in the morning and evening; about half the patients reported better function in the evening than the morning, although function often remained impaired all day. Further discussion with patient research partners about the face validity of HAQ in PMR revealed that almost all the items in the HAQ had potential relevance to activities affected by PMR.

**4. Qualitative Study**

R. Hughes described a multicenter study on the meaning of stiffness for patients with PMR. Ethical approval was obtained (REC 12/LO/0120) and participants provided informed consent. Eight focus group discussions were held, each involving 6 to 8 patients with PMR. Discussions were guided by the same set of broad introductory questions, recorded, transcribed, and analyzed by formal qualitative methods using thematic analysis[15]. A full report is being prepared, but saturation of themes was achieved, and progress is being made toward explicitly defining stiffness in PMR and its relationship to pain. Further, inductive analyses also saw themes emerging about the effect of PMR on participants' lives.

**Discussions at the OMERACT PMR SIG**

Potential new opportunities to improve the treatment of PMR[16] make the definition of appropriate outcome measures a pressing need. From an industry perspective, outcomes used to support labeling claims need to meet the criteria laid down by regulatory bodies such as the US Food and Drug Administration[17]. Typically 2 well-controlled clinical trials each with $p < 0.05$ for a single indication are required for drug licensing using accepted primary efficacy endpoints (e.g., the American College of Rheumatology 20% response criterion for rheumatoid arthritis); and any patient-reported outcome measures used in a study must be adequately validated. From this perspective, the VAS for pain would be acceptable.

While "stiffness" clearly emerged as an important outcome from the patient perspective, the proper wording to use and the distinction of stiffness from pain requires clarification. Both stiffness and pain had high effect sizes, so that the primary outcome measure of pain would be adequate while other outcomes such as stiffness and function (and blood inflammatory markers) could remain as secondary or exploratory. The importance of assessing comorbidity as potential confounders of measures of pain and stiffness was also discussed. The preliminary work on HAQ suggests that HAQ is probably adequate to measure functional change in response to therapy.

A broader view of the published studies and what happens to the outcome measures in the longer term led to the suggestion that there may be a very large initial effect size of treatment with prednisone 15 mg daily, but that subsequently there is a "tail" of symptoms that persists in some patients. Whether these symptoms in treated patients are due to uncontrolled disease, or comorbid conditions that can also cause pain and stiffness, is unclear. It is possible that this "tail" phenomenon might be due to heterogeneity within the group, in that a small number of patients with poor response to treatment might affect the summary statistics for the whole patient group. This could be explored in future data analysis. Overall, the view of the SIG participants was that there are sufficient data on the main outcomes discussed above to allow the design of randomized controlled trials in PMR using pain VAS as the primary outcome measure but also measuring stiffness.

In recommending outcome measures for clinical trials of patients with untreated PMR, the large standardized effect sizes observed with initial therapy for PMR suggest that pain VAS is likely to be satisfactory as a primary outcome measure for assessing response to initial therapy. Issues raised by patients as key concerns also included delay to diagnosis, and fear of glucocorticoid adverse effects and/or disease relapse.

In recommending outcome measures for longitudinal observational studies, attention should be given to possible heterogeneity in reasons for the ongoing "tail" of symptoms, and the potential confounding role of comorbidity.

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