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Development of a provisional core domain set for polymyalgia rheumatica: report from the OMERACT 12 Polymyalgia Rheumatica Working Group

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Abstract

Objectives: The OMERACT Polymyalgia Rheumatica Working Group aims to develop a core set of outcome measures to be used in clinical trials for PMR. Previously-reported work from OMERACT 11 included a qualitative study of the patient experience and a preliminary literature review.

Methods: A three-round Delphi survey of clinicians and PMR patients was undertaken to identify a candidate core domain set for PMR research. Additionally a literature review of outcome measures and their respective measurement instruments was undertaken. Meetings of patient research partners and clinicians were convened in order to review face validity of the provisional core domain set, which was subsequently presented and discussed at the OMERACT 12 congress.

Results: Of the 60 clinicians taking part in Round 1, 55 took part in round 2 and 51 in round 3. Of the 55 patients that took part in round 1, 46 and 35 took part in subsequent rounds. 91% of participants in round 3 deemed the resulting draft core domain set reasonable. The literature review identified 28 studies for full review. Measurement instruments for each proposed domain were identified. Clinicians are highly aware of glucocorticoid-related adverse effects, but there is relatively little evidence about their true prevalence and severity especially in PMR.

Conclusions: A provisional core domain set is presented for clinical trials in PMR, comprising: acute phase markers, physical function, death, glucocorticoid-related adverse events and development of giant cell arteritis. Measurement instruments are suggested that may cover each domain but these require formal validation for clinical trials in PMR.

Introduction

Polymyalgia rheumatica (PMR) is the inflammatory rheumatic disease which has the highest incidence in those over 60 years of age with an estimated prevalence of 711000 adults in the USA [1]. Its effects can be devastating to patients' lives (Box 1). Treatment with glucocorticoids remains the cornerstone of treatment [2,3]. The OMERACT PMR special interest group (SIG) was set up to identify a set of core outcome measures using OMERACT Filter 2.0 methodology [4] and builds on work previously presented at OMERACT 11 [5].

Box 1: A Patient's story

"….I started getting fit for a summer hill-walking and after the first long day's walking, came back with soreness and stiffness in the right groin. I thought I had pulled a muscle or damaged a tendon so rested it for a few days. At the point where I could hardly walk as far as the bus stop, had great difficulty getting in or out of a car and could no longer drive because my legs would not do what I wanted them to, I should probably have seen my GP.

Both shoulders became acutely painful and I could not straighten my knees. This was no longer an ache but severe pain which prevented me sleeping at night and forced me to lie flat on my back so that I did not turn over on to sore hips and shoulders

I could not get out of bed without help, was having night sweats, I had lost my appetite and felt really ill. When I needed to ask for assistance with dressing in the morning, I finally accepted that I was needing more help than my new granddaughter.

The next day I was given a provisional diagnosis of PMR with what I was told were classic symptoms. This was confirmed by my blood tests and I was started on 15mg of prednisolone. Within two weeks I stopped sleeping all day and could move back to my own bedroom, which had been inaccessible as I was quite unable to climb stairs….."

Over the four years my symptoms have varied in strength around my body, from month to month and over any 24 hour period so that if asked to complete any survey question on pain, stiffness or functioning it would have to be very clear whether this referred to now, in the last week, or on average since last seen by the doctor."

Lorna Neill. OMERACT Patient research partner

Delphi survey of clinicians and patients

A three-round Delphi survey of 60 international clinicians with an interest in PMR and 55 UK PMR patients was conducted. In Round 1, a list of candidate domains was provided which had been identified from a previous work [5]. Participants were invited to identify their 'top ten' domains and to add further domains or comments. Patient and clinician surveys were conducted in parallel for Rounds 1 and 2 and combined for round 3. Domains from Round 1 placed by >70% of either group in their top ten were deemed included. The remaining domains identified by at least 20% of either group were distributed for a second round of voting to determine which were essential additions to those already included. In the final round, an overall opinion on the combined outcome set was sought, and suggestions invited for potential instruments. Lastly, the survey results were discussed at meetings of patient research partners and clinicians.

60 clinicians participated in Round 1, 55 in round 2 and 51 in round 3. Of the 55 patients who took part in round 1, 46 and 35 took part in subsequent rounds. Table 1 illustrates the draft core domain set after Rounds 1 and 2 which was provided to respondents for Round 3 with 91% agreeing that this was a reasonable draft core domain set.

The most common reason given by clinicians for non-agreement (n=6) was concern about including the domain "muscle weakness" that had been identified by patients, therefore this could not be included in the provisional core domain set but was identified as an item for future research. Glucocorticoid-related adverse effects were identified as important, but there was no consensus on how they should be measured.

Table 1. Draft core domain set provided for round 3

Patients requested that "stiffness" was considered instead of "morning stiffness". It was also suggested from the clinician group that development of GCA should also be reported in any clinical trial of patients with PMR.

Drug adverse effects have not in the past been included as domains within OMERACT Core Domain Sets, but OMERACT Filter 2.0 makes provision for identifying specific adverse effects of interest [4]. The concerns of both patients and clinicians about potential adverse effects of glucocorticoids, suggested that recording specific glucocorticoid adverse effects might need to be included in the core set.

Literature review of outcome measures and respective measurement instruments used in PMR research

A literature search was performed of the major medical databases. Relevant PMR terms for Medline and EMBASE illustrated in box 2 were used. Additionally the thesaurus function which performs searches using all relevant associated terms was used for each database. Identified titles and the subsequent abstracts were screened. The final full text articles were then reviewed to identify any outcome measures and associated instruments that had been reported.

Box 2. Search terms used to search Medline and EMBASE medical databases

562 abstracts were identified with 28 papers included for full text review. The identified outcome measures and respective instruments relevant to the identified candidate core domains are presented in table 2.

Medline

- Polymyalgia Rheumatica/
- polymyalgia.mp.
- (senile adj2 gout).mp.
- (rheumatic adj2 gout).mp.

Embase

- exp rheumatic polymyalgia/
- (polymyalgia adj2 rheumatic$).mp.
- (senile adj2 gout).mp.
- (rheumatic adj2 gout).mp.

Table 2 Instruments identified relevant to identified candidate core domains

Instruments were found that covered all of the candidate domains in the provisional core domain set from the Delphi survey, except for glucocorticoid-related adverse effects. One study reported poor test-retest reliability for fatigue VAS, morning stiffness duration and the SF36 mental component score although it was unclear whether this represented variation in the underlying symptoms rather than issues with the instruments themselves [6]. The HAQ has also been evaluated in PMR, and was found to be responsive to change and correlated with other outcome measures[7].

Stiffness

Qualitative work relating to the patient experience of stiffness in rheumatoid arthritis (RA) that allowed a comparison with stiffness in PMR was reported at OMERACT 12. Patients with RA reported that their stiffness was highly variable in relation to time, duration and intensity, and had an impact on many aspects of their daily life. This parallels the experience of stiffness in PMR and its relationship to physical function [5] although it cannot be directly compared as no established DMARD therapy and no data on widely used biological therapies are available for PMR.

Glucocorticoid-related adverse events

A large number of adverse events of glucocorticoids (GC) have been described, but extensive review work done by the EULAR Task Force demonstrated that good evidence on their prevalence and severity at different daily and cumulative doses is mostly lacking [8]. This is an important issue since it challenges many of our assumptions about the risks of treatment in PMR.

In OMERACT Filter 2.0 a Core Adverse Event has been defined as an adverse event that should be measured in every study to which the 'parent' core set pertains. As PMR is currently predominantly treated with GC, and fear of adverse effects is an important factor affecting treatment in routine practice, core set developers might consider designating (some) GC adverse effects as Core Adverse Events. This would allow the collection of high quality data on the actual incidence of GC-related adverse events. This harmonisation of data collection to facilitate data synthesis and meta-analysis is one of the key arguments for a core outcome set.

Considerations from the group included the observation that adverse events are always reportable in trials that comply with ICH-Good Clinical Practice requirements, but that naming certain events as core would allow better attention to detail and mandatory reporting even if zero events occurred in a trial.

Summary OMERACT 12 SIG

The work described above was presented at the PMR Special Interest Group (SIG) at the OMERACT 12 congress in Budapest. The aim of the discussion was to discuss a feasible programme of work for the next 2 years to work towards a core outcome measurement set. Each of the Core Areas within Filter 2.0 was considered in turn.

Pathophysiological manifestations: Although simply measuring the acute phase markers may not be sufficient to measure all aspects of disease activity in PMR, it

was felt that acute phase markers (particularly CRP) are the most useful biomarker employed in routine clinical practice. Ultimately a biomarker for PMR that reflects disease activity better than the current acute phase markers needs development; imaging may have a possible role here. It was concluded that much useful data could be obtained from longitudinal observational studies, especially as it is currently considered unethical to justify withholding glucocorticoids in a long-term RCT of PMR.

Life Impact: Pain and stiffness were also identified as important by the Delphi. Prior work suggested that, as in RA, for some patients with PMR pain and stiffness are closely related [5]; hence in the provisional core domain set they are provisionally grouped together. The subjective experience of muscle weakness appeared important to patients but its cause, whether related to PMR or its treatment with glucocorticoids requires further elucidation. Overall, considerations of parsimony and discussions with patients identified physical function as the item that best captured the impact of PMR on their lives. The HAQ, MHAQ and/or SF-36 may be adequate for capturing at least part of this. However, these generic instruments are unlikely to capture the full extent of the patient experience in PMR and their content validity may not be optimal. Development of a patient-reported outcome tool for PMR requires a formal, rigorous approach and this remains part of the agenda for future research.

Glucocorticoid-related adverse effects: Meta-analysis of clinical trial data of the adverse effects of low-dose glucocorticoids in rheumatoid arthritis failed to show evidence of substantively elevated risk of glucocorticoids. This challenges traditional teaching about the risks of glucocorticoid therapy. However, many clinicians felt that these data may not be applicable to PMR where patients are older and arguably more vulnerable to adverse effects. Data is lacking to settle this question either way; yet the question is important as it is fundamental to arguments for development of new treatments in PMR and to determine whether that very slow reduction of glucocorticoids is very nearly as safe as the usual recommendation of fast reduction.

In order to perform a similar meta-analysis in the context of PMR, ideally glucocorticoid-related adverse effects should be captured in a consistent way across studies. Feedback from the industry perspective suggested that the standard methods for capturing adverse events in clinical trials may not provide the uniformity of data collection that would be needed for this.

Conclusion

The draft core domain set after feedback from the OMERACT 12 PMR SIG is illustrated in figure 1. The concept of parsimony is particularly relevant to trials of PMR: in many countries including the UK and the Netherlands, PMR is predominantly managed in primary care by general practitioners and as such routine

and on-going data collection may be most appropriately undertaken in this setting. The concept of an “inner core” is thus particularly important for PMR.

Except for glucocorticoid-related adverse events, within the “inner core” of essential items, candidate instruments that may be adequate for a preliminary outcome set were identified for each domain. The next step will be to begin the process of validating these according to the OMERACT Filter using existing datasets and collection of new datasets where possible.

Figure 1. Provisional core domain set for PMR

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