Outcome Measures in Polymyalgia Rheumatica. A Systematic Review

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ABSTRACT. ***Objective.*** To identify the instruments used to assess polymyalgia rheumatica (PMR) in published studies.

Methods. A systematic literature review of clinical trials and longitudinal observational studies related to PMR, published from 1970 to 2014, was carried out. All outcome and assessment instruments were extracted and categorized according to core areas and domains, as defined by the OMERACT (Outcome Measures in Rheumatology) Filter 2.0.

Results. Thirty-five articles (3221 patients) were included: 12 randomized controlled trials (RCT); 3 nonrandomized trials; and 20 observational studies. More than 20 domains were identified, measured by 29 different instruments. The most frequently used measures were pain, morning stiffness, patient global assessment and physician global assessment, erythrocyte sedimentation rate, and C-reactive protein. The definition of outcomes varied considerably between studies.

Conclusion. The outcome measures and instruments used in PMR are numerous and diversely defined. The establishment of a core set of validated and standardized outcome measurements is needed. (First Release November 15 2015; J Rheumatol 2015;42:2503–11; doi:10.3899/jrheum.150515)

Key Indexing Terms:
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Polymyalgia rheumatica (PMR) is an inflammatory disease with a lifetime risk estimated at 2.4% for women and 1.7% for men[1] and a peak incidence after 60 years of age. The diagnosis of PMR relies on clinical and laboratory manifestations, supported by a rapid, favorable response to glucocorticoid (GC) therapy at medium doses (15–20 mg/day of prednisone or equivalent). When untreated, PMR can cause profound disability. GC remains the gold standard therapy for PMR and is usually efficacious. However, the potential toxicity of longterm GC therapy[2] imposes the need to search for safer alternatives.

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Future research in PMR requires the use of valid and reliable outcome measures that encompass the relevant scope of disease manifestations. A variety of outcomes have been used to assess disease activity, including clinical features (pain and morning stiffness), ultrasonography (US) variables, and laboratory measures such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6) levels. Composite scores of disease activity[3], and definitions of good response, remission and relapse have been proposed[3,4,5,6]. However, these measures have not yet been extensively validated in PMR and do not incorporate patient viewpoints.

The Outcome Measures in Rheumatology (OMERACT) initiative aims to develop core sets of outcome measures capable of providing consistent estimates of the benefits of interventions for each given condition in clinical trials[7]. According to the OMERACT Filter 2.0, such core sets should include at least 1 domain from each core area. Four core areas, broad aspects of a health condition, are defined: 3 encompass the "impact of health conditions" — life impact, resource use, and death; and a fourth core area encompasses pathophysiological manifestations[8,9]. This filter also considers domains, as subspecifications within 1 area[9,10]. In order to be included in a core set, a domain should be measurable by truthful, discriminative, and feasible instruments[9,11].

The OMERACT PMR working group was formed to define a core set of outcome measures to be used in future clinical research in PMR. With the present systematic liter-

ature review we aimed to supply this endeavor with objective information on outcome measures currently used to assess PMR disease activity and response to treatment.

MATERIALS AND METHODS

Search strategy. The literature search was performed in MEDLINE, CINAHL, Science Citation Index from the Web of Science, Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews). The research strategy was based on the following key words: ["Polymyalgia Rheumatica" (Medical Subject Headings)], and covered material published from January 1, 1970 to June 30, 2014.

Inclusion criteria. Studies were included if they: (1) used published classification criteria to select patients; (2) were written in English, French, Portuguese, or Spanish languages; (3) followed a design of either clinical trial or longitudinal observational study, and (4) were available in full text.

Studies that included heterogeneous patient samples and published data that did not allow differentiating subjects with PMR from those with other diseases (e.g., giant cell arteritis or late onset rheumatoid arthritis) were excluded.

Study selection. Titles, abstracts, and full reports of articles identified were systematically and independently screened by 2 authors (CD and RF) with regards to inclusion and exclusion criteria. In the first step, selection was based on titles and abstracts. Full reports of articles selected in this phase were evaluated (second step) to select articles to include in this systematic review. Disagreements regarding selection of an article were discussed between both reviewers until consensus was reached. Persistent disagreements were resolved by a third evaluator (JAPS).

Data extraction. During data extraction, special attention was given to Patients and Methods and Results sections of each article. All data were extracted using a standardized template designed for this review, which had been piloted and improved, and which included study design, sample size, followup period, outcome measures used, and the method of assessment.

Each outcome was characterized according to the OMERACT Filter 2.0 considering core areas (pathophysiological manifestations, life impact, death, resource use) and domains[8].

RESULTS

Results of the literature search and selection of articles are presented in Figure 1. The electronic search strategy yielded 868 articles, 43 of which were selected, on the basis of title and abstract, for further assessment/detailed review. Ultimately, 35 studies[12-21,22-31,32-41,42,43,44,45,46] met inclusion criteria for this systematic review (Figure 1). Agreement between the 2 reviewers was 96.6% and 100% for the first and second steps of article selection, respectively.

Included studies. Table 1 shows the study design characteristics of included articles. Twelve of the included studies are randomized drug trials, controlled against either placebo or conventional PMR treatment[12-21,22,23]. Three are nonrandomized interventional studies or ones without clear information about randomization[24,25,26]. Longitudinal observational studies represent more than one-half of selected articles (20 of 35)[27–36,37-46]. One of these observational studies[36] is a longterm followup of an already included RCT[20]. The study size ranged from 4[24] to 781 subjects[32,41], with followup periods varying between 14 days[22] and 34 years[32]. All studies included a majority of females and patients older than 50 years, which is in agreement with classical PMR features[47,48,49,50].

Studies identified in this literature review include outcomes and instruments pertinent to all core areas defined by OMERACT, except resource use. The core area most represented is pathophysiological manifestations, which included a total of 6 domains, followed by life impact with 5 domains (Table 2).

Pain. Pain was used as an outcome in 17 studies[12,13,14,15,16,18,19,22,25,34,36,39,40,43,44,45,46]. A visual analog scale (VAS)

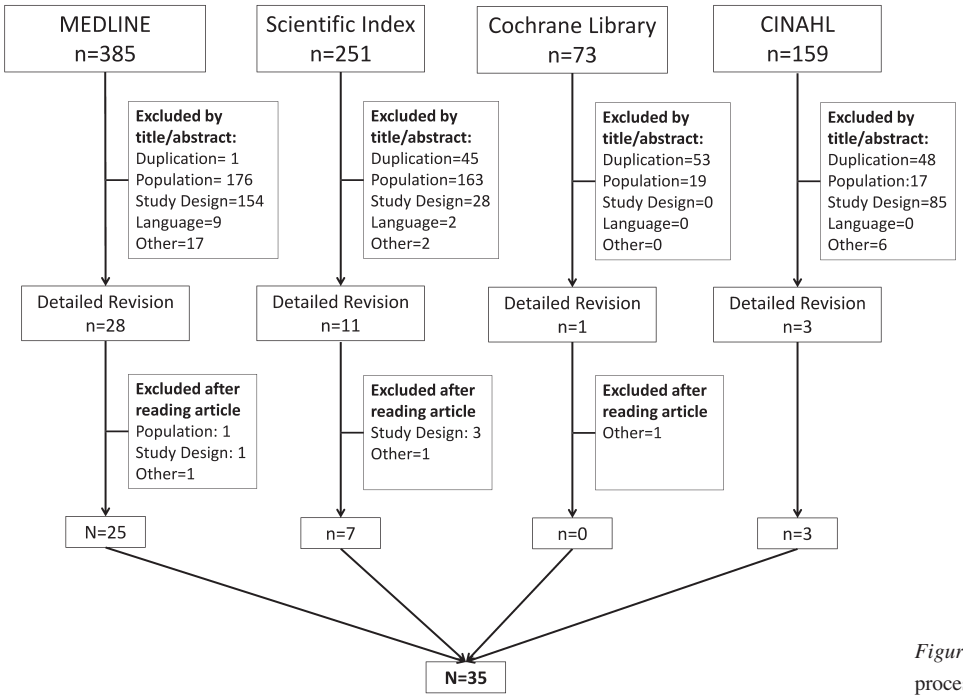

Figure 1. Flow chart of the search and selection process.

Table 1. Characterization of the studies included in the analysis.

Year	First Author and Reference	Study Design/ Protocol	Intervention	Sample Size	PMR Definition / Stage of Disease	Followup
Randomized clinical trials						
1987	Lund[12]	RCT, double blind, crossover (after a single blind parallel 3 arms)	Deflazacort vs prednisone, weight ratios of 1:1.2, 1:1.5, and 1:1.8	41	Bird / maintenance phase	12 wks
1995	Littman[13]	RCT, multicenter, placebo controlled	Tenidap 120 mg/day + PDN 10 mg/day vs placebo + PDN 10 mg/Day	32	Study definition/ stable disease	15 wks
1995	Krogsgaard[14]	RCT, double blind, controlled	Deflazacort vs prednisolone	30	Bird / new diagnoses	12 mos
1995	Di Munno[15]	RCT, double blind, crossover	Deflazacort vs methylprednisone	29	Study definition / new diagnoses	12 wks
1996	Krogsgaard[16]	RCT, double blind, controlled	Deflazacort vs prednisolone	30	Bird / new diagnoses	12 mos
1996	Ferraccioli[17]	RCT, open	Prednisone 15 mg vs prednisone 25 mg + MTX 10 mg/wk	24	Study definition / new diagnoses	12 mos
1998	Dasgupta[18]	RCT, double blind, multicenter	Methylprednisone depot vs prednisolone po	60	Study definition / new diagnoses	96 wks
2000	Salvarani[19]	RCT, double blind placebo controlled	Shoulder injection of 40 mg of methylprednisone	20	Healey / new diagnoses	7 mos
2004	Caporalli[20]	RCT, multicenter, double blind, placebo controlled	MTX 10 mg/wk + GC vs placebo + GC	72	Chuang / new diagnoses	18 mos
2007	Salvarani[21]	RCT, multicenter, double blind, placebo controlled	Infliximab 3 mg/kg vs placebo	51	Healey / new diagnoses	52 wks
2010	Kreiner[22]	RCT, double blind, placebo controlled	Etanercept 25 mg 2/wk vs placebo	20	Chuang / New diagnoses	2 wks
2011	Björman[23]	RCT, crossover, double blind	Casein vs protein-enriched dairy product	60	Rheumatologist definition*	20 wks
Non-randomized clinical trials						
2003	Salvarani[24]	Open, pilot, uncontrolled study	Infliximab + prednisone	4	Healey / longstanding disease	49 wks
2007	Catanoso[25]	Clinical trial, open, uncontrolled	Etanercept 25 mg twice/wk, 24 wk	6	Healey / relapsing/ longstanding	36 wks
2011	Cimmino[26]	Clinical trial not randomized, uncontrolled	Prednisone 12.5 mg/id	60	Bird / new diagnoses	6 mos
Observational studies						
1999	Weyand[27]	Prospective observational study	NA	30	Study definition / new diagnoses	12-33 mos
2000	Cantini[28]	Prospective observational study	NA	177	Healey / new diagnoses	5 yrs
2003	Myklebust[29]	Prospective observational study; gender-age matched controls	NA	65	Bird or Harlim / any stage	1987-1997
2005	Salvarani[30]	Prospective observational study	NA	94	Healey / new diagnoses	24 mos
2006	Boiardi[31]	Prospective observational study	NA	112	Healey / new diagnoses	24 mos
2007	Kremers[32]	Prospective observational study	NA	364	Chuand and Hunder / new diagnoses	1970-2004
2007	Leeb[33]	Prospective observational study	NA	39	Bird	18 mos
2007	Hutchings[34]	Prospective observational, multicenter study	NA	129	Hazelman / new diagnoses	12 mos
2008	Binard[35]	Prospective observational study	NA	89	Rheumatologist definition*	Not defined
2008	Cimmino[36]	Longterm followup of RCT[20]	MTX 10 mg/wk	57	Chuang / new diagnoses	5 yrs
2008	Pulsatelli[37]	Prospective observational study	NA	93	Healey / new diagnoses	24 mos
2009	Macchioni[38]	Prospective observational study	NA	57	Healy / new diagnoses	41 mos
2010	Calvo[39]	Case Cohort study	NA	20	ACR criteria (Chuang and Healey) / new diagnoses	12 mos
2010	Jiménez-Palop[40]	Prospective observational, multicenter study	NA	59	Study definition / new diagnoses	12 wks
2011	Kang[41]	Prospective observational study	NA	781	Rheumatologist definition* / new onset cases	3 yrs
2012	Mazzantini[42]	Retrospective observational study	NA	222	Bird / longstanding disease	Not defined
2012	Cleuziou[43]	Prospective observational study	NA	89	Rheumatologist definition*	Not defined
2012	Matteson[44]	Prospective observational study	NA	85	ACR/EULAR / new diagnoses	6 mos
2013	McCarthy[45]	Prospective observational study	NA	60	Jones & Hazleman / new diagnoses	6 wks
2014	McCarthy[46]	Prospective observational study	NA	60	Jones & Hazleman / new diagnoses	6 wks

*Autonomous clinical diagnoses by attending rheumatologist. PMR: polymyalgia rheumatica; RCT: randomized clinical trials; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; PDN: prednisolone; MTX: methotrexate; GC: glucocorticoid; NA: not applicable.

Table 2.Health areas, domains and instruments reported in the 35 selected articles.

Core Area	Domain	No. of Studies	Instrument	No. of Studies Using the Instrument
Pathophysiological	Laboratory markers	30	ESR	29
			CRP	23
			IL-6, fibrinogen	12
	Ultrasonography	4	Girdles US evaluation	4
	Pain	17	VAS 0–10 cm	11
			VAS 0–100 mm	2
			VAS 0–32	1
			Grade 0–3	3
	Morning stiffness	26	Duration (min)	11
			Grade	4
			Severity (VAS 0–10)	1
			As a parameter of *compositum* measure or definition	15
Life impact	PGA	9	VAS 0–10	7
			5 point–scale	2
	PhGA	14	VAS 0–10	12
			5 point scale	2
	PATSAT	1	Range 1–5	1
	Function	5	HAQ	5
	Quality of life	2	MOS–SF36	1
			VAS 0-100	1
Death	Mortality	1	SMR	1
Resource	—	0	—	—
Composite measures	Disease activity	8	PMR-AS	8
	Remission	6	Own definition	6
	Recurrence/Relapse	8	Own definition	8
Contextual factors; adverse events	Side effects	14	General	12
			Bone mineral content	2
			Vertebral fracture	2
	Glucocorticoid therapy	6	Minimal dose	2
			Cumulative dose	3
			Discontinuation	4
	Vascular disease	3	AMI, HF, CVA, PVD	3

AMI: acute myocardial infarction; PGA: patient global assessment; PhGA: physician global assessment; PATSAT: patient's satisfaction with disease status; CVA: cerebrovascular accident; HAQ: Health Assessment Questionnaire; HF: heart failure; PMR-AS: Polymyalgia Rheumatica Activity Score; PVD: peripheral vascular disease; SMR: standardized mortality rate; SF-36: Medical Outcome Study Short Form 36; VAS: visual analog scale; IL-6: interleukin 6.

was commonly used to quantify pain, usually as a 0–10 cm scale (11 studies). In 3 of them[12,14,16], pain was graded using an ordinal scale form "0" to "3."

Most published reports do not provide a clear definition of the pain being assessed. The description of pain localization varies: "shoulder and pelvic girdle pain,"[15] "proximal pain,"[34] "proximal muscle pain,"[14,16] or "joint or muscle pain."[13] Matteson and colleagues evaluated pain considering different locations including shoulder, limbs, and global[44]. None of the published reports specified the period of time under evaluation when asking patients about their "pain."

Morning stiffness. Stiffness, more commonly morning stiffness, was considered in almost all the included studies[13,14,15,16,18,19,20,21,22,24,25,26,27,28,30,33,34,35,36,37,38,40,43,44,45,46]. It was evaluated as an independent outcome in 11 studies[13,14,15,16,18,19,25,27,34,40,44], and was included as a variable in composite disease activity scores or in the definition of relapse/recurrence/remission in an additional 15 studies[19,20,22,24,26,28,33,35,36,37,38,43,44,45,46].

Morning stiffness was measured in terms of duration ("minutes") in the majority of the studies. In 1 RCT[18], morning stiffness duration was reported in 1 study through a 4-point scale (1: < 30 min; 2: 30–60 min; 3 = 60–120 min; and 4: > 120 min). In 2 studies, stiffness was graded from 0 to 3, where "0" means no symptoms; but it is unclear whether severity, duration, or both was being assessed[14,16]. No information is given to the meaning of the other values in the scale. Only Weyand and colleagues[27] evaluated the severity of morning stiffness using a 0–10 cm VAS. Only 1 RCT[13] and 1 observational study[27] gave precise information about the time interval under evaluation ("average of last week").

Patient and physician global assessment. Patient Global Assessment (PGA) of disease activity was measured in 9 studies[13,19,22,25,27,33,35,38,46], always as a 0–10 cm VAS except in 2 studies[13,17], where a 5-point ordinal scale was used.

Physician Global Assessment (PhGA) was used in 14 studies[12,13,19,22,25,27,33,35,36,38,43,44,45,46], 12 of them as a 0–10 cm VAS and 2[13,27] as 5-point ordinal scales.

In 9 studies[22,25,35,36,38,43,44,45,46] both PGA and PhGA were included as a variable within a predefined composite disease activity score.

Two instruments were employed by a single study[33]: (1) PGA of General Health and (2) Patient Satisfaction with Disease Status (classification of disease state according to the Austrian school mark system: 1 = excellent, 2 = good, 3 = average, 4 = moderate, 5 = unsatisfactory).

Function and quality of life. Function was assessed in 5 observational studies[34,36,38,44,46], 1 open label trial[25], and 3 RCT[21,22,23]. In all studies, function was assessed through the generic Health Assessment Questionnaire (HAQ)[51].

Health-related QoL was considered in 2 large observational studies[34,44] and was assessed through the generic tool Medical Outcome Study Short Form 36 Survey[52]. In a single observational study[46], QoL during the past month was assessed using a 0–100 mm VAS, where 0 means normal and 100 the worst QoL.

Other clinical outcomes. Elevation of upper limbs was considered an outcome in some studies[22,25,33,35,46], always as a component of a composite disease activity score. Upper limb elevation was measured on a 0–3 scale with the following levels: 3 = no upper limb elevation; 2 = elevation below shoulder level (< 90º); 1 = elevation at shoulder level (90º); and 0 = elevation above shoulder level (> 90º). Muscle function[23] (hand grip strength and jump test), chair stand test[23], 10-meter walking[23], and time to onset of fatigue (hours)[13] were used as outcomes in a single study each. Intensity of fatigue reported by the patient, using 0–100 mm VAS, was assessed in a single study[44].

ESR and CRP. ESR[12,13,14,15,16,17,18,19,21,22,24,25,26,27,28,30,31,33,34,35,36,37,38,39,40,43,44,45,46] and CRP[12,13,15,17,19,21,23,24,25,26,28,30,31,33,34,35,36,37,38,40,43,44,45,46] were used in the assessment of disease activity by most but not all RCT and observational studies.

Other laboratory measures. Other laboratory outcome measures used in some observational and clinical trials include serum fibrinogen[12,15,16,45,46] and IL-6 levels[19,22,24,27,30,31,37], mainly as experimental evaluations.

Ultrasonography. US was used in 3 prospective observational studies[38,40,44] and in 1 open label trial[25]. Different studies used different evaluation protocols, there being no formal proposal for the standardization of US evaluation of response to therapy in PMR. Jiménez-Palop and colleagues considered the evaluation of intraarticular synovitis at the shoulder and hip, tenosynovitis, and bursitis in the shoulder. This study demonstrated good inter and intraobserver reliability (0.96 and 0.99, respectively) but no statistically significant correlation was found with clinical and laboratory variables of disease activity[40].

Composite measures. Most of the studies integrated the individual outcome measures into composite indices, considered as response/relapse criteria or activity scores. This is summarized in Table 3. Most of them defined relapse or recurrence as the observation of new symptoms, increase of ESR (usually > 30 mm), or increase of CRP (> 0.5 mg/dl or 1 mg/dl), after remission has been achieved, in patients receiving GC or after discontinuation of GC, respectively. Proposed response criteria include improvement of symptoms and reduction/normalization of inflammatory variables (ESR and CRP). In 2003, the European Collaborating Polymyalgia Rheumatica Group proposed a core set of response criteria. These EULAR response criteria comprise an improvement in VAS pain (obligatory) and at least 3 of the following 4 items: CRP (mg/l) or ESR (mm/h), morning stiffness (min), elevation of upper limbs (0–3), and VAS PhGA[4]. However, there is considerable discrepancy in the definition of "improvement" and in the duration of improvement required to define "response."

One of the most common composite disease activity scores used was the Polymyalgia Rheumatica Activity Score (PMR-AS), developed by Leeb and Bird[6] and defined as PMR-AS = CRP (mg/dl) + elevation of upper limbs (0–3) + 0.1 × morning stiffness(min) + VAS patient pain (0–10) + VAS physician global (0–10)[1].

The PMR-AS score showed a good correlation with other outcome measures, namely with VAS PGA (r = 0.76) and ESR (r = 0.32)[6,33]. Given that CRP is a component of PMR-AS, it is not surprising that the composite score correlated with ESR, which is closely associated with CRP. Similarly, another component of PMR-AS is the patient pain VAS; and patient global VAS is usually strongly correlated with pain VAS. PMR-AS also showed very good internal consistency in 2 different cohorts (Cronbach-α 0.90 and 0.88)[6] and demonstrated reliability[3,33,53].

GC therapy. The characterization of the GC treatment regime employed is extremely variable. Only a few studies included the cumulative GC dose[21,27,36], the minimum dose required[13,17,21], the duration of therapy[21], or the percentage of discontinuation of steroids after a specified duration of followup[13,20,21,36].

Adverse events. The incidence and characterization of adverse events related to interventions were described in the majority of the clinical trials[15-24,25], and in the longterm followup study of patients treated with methotrexate[36]. None of the studies performed a systematic and structured evaluation of safety.

Some observational studies were designed to assess specific adverse events related to GC, such as vertebral fractures[39,42], bone mineral content[16,42], cardiovascular and cerebrovascular events[32,42]. One study described mortality and its causes[29]. The methods used to elicit adverse effects in observational studies was variable, but death registries and patient files were the most common sources of information.

DISCUSSION

This systematic literature review highlights a remarkable

Table 3. Summary definitions of good response, remission, relapse, recurrence, and disease activity used in different studies.

Year	Study	Good Response	Remission	Relapse (on GC therapy) or Recurrence (after GC therapy)	Activity Score
1995	Di Munno[15]	At the end of 2 wks of GC: > 50% of pain, morning stiffness, ESR and CRP improvement; at the end of 12 wks of GC: > 80% of improvement in pain and morning stiffness; ESR and CRP normal	NA	NA	NA
2000	Cantini[28]	NA	NA	Joint signs or symptoms; ESR > 30 mm/h; restart or increase GC	NA
2000	Salvarani[19]	> 70% improvement in pain-VAS, PGA and PhGA, and morning stiffness	NA	NA	NA
2003	Salvarani[24]	NA	NA	Typical symptoms; morning stiffness > 1 h; ESR > 30 mm/h; CRP > 0.5 mg/dl	NA
2004	Caporali[20]	NA	NA	Joint signs or symptoms; (aching and stiffness of shoulder, hip girdle or both); ESR > 30 mm/h; CRP > 0.5 mg/dl	NA
2005	Salvarani[30]	NA	NA	Increase of symptoms; ESR > 30 mm/h or CRP > 0.5 mg/dl; good response after increase or restart GC	NA
2007	Catanoso[25]	EULAR Response Criteria	NA	NA	PMR-AS
2007	Hucthings[34]	No pain or improvement of > 50% in VAS girdles-pain; morning stiffness < 30 min; ESR < 30 mm/h and CRP < 1 mg/dl	NA	New symptoms and worsening laboratory tests requiring increase of GC	NA
2007	Leeb[33]	NA	NA	NA	PMR-AS
2007	Salvarani[21]	NA	No symptoms or signs; normal ESR	Increase of symptoms (aching and stiffness of shoulder, hip girdle or both); ESR > 30 mm/h or CRP > 0.5 mg/dl; good response after increase or restart GC	NA
2008	Binard[35]	NA	NA	NA	PMR-AS
2008	Cimmino[36]	NA	NA	Joint signs or symptoms; (aching and stiffness of shoulder, hip girdle or both); ESR > 30 mm/h; CRP > 0.5 mg/dl	NA
2008	Pulsateli[37]	NA	NA	Recurrence of symptoms ESR > 30 mm/h; CRP > 0.5 mg/dl; good response after restart or increase GC	NA
2009	Machioni[38]	NA	NA	Reappearance of clinical manifestations; ESR > 30 mm/h; CRP > 0.5 mg/dl	PMR-AS
2010	Kreiner[22]	NA	NA	NA	PMR-AS
2011	Cimmino[26]	NA	≥ 70% improvement in clinical symptoms of PMR; ESR and CRP normal 1 month after start therapy	NA	NA
2012	Cleuziou[43]	NA	NA	NA	PMR-AS
2013	McCarthy[45]	NA	NA	NA	PMR-AS
2014	McCarthy[46]	NA	NA	NA	PMR-AS

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; GC: glucocorticoids; PGA: patient global assessment; PhGA: physician global assessment; NA: not applicable/available; PMR-AS: Polymyalgia Rheumatica Activity Score; VAS: Visual Analog Scale; Relapse (increase of symptoms/signs after remission or good response, in patients still receiving GC or recurrence (reappearance of symptoms and laboratory changes after remission or good response, following discontinuation of GC).

variability in the assessment of PMR in research settings. Patient reported outcomes (PRO) are the most commonly studied outcomes and were assessed in almost all studies included in this review. Fatigue, however, was evaluated in 2 studies only. Function and QoL were evaluated in less than 10% of the studies, in spite of their importance to patients[54].

The instruments used to measure PRO in the selected articles were very heterogeneous. Also, there was, in general, a poor definition of what is actually being measured (e.g., concerning morning stiffness: Is the question referring to the girdles, the hands, or elsewhere? At what time of the day? What is the time period being assessed? Are we measuring duration, severity, or both?).

There are no studies addressing the relative importance of each outcome from the patient's perspective. During OMERACT 11 (North Carolina, USA, May 2012), the PMR-SIG Group presented data from a preliminary "scoping" consultation exercise involving 104 patients with

PMR from 3 centers in the UK and 1 in Belgium. In their study, patients were invited to express their concerns regarding disease and treatment. Symptoms and "impairment" were clearly important to patients, with pain, stiffness, fatigue, and sleep disturbance being mentioned very often. Physical activity and treatment aspects like GC-related adverse effects were also considered important[54]. It is important that patients' concerns and wishes are incorporated into any core outcome set.

Outcomes assessed by physicians rather than patients were less heterogeneous. Physician-reported outcomes were used less frequently in comparison to PRO, with PhGA (0–10 cm VAS) being the most commonly used. Given the discrepancies between patient and physician evaluations that have been found in several diseases[55,56,57], it is generally considered that both PRO and physician reported outcomes should be included to capture the burden of disease.

All selected articles reported either ESR or CRP, except in studies designed to evaluate specific adverse events[29,32,41,42]. Other laboratory variables, such as IL-6 and fibrinogen, or US have been considered so far as "experimental" outcomes.

Disease activity scores or definitions of remission, incorporating both physician and patient-reported outcomes are well-established in other rheumatic diseases and may prove useful also in PMR. The concepts of remission/relapse/recurrence are not consistently defined for PMR. A composite score of disease activity, the PMR-AS, was developed by Leeb and colleagues in 2007[33] and has been used in about 40% of selected articles published after 2007.

We recognize some strengths and limitations to our study. We used the most important databases of medical research articles, considered other languages beside English, and scrutinized a long period of time. The lack of evaluation of the quality of papers may be seen as a limitation, but we believe this was the most adequate strategy to serve the primary goal of identifying all possible outcomes under current use. As a limitation, we did not search conference abstracts or contact the authors in order to enlarge our scope. By including only longitudinal observational studies and clinical trials with a PMR population, we may have lost some outcomes used in cross-sectional studies or in larger studies of rheumatic diseases. We did not perform any psychometric analysis of each instrument, as this was outside the intended scope of this work.

In conclusion, our study revealed that a great heterogeneity exists in the assessment of PMR. Most instruments have been insufficiently validated according to the OMERACT Filter, and the patients' perspective may not always have been fully covered. These data suggest that further work is needed to define and validate relevant outcome measures for assessment of PMR in order to promote clinical research in this field and enhance comparability of studies. Core areas and domains need to be defined according to OMERACT procedures. Evaluation instruments capable of satisfying the properties required by the OMERACT Filter 2.0 need to be developed, including validity, reliability, feasibility, and responsiveness.

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