Patient-reported Outcomes in Polymyalgia Rheumatica

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ABSTRACT. ***Objective***. To prospectively evaluate the disease course and the performance of clinical, patient-reported outcome (PRO) and musculoskeletal ultrasound measures in patients with polymyalgia rheumatica (PMR).

Methods. The study population included 85 patients with new-onset PMR who were initially treated with prednisone equivalent dose of 15 mg daily tapered gradually, and followed for 26 weeks. Data collection included physical examination findings, laboratory measures of acute-phase reactants, and PRO measures. Ultrasound evaluation was performed at baseline and Week 26 to assess for features previously reported to be associated with PMR. Response to corticosteroid treatment was defined as 70% improvement in PMR on visual analog scale (VAS).

Results. At baseline, 77% had hip pain in addition to shoulder pain and 100% had abnormal C-reactive protein or erythrocyte sedimentation rate. On ultrasound, 84% had shoulder findings and 32% had both shoulder and hip findings. Response to corticosteroid treatment occurred in 73% of patients by Week 4 and was highly correlated with percentage improvement in other VAS measures. Presence of ultrasound findings at baseline predicted response to corticosteroids at 4 weeks. Factor analysis revealed 6 domains that sufficiently represented all the outcome measures: PMR-related pain and physical function, an elevated inflammatory marker, hip pain, global pain, mental function, and morning stiffness.

Conclusion. PRO measures and inflammatory markers performed well in assessing disease activity in patients with PMR. A minimum set of outcome measures consisting of PRO measures of pain and function and an inflammatory marker should be used in practice and in clinical trials in PMR. (First Release March 15 2012; J Rheumatol 2012;39:795–803; doi:10.3899/jrheum.110977)

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Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatic disease of the elderly and represents the most common indication for longterm corticosteroid therapy in the community[1,2,3]. There is wide variation in management of PMR in the clinical setting, in part due to the uncertainties related to diagnosis and the heterogeneous and unpredictable disease course. Corticosteroid (CS) treatment lasts for several years and can result in serious adverse effects, of which osteoporosis, fractures, diabetes, and infections are among the worst[4]. As a result, treatment of PMR remains largely empiric[5,6].

Uniform responsiveness to low doses of CS has been assumed to be a cardinal feature of PMR. It is included in several popular diagnostic criteria and is commonly used by clinicians in both primary and secondary care to make a diagnosis of PMR. However, there is little hard evidence to substantiate this, and a previous prospective inception cohort study of PMR showed that, 3 weeks after starting prednisolone 15 mg daily, more than 55% of patients failed a complete response to therapy as defined by greater than 70% improvement in pain, morning stiffness less than half-hour, and normal inflammatory markers[7]. This emphasizes the need for clinical trials of disease-modifying antirheumatic drugs and novel agents in order to improve treatment efficacy in PMR.

The 2 foremost factors that have hampered development of new therapeutic approaches to management of PMR are, first, lack of standardized classification criteria for inclusion of subjects with PMR in clinical trials, and second, lack of reliable, valid, and sensitive outcome measures. These deficiencies have led to an inability to accurately distinguish this clinical disease entity from other conditions presenting with the polymyalgic syndrome, and difficulty with evaluation and comparison of the efficacy of different therapeutic approaches, including novel drug therapies. Better and validated measures to evaluate disease activity and outcomes may also help to reduce the CS treatment burden in the daily practice of PMR management.

In order to tackle these challenges, an international PMR Classification Criteria Work Group initiated a multinational effort in 2005 and recently proposed new classification criteria for PMR[8]. Candidate classification criteria were developed through consensus meetings and a wider survey. The performance characteristics of the candidate criteria items were then analyzed in a 6-month prospective study of patients presenting with new-onset bilateral shoulder pain. PMR cases were recruited prior to steroid therapy and treated with standardized doses of CS. As part of the same effort, the work group collected prospective data on various outcome measures in patients with PMR. The initial face and content validity of our proposed set of outcome measures were evaluated through the previous consensus meetings and Delphi surveys[8,9].

We report on the disease course of patients with PMR over a 6-month period following disease onset. The goal of our study was to prospectively evaluate the performance of various clinical, laboratory, and patient-reported outcome (PRO) measures and musculoskeletal ultrasound findings in patients with PMR, and to identify a minimum set of outcome measures that can be used in practice and in future clinical trials.

MATERIALS AND METHODS

Study population. Our study was conducted as part of a prospective cohort study aimed at developing classification criteria for PMR[8]. Assessment of outcome measures was planned as part of the original study. Briefly, the study population included a cohort of patients with new-onset PMR recruited at 21 community-based and academic rheumatology clinics in 10 European countries and the United States. Inclusion criteria for patients with PMR were age ≥ 50 years, new-onset bilateral shoulder pain, and no corticosteroid treatment (for any condition) within the 12 weeks prior to study entry, who fulfilled all the inclusion criteria [i.e., morning stiffness > 45 min, raised markers of C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR)] and exclusion criteria at presentation [i.e., no infection, active cancer, giant cell arteritis (GCA), or clinical features of the common PMR mimics] as defined by our previous report and in accord with expert clinician judgment of the participating investigator that the patient had PMR[10]. The clinical disease manifestations represented the clinical spectrum of PMR disease from mild to severe, but excluding patients with GCA. The "gold standard" for the presteroid diagnosis of

PMR was established as above at presentation and where the diagnosis was maintained without an alternative diagnosis at Week 26 of followup. Analyses of outcome measures included only the subset of patients who met the proposed classification criteria for PMR, i.e., a score ≥ 4 based on morning stiffness > 45 min (2 points), hip pain/limited range of motion (1 point), normal rheumatoid factor and/or anticitrullinated protein antibodies (2 points), and absence of peripheral joint pain (1 point)[8]. Adding 1 point for typical ultrasound findings increased sensitivity and specificity of the criteria[8]. To establish evaluation measures for ultrasonographic findings, we conducted ultrasonography of the target joint structures in 21 comparator subjects who had no history of musculoskeletal diseases.

During the 6-month duration of the study, CS treatment for the majority of the patients with PMR was maintained according to a predefined treatment protocol starting with 15 mg daily oral prednisone equivalent (prednisone or prednisolone) for Weeks 1 and 2, 12.5 mg daily for Weeks 3 to 5, 10 mg daily for Weeks 6 to 11, 10 mg/7.5 mg every other day for Weeks 12 to 15, 7.5 mg daily for Weeks 16 to 25, and tapering according to treatment response from Week 26 onward.

Followup and data collection. All patients with PMR were evaluated at baseline, 1 week, 4 weeks, 12 weeks, and at 26 weeks according to a standardized protocol. At each followup visit, clinical evaluation included opinion of the treating physicians on emergence of alternative diagnoses. Patients not considered as having PMR at any time during followup were excluded from the analysis. Data were collected using standardized data collection forms and patient questionnaires translated into national languages.

Standardized data collection forms included various inclusion/exclusion criteria items for classification of PMR (summarized previously[8]), signs and symptoms, physical examination findings, laboratory measures of acute-phase reactants (ESR, CRP), and PRO measures corresponding to various important domains in PMR. Physical examination included presence or absence of tenderness and pain on movement and limitation of the shoulders and hips. Aspects of CS therapy including change in dose and discontinuation of therapy were documented. Data regarding laboratory measures (ESR, CRP) were obtained from clinically ordered tests performed at each study center. Since values from laboratory assays used at each center varied, test results were classified as normal/abnormal using the reference ranges from each center (Table 1). A 100-mm visual analog scale (VAS) was used for recording global pain measures (shoulder pain, hip pain, global pain, and PMR) and fatigue, with 0 indicating no pain or fatigue and 100 indicating worst pain or fatigue. Data on PMR VAS scale were derived based on patients' responses to the following question, "On a scale from no effect to maximum effect, how would you rate how your PMR affects you today?". Morning stiffness was assessed by directly questioning the patient on duration of morning stiffness in minutes in the last 24 h. Functional status and quality of life were assessed using the modified Health Assessment Questionnaire (MHAQ) and Medical Outcomes Study Short Form-36 (SF-36)[11,12]. The SF-36 yields physical component summary (PCS) and mental component summary (MCS) scores that range from 0 to 100, 0 indicating the least favorable and 100 the most favorable score.

Patients who were seen at clinics with musculoskeletal ultrasound availability and expertise underwent ultrasound evaluation of the shoulders and hips at baseline visit and at Week 26 of followup. Ultrasound evaluation was performed according to European League Against Rheumatism guidelines to assess for features previously reported to be associated with PMR, including bicipital tenosynovitis, subacromial and subdeltoid bursitis, trochanteric bursitis, and glenohumeral and hip effusion[13]. A rheumatologist or radiologist experienced in musculoskeletal ultrasound of shoulders and hips performed the ultrasound examinations at each participating institution. For the shoulders, linear probes providing frequency range 6–10 MHZ and for the hips linear or curved array probes with frequency range 5–8 MHZ were used. Ultrasound measures were also obtained at 1 institution for a group of 21 subjects with normal health for comparison to patients with PMR.

Statistical analysis. Descriptive statistics (percentages, medians, interquartile ranges, etc.) were used to summarize the data. Comparisons between patients at different timepoints were performed using paired t tests for continuous measures and McNemar's test of agreement for dichotomous measures.

Table 1. Test results were classified as normal/abnormal using the reference ranges from each center.

Center	ESR, mm/h	CRP, mg/l	RF, IU/ml	ACPA, U/ml
1	< 25	< 5	< 40	< 20
2	2–37 in 1st hour	< 5	< 30	0–10
4	< 10	< 5	< 40	< 20
6	< 8 in 1st hour, < 18 in 2nd hour	< 5	< 14	< 10
8 (2 sites)	0–9	< 5	0–13	0–6
		< 8	0–14	0–10
13	Female 2–20 Male 2–15	< 10	< 16	< 7
14	Male: yrs divided by 2 Female: yrs + 10 divided by 2	< 5	1–20	< 25
18	1–20	< 10	< 25	< 25
20	< 15	< 5	< 50	< 50
21	< 28	< 5	< 20	< 26
22	< 30	< 5	< 20	< 10
23	< 37	< 10	16	< 8
24	< 37	< 10	16	< 8
25	1–15	< 10	< 40	< 7
30	< 37	< 10	16	< 8
31	0–29	< 8	< 10	< 15.6
32	Male 0–22 Female 0–29	≤ 8	< 10	< 15.6
33	0–29	< 8	< 14	< 20
34	< 20	< 8	< 14	< 16
40	< 20 women < 14 men	< 5	1–20	< 251
41	Women: (age + 10)/2 Men: age/2	≤ 8	≤ 35	< 7, negative; > 10 positive

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies.

Logistic regression models were used to examine potential predictors of response to CS treatment at Weeks 1, 4, and 26. Potential predictors included age, sex, and baseline disease characteristics including PRO and ultrasound measures.

Test-retest reliability of continuous measures was assessed in a subset of patients who reported little change (± 10 mm) on PMR VAS between baseline and Week 1 visits using intraclass correlation coefficient (2,1)[14]. The smallest detectable difference (SDD), a measure of reliability or precision, was also estimated[15]. SDD is a measure of the smallest difference for which anything smaller cannot be distinguished from random measurement error. The percentage minimal detectable change (%MDC) expressed the SDD as a percentage of the maximum possible score, which allows comparison of reliability across outcome measures.

Exploratory factor analysis was used to examine the interdependencies between outcome measures[16]. Maximum likelihood factor analysis with varimax rotation was used. Maximum likelihood tests were used to examine goodness-of-fit (e.g., to determine the number of factors). This method is thought to be superior to the eigen value > 1 or Cattell's scree plot method for selecting the number of factors[16]. This technique identified potential domains to help group the outcome measures. For each factor, variables with factor loadings > 0.5 were considered to measure similar constructs. Internal consistency (i.e., the degree to which outcome meas-

ures in the same domain hold together, or the degree to which they measure the same underlying construct) was determined by Cronbach's alpha, with cutoff values > 0.9 as indication of perfect consistency (or redundancy) and < 0.6 as poor consistency[17].

RESULTS

The study population included 85 patients with new-onset PMR who were initially treated with prednisolone/prednisone 15 mg daily tapered gradually, and assessed at baseline and Weeks 1, 4, 12, and 26 following start of CS therapy. Their mean age was 72.6 years (minimum 52, maximum 95) and 60% were women.

At initial presentation, all patients had shoulder pain and abnormal CRP and/or ESR, and 77% had hip pain (Table 2). Median duration of morning stiffness was 120 minutes with median PMR VAS 66, global pain VAS 59, fatigue VAS 58, and median MHAQ score 1.1. With the exception of the MCS, significant improvements between baseline and Week 1 were noted in all outcome measures ($p < 0.001$ for all; Table 2 and Figure 1). Between Weeks 1 and 4, improvements were noted in all outcome measures, but the improvement in fatigue VAS (median 20 at Week 1 vs median 11 at Week 4) did not achieve statistical significance ($p = 0.10$). Similarly, the improvement in the percentage of patients with hip pain (31% at Week 1 vs 23% at Week 4) did not reach statistical significance ($p = 0.09$). Of note, a significant improvement in MCS was noted between Weeks 1 and 4 ($p = 0.004$). The majority of outcome measures did not improve significantly between Weeks 4 and 26. However, the MHAQ continued to improve between Weeks 4 (median 0.1) and 26 (median 0; $p = 0.03$). As expected by the plan for tapering the CS treatment, the median prednisone dose decreased from 15 mg at baseline to 5 mg at 26 weeks. Steroid doses above the level specified in the protocol were required for 15% of patients at Week 4 and for 15% of patients at Week 26.

Ultrasound findings. Ultrasound data were available for 82 patients (Table 3). On ultrasound examination at baseline, 84% had at least 1 shoulder with findings of subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis, 57% had both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis, and 32% had at least 1 of these ultrasound findings in at least 1 shoulder and 1 hip. All ultrasound measures improved significantly between baseline and Week 26 ($p < 0.001$ for all). We also compared these ultrasound findings with a group of 21 normal subjects (mean age 67 yrs, minimum 62, maximum 71; 76% women). Significant differences between patients with PMR and normal subjects were noted for all ultrasound measures at baseline except the percentage of patients with ultrasound findings in both shoulders and both hips (16% in PMR vs 0% in normal subjects; $p = 0.05$). At Week 26, ultrasound findings involving the shoulders remained significantly higher among patients with PMR than among normal subjects, but the percentage with ultrasound findings of the hips or the hips and shoulders combined were not significantly elevated in patients with PMR compared to normal subjects.

Table 2. Clinical and patient-reported outcomes in patients with polymyalgia rheumatica (PMR). Percentages are calculated using available (nonmissing) data. The proportion of patients without C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) measurements was similar for all visits.

Feature	Baseline n = 85	Week 1 n = 77	Week 4 n = 79	Week 12 n = 77	Week 26 n = 81	p, Baseline vs Week 1	p, Week 1 vs Week 4	p, Week 4 vs Week 26
Shoulder pain, n (%)	85 (100)	52 (68)	33 (42)	25 (32)	24 (30)	< 0.001	< 0.001	0.51
Hip pain, n (%)	65 (77)	24 (31)	18 (23)	6 (8)	13 (16)	< 0.001	0.09	0.32
Morning stiffness duration, min, median (IQR)	120 (80, 240)	15 (0, 30)	0 (0, 10)	0 (0, 0)	0 (0, 2.5)	< 0.001	0.001	0.18
PMR VAS, median (IQR)	66 (46, 84)	20 (8, 44)	6 (2, 26)	4 (0, 11)	4 (1, 14)	< 0.001	< 0.001	0.79
Global pain VAS, median (IQR)	59 (47, 83)	20 (7, 43)	7 (2, 18)	4 (0, 13)	6 (2, 20)	< 0.001	< 0.001	0.70
Shoulder pain VAS, median (IQR)	60 (42, 82)	22 (5, 47)	6 (2, 22)	3 (0, 10)	4 (1, 13)	< 0.001	< 0.001	0.30
Hip pain VAS, median (IQR)	47 (17, 71)	8 (1, 28)	3 (0, 13)	2 (0, 8)	3 (0, 9)	< 0.001	0.004	0.63
Fatigue VAS, median (IQR)	58 (35, 78)	20 (9, 41)	11 (2, 34)	8 (0, 30)	8 (1, 27)	< 0.001	0.10	0.15
MHAQ, median (IQR)	1.1 (0.8, 1.7)	0.3 (0.1, 0.8)	0.1 (0, 0.4)	0 (0, 0.1)	0 (0, 0.1)	< 0.001	< 0.001	0.031
SF-36 PCS, median (IQR)	35 (31, 40)	42 (35, 46)	46 (41, 50)	49 (43, 51)	48 (39, 51)	< 0.001	< 0.001	0.50
SF-36 MCS, median (IQR)	46 (41, 52)	45 (40, 51)	49 (43, 52)	49 (45, 52)	50 (46, 53)	0.46	0.004	0.43
Abnormal ESR, n (%)	74 (90)	30 (60)	19 (30)	24 (35)	19 (31)	< 0.001	< 0.001	0.25
Abnormal CRP, n (%)	77 (95)	18 (38)	12 (23)	12 (20)	10 (18)	< 0.001	0.035	0.53
Abnormal CRP or ESR, n (%)	85 (100)	40 (73)	23 (35)	26 (38)	23 (35)	—	< 0.001	0.32
Prednisone dosage, median (IQR), mg	15 (15, 15)	15 (13.8, 15)	12.5 (12.5, 12.5)	8.8 (7.5, 10)	5.1 (5, 7.5)	0.13	< 0.001	< 0.001
Prednisone dosage, n (%)						—	—	—
Below protocol	13 (15)	17 (22)	17 (22)	8 (10)	0 (0)			
On protocol	66 (78)	48 (62)	50 (63)	57 (74)	69 (85)			
Above protocol	6 (7)	12 (16)	12 (15)	12 (16)	12 (15)			

IQR: interquartile range (25th percentile, 75th percentile); MHAQ: modified Health Assessment Questionnaire; VAS: visual analog scale; PCS: physical component score of the Short-Form 36 (SF-36); MCS: mental component score of the Short-Form 36.

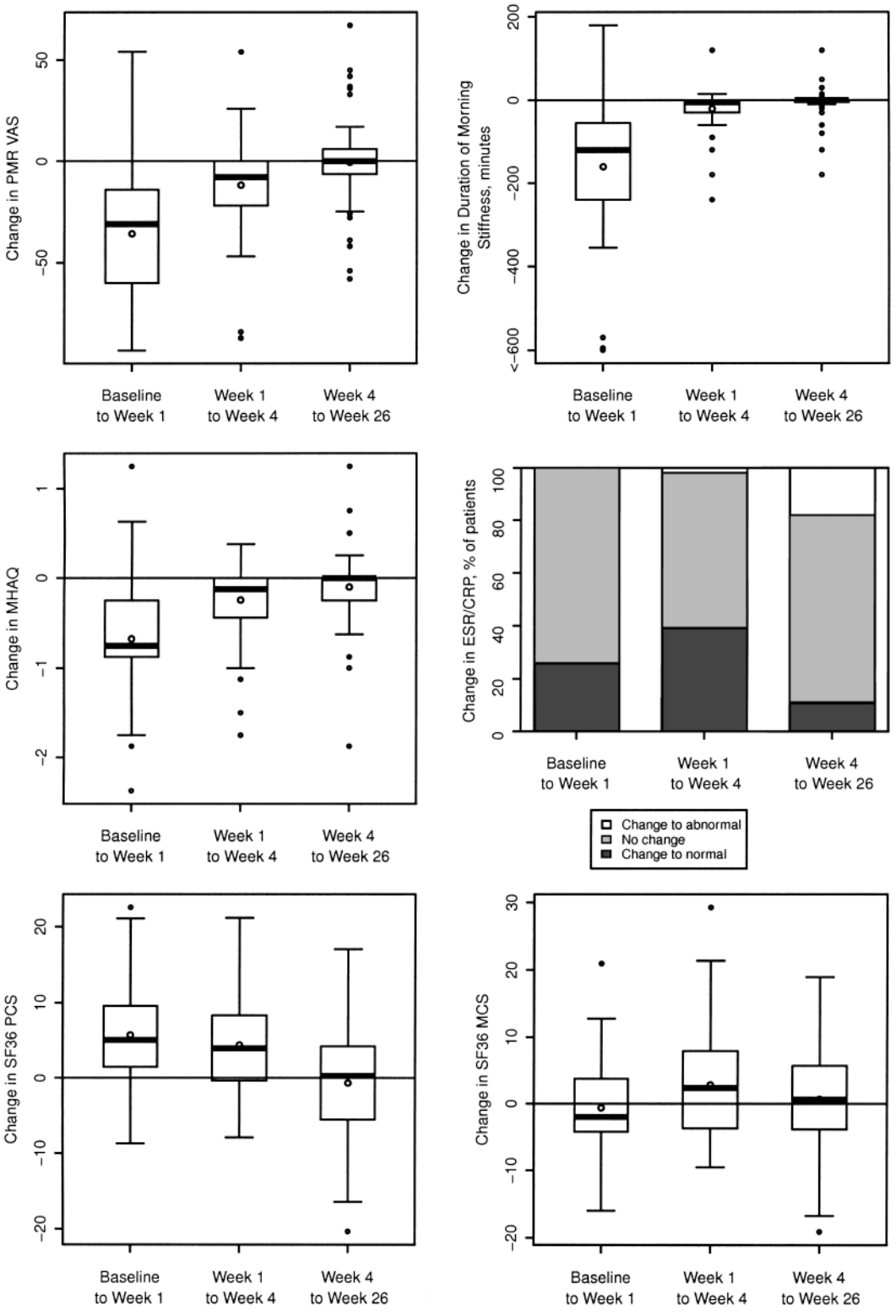

Figure 1. Change from visit to visit in patient-reported outcomes, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) in patients with polymyalgia rheumatica (PMR). VAS: visual analog scale; MHAQ: modified Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; MCS: mental component summary.

Table 3. Ultrasound findings in patients with polymyalgia rheumatica and normal subjects. Data are no. (%).

Feature	Week 0, n = 82	Week 26, n = 74*	Healthy Subjects, n = 21	p, Week 0 vs Healthy	p, Week 26 vs Healthy
At least ONE shoulder with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	69 (84)	36 (49)	4 (19)	< 0.001	0.015
BOTH shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	47 (57)	18 (24)	0 (0)	< 0.001	0.012
At least ONE shoulder with subdeltoid bursitis or biceps tenosynovitis	68 (84)	33 (45)	4 (19)	< 0.001	0.034
BOTH shoulders with subdeltoid bursitis or biceps tenosynovitis	46 (56)	15 (20)	0 (0)	< 0.001	0.025
At least ONE hip with synovitis or trochanteric bursitis	27 (36)	7 (10)	0 (0)	0.001	0.13
BOTH hips with synovitis or trochanteric bursitis	17 (21)	3 (4)	0 (0)	0.022	0.35
At least ONE shoulder and ONE hip with findings as above	26 (32)	6 (8)	0 (0)	0.003	0.18
BOTH shoulders and BOTH hips with findings as above	13 (16)	1 (1)	0 (0)	0.051	0.59

* McNemar's test of agreement for Week 0 vs Week 26 among subjects with polymyalgia rheumatica ($p < 0.001$ for all comparisons of ultrasound findings).

Response to corticosteroids. Response to CS treatment (defined as 70% improvement in PMR VAS) occurred in a majority (73%) of the patients by Week 4 and in 80% of patients by Week 12 (Table 4). Improvement of 70% by Week 4 was also noted in 70% of patients for global pain VAS and in 52% of patients for fatigue VAS. Response to treatment (percentage improvement in PMR VAS at Weeks 4 and 26) was highly correlated with percentage improvement in other VAS measures (correlation > 0.5 and $p < 0.001$ at Weeks 4 and 26), but was not correlated with change in CS dose ($p = 0.24$ at Week 4; $p = 0.41$ at Week 26). There was no association between severity of PMR at baseline (as measured by VAS, abnormal CRP and/or ESR, MHAQ, SF-36 PCS, SF-36 MCS, or ultrasound) and response to CS treatment at Week 1 or Week 26. The presence of ultrasound findings of at least 1 hip with synovitis and/or trochanteric bursitis at baseline was associated with response to CS at Week 4 (OR 3.6, 95% CI 0.9, 14.4; $p = 0.06$). Similarly, the presence of ultrasound findings of at least 1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis AND at least 1 hip with synovitis and/or trochanteric bursitis was significantly associated with response to CS at Week 4 (OR 3.1, 95% CI 0.8, 12.1; $p = 0.10$). Patients with lower baseline SF-36 MCS were also more likely to respond to CS treatment at Week 4 (OR 0.88, 95% CI 0.81, 0.97; $p = 0.006$).

Complete response was defined as all 3 of the following: (1) ≥ 70% improvement in PMR VAS; (2) ≥ 70% reduction in duration of morning stiffness; and (3) normal CRP and/or ESR. Partial response was defined as 2 of the 3, and nonresponse was none or 1 of the 3. At Week 4, complete response was achieved by 53% of patients and partial response occurred in 32% of patients. At Week 26, complete response was reported in 56% of patients and partial response was reported in 33% of patients.

The test-retest reliability of patient self-reported measures was evaluated in 14 patients with PMR who had minimal change in PMR VAS (± 10 mm) between baseline and Week 1 (Table 5). Intraclass correlation coefficients (ICC) revealed poor reliability (defined as ICC < 0.6) for fatigue VAS, morning stiffness, and SF-36 MCS. The SDD was also large (> 50) for fatigue VAS.

Table 4. Response to corticosteroids (≥ 70% improvement) in patients with polymyalgia rheumatica (PMR). Data are no. (%).

Feature	Week 1, n = 77	Week 4, n = 77	Week 12, n = 79	Week 26, n = 81
PMR VAS	31 (46)	52 (73)	56 (80)	52 (73)
Global pain VAS	27 (40)	48 (70)	56 (80)	50 (68)
Shoulder pain VAS	26 (38)	49 (68)	59 (82)	55 (72)
Hip pain VAS	33 (55)	49 (75)	51 (78)	54 (78)
Fatigue VAS	29 (43)	36 (52)	46 (66)	43 (59)
Duration of morning stiffness	48 (69)	68 (93)	69 (97)	69 (92)
Level of response*				
Nonresponse	23 (47)	9 (16)	7 (12)	6 (10)
Partial response	22 (45)	18 (32)	21 (36)	19 (33)
Complete response	4 (8)	30 (53)	31 (52)	32 (56)

* Complete response defined as improved > 70% in PMR VAS, morning stiffness, and normal CRP and/or ESR; partial response: only 2 of the 3; nonresponse: one or none of 3. VAS: visual analog scale; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table 5. Test-retest reliability of patient self-reported measures in 14 patients with polymyalgia rheumatica (PMR) who had minimal change in PMR VAS (± 10 mm) between baseline and Week 1.

	Scale	Mean	Maximum	ICC	SDD	% MDC
PMR VAS	0–100	47.9	92	0.98	10.6	10.6
Global pain VAS	0–100	40.0	83	0.82	28.9	28.9
Shoulder pain VAS	0–100	46.2	96	0.77	34.7	34.7
Hip pain VAS	0–100	30.0	69	0.88	23.1	23.1
Fatigue VAS	0–100	37.7	73	0.32	57.4	57.4
MHAQ	0–3	0.89	1.9	0.72	0.78	25.9
SF-36 PCS	0–100	34.7	48.7	0.79	9.2	9.2
SF-36 MCS	0–100	49.0	62.9	0.30	16.7	16.7
Morning stiffness duration, min	0–1440	92.1	210.0	0.11	231	16.1

ICC: Intraclass correlation coefficients; SDD: smallest detectable difference; %MDC: minimal detectable change expressed as percentage of the maximum score; VAS: visual analog scale; PCS: physical component score of the Medical Outcomes Study Short Form-36 (SF-36); MCS: mental component summary of the SF-36; MHAQ: modified Health Assessment Questionnaire.

Factor analysis. Factor analysis was performed on the changes between baseline and subsequent weeks to examine the variable domains of the outcome measures (Table 6). A total of 6 factors (or domains) were found to be sufficient to represent all the outcome measures. These 6 domains were PMR-related pain and physical function (PMR VAS, global pain VAS, and shoulder VAS, MHAQ, and SF-36 PCS), inflammatory markers (CRP and ESR), hip pain (hip VAS), global pain, mental functioning (SF-36 MCS), and morning stiffness. Internal consistency was assessed using Cronbach's alpha. There was almost perfect consistency between PMR VAS, global pain VAS, and shoulder VAS in the first domain (Cronbach's alpha = 0.91; pairwise correlation coefficients ranged from 0.73 to 0.86), indicating that these measures were redundant. Internal consistency remained high (Cronbach's alpha = 0.79) when all 5 measures in the PMR-related pain and physical functioning factor were considered together.

DISCUSSION

The goal of our study was to report on the disease course in patients with PMR, and to assess the performance of various PRO measures and their correlation with laboratory measures and response to CS therapy. We also sought to identify a minimum set of outcome measures that can be used in future clinical trials. Our findings indicate that the majority of patients with PMR respond rapidly to CS treatment, and show significant improvement in PRO measures, inflammatory markers, and ultrasound findings. In addition, PRO measures perform well in assessing disease activity in patients with PMR. However, complete response is seen in only about half the cases at Weeks 4 and 26, and up to 16%

Table 6. Factor analysis: factor loadings for individual outcome measures.

Outcome Measure	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
PMR VAS	0.89					
Global pain VAS	0.68			0.60		
Shoulder pain VAS	0.78					
Hip pain VAS			0.90			
Fatigue VAS*						
Morning stiffness duration						0.54
MHAQ	0.64					
SF-36 PCS	0.70					
SF-36 MCS					0.76	
Abnormal ESR		0.98				
Abnormal CRP		0.73				
Prednisone dosage*						

* Only factor loadings > 0.5 are shown. VAS: visual analog scale; PCS: physical component score of the Medical Outcomes Study Short Form-36 (SF-36); MCS: mental component summary of the SF-36; PMR: polymyalgia rheumatica; MHAQ: modified Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

and 10% of cases fail to respond at Weeks 4 and 26, respectively. We suggest that a minimum set of outcome measures consisting of patient-reported global pain, hip pain, morning stiffness, physical function (MHAQ), mental function, and an inflammatory marker be used in practice and clinical trials in PMR. Our study also indicates that all measures (clinical, patient-reported, and laboratory measures) of disease activity improve by 4 weeks. Therefore, future clinical studies, including those evaluating factors influencing CS response and clinical trials of novel therapies, should have their primary outcome evaluation early in the treatment course, certainly by the 4-week timepoint after initiation of treatment.

A future goal of our group is to consider all these domains and measures for inclusion in the definition of disease activity to derive a composite disease activity score and remission criteria incorporating these core domains. Our findings complement a recently published literature search and a Delphi-based expert consensus. That report[10], among other findings, highlights assessment of hip pain — a disease activity domain also found to be significant in our prospective study. We need to be mindful of our test-retest findings showing poor reliability for fatigue VAS and morning stiffness with large SDD for fatigue VAS. Combined with the recently proposed classification criteria[8], the next step would be development of a validated score to be used in protocols designed for randomized clinical trials of future therapeutic agents.

Although previous studies have used several outcome and clinical response measures, there is no consensus about the optimal endpoints for evaluating efficacy of treatment in PMR[18]. None of the previously proposed measures has been validated, particularly use of patient-reported measures. A PMR activity score has been proposed and assessed in 2 patient cohorts[18]. However, the validation cohorts suffered from lack of clarity on eligibility, patient selection, and followup assessments. Further, the assessments did not include validated instruments for assessing function and quality of life. They included the physician's global assessment, a criterion item that did not achieve 50% agreement in a consensus and Delphi survey of relapse and remission in PMR[10].

Previously used measures were somewhat arbitrary in several respects, in particular with no consideration of the validity of various measures at different stages of the disease, time/duration of the disease activity and remission states, correlation with prognostic markers, and failure to account for the continuity of the disease activity process. The validity and sensitivity of measures can vary at different stages of the disease course (e.g., pain resolves early but laboratory markers of inflammation may remain high for longer). Also, it is unknown whether a patient truly has PMR even if he or she does not respond to CS treatment at a specified dose. Our study shows that 16% and 10% did not have a response to CS at 4 and 26 weeks, respectively. Whether these patients have more severe PMR requiring bigger CS doses and/or need disease-modifying drugs or have an alternative diagnosis is the focus of our continuing work.

Although not a primary outcome assessment, our finding that patients with low mental SF-36 scores responded better to CS therapy likely indicates that the disease/inflammatory state is pathophysiologically relevant to mental function and well-being. A previous PMR study found association of MCS with inflammatory markers, suggesting neuropsychological effects of elevated circulating cytokines such as interleukin 6[7]. Future studies in PMR should include evaluation of this important PRO. It is likely that the often-reported fatigue is also related, and should be evaluated as an important domain of outcome in future studies of PMR. Disturbance of sleep by pain and stiffness (not measured in our study) may be another contributory factor of low MCS in patients with active PMR.

An exciting finding of our study is that characteristic ultrasound abnormalities not only contribute to the classification of patients with PMR[7] but also are associated with a good response to steroids at 4 weeks. We suggest that future PMR clinical trials should evaluate ultrasound as an independent measure of outcome alongside clinical and PRO measures and laboratory markers, especially early in the course of the disease.

This international study is the first comprehensive assessment of outcome measures in patients with PMR. Standardized inclusion and exclusion criteria, standardized CS treatment schedule, and standardized prospective data collection at predefined intervals improve the validity of our findings. This study brings together the expertise and commitment of an international group of investigators who continue their efforts in this area. Validated and standardized classification and outcome criteria in PMR will open the way to well-designed clinical studies and new therapeutic targets with the aim of improving patient care. Nevertheless, the results should be interpreted in light of some potential limitations. First, the external validity of the findings needs to be evaluated in other prospective studies. Given the uncertainties associated with the etiology of PMR, the outcome criteria represent clinical outcomes and not biological remission of the disease. The duration of followup (6 months) may be too short to identify longterm outcomes of PMR, especially while off CS therapy. Patients in the study had a range of disease severity; however, cases with GCA were excluded, as they would be managed with different treatment strategies. Future validation studies of the new classification criteria and outcomes measures will offer the opportunity to examine their utility across the disease spectrum of PMR.

The best measures of disease activity and treatment response in PMR appear to be patient-reported global pain, hip pain, morning stiffness, physical function (MHAQ),

mental function, and an inflammatory marker. Ultrasound may have utility in PMR classification as well as an outcome measure. Our study also highlights the need for better biomarkers of disease activity in PMR.

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