

Treatment of Polymyalgia Rheumatica

A Systematic Review

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Background: Polymyalgia rheumatica (PMR) treatment is based on low-dose glucocorticoids. Glucocorticoid-sparing agents have also been tested. Our objective was to systematically examine the peer-reviewed literature on PMR therapy, particularly the optimal glucocorticoid type, starting doses, and subsequent reduction regimens as well as glucocorticoid-sparing medications.

Methods: We searched Cochrane Databases and MEDLINE (1957 through December 2008) for English-language articles on PMR treatment (randomized trials, prospective cohorts, case-control trials, and case series) that included 20 or more patients. All data on study design, PMR definition criteria, medical therapy, and disease outcomes were collected using a standardized protocol.

Results: Thirty studies (13 randomized trials and 17 observational studies) were analyzed. No meta-analyses or systematic reviews were found. The PMR definition criteria, treatment protocols, and outcome measures differed widely among the trials. Starting prednisone doses higher than 10 mg/d were associated with fewer re-

lapses and shorter therapy than were lower doses; starting prednisone doses of 15 mg/d or lower were associated with lower cumulative glucocorticoid doses than were higher starting prednisone doses; and starting prednisone doses higher than 15 mg/d were associated with more glucocorticoid-related adverse effects. Slow prednisone dose tapering (<1 mg/mo) was associated with fewer relapses and more frequent glucocorticoid treatment cessation than faster tapering regimens. Initial addition of oral or intramuscular methotrexate provided efficacy at doses of 10 mg/wk or higher. Infliximab was ineffective as initial cotreatment.

Conclusions: The scarcity of randomized trials and the high level of heterogeneity of studies on PMR therapy do not allow firm conclusions to be drawn. However, PMR remission seems to be achieved with prednisone treatment at a dose of 15 mg/d in most patients, and reductions below 10 mg/d should preferably follow a tapering rate of less than 1 mg/mo. Methotrexate seems to exert glucocorticoid-sparing properties.

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POLYMYALGIA RHEUMATICA (PMR) is a syndrome characterized by aching and morning stiffness in the shoulder and pelvic girdles and neck in persons 50 years or older.^{1,2} Systemic manifestations such as low-grade fever, fatigue, and weight loss are frequently present, as are increased acute-phase reactants including high erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and anemia of chronic disease.^{1,2}

Treatment with glucocorticoids is the preferred therapy for PMR.^{1,2} Before the glucocorticoid era, the occasional self-limiting nature of PMR was evidenced by spontaneous improvements in some patients,^{3,4} and musculoskeletal symptoms were treated with nonsteroidal anti-inflammatory drugs (NSAIDs).^{3,5} Today, prednisone and its principal active me-

tabolite, prednisolone, considered to be equipotent at equivalent doses, are universally used in PMR. Other currently used glucocorticoids include methylprednisolone and deflazacort (not available in the United States).

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An initial prednisone dosage of 10 to 20 mg/d is deemed appropriate for most patients who have PMR without associated giant cell arteritis (GCA).^{1,2,6} Symptoms usually resolve completely after a few days. Most patients require at least 2 years of treatment, but others have a more chronic, relapsing, or refractory course requiring steroid treatment for much longer.^{1,2} The adverse effects of long-term glucocorticoid therapy are common

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and sometimes deleterious in patients with PMR.^{1,2,7} To reduce the total cumulative dose of glucocorticoids and their adverse effects, some researchers have investigated the addition of cytotoxic drugs and, more recently, biologic agents with potential glucocorticoid-sparing effects to the PMR regimen.¹

To our knowledge, no reports have summarized the evidence for glucocorticoid treatment or glucocorticoid-sparing therapies in PMR. The present review systematically analyzes the reported evidence on PMR therapy, especially the preferentially used glucocorticoid, its optimal initial and maintenance doses and tapering regimens, and glucocorticoid-sparing agents used.

METHODS

DATA SOURCES AND SEARCHES

We systematically searched the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and MEDLINE/PubMed for English-language articles published between 1957 and December 2008, using the MeSH term *polymyalgia rheumatica* in combination with the terms *treatment*, *glucocorticoids*, *prednisone*, *prednisolone*, *methylprednisolone*, *deflazacort*, *methotrexate*, *azathioprine*, *NSAIDs*, and *biological therapy*. References of relevant articles retrieved were searched manually. Studies that included 20 patients or more were selected.

DATA EXTRACTION AND QUALITY ASSESSMENT

Two of us (J.H.-R. and X.B.) independently read titles and abstracts searching for articles on medical interventions in PMR. Articles considered to meet inclusion criteria, and those with inconclusive abstracts were fully reviewed to decide on their final inclusion. Three of us (J.H.-R., A.L.-S., and X.B.) recorded the types and initial doses of glucocorticoids and other therapies tested, subsequent tapering schedules, proportion of patients discontinuing glucocorticoid treatment, time to treatment cessation, and relapse rate during follow-up. Additional data recorded included primary end points, inclusion and exclusion criteria, number of patients enrolled, baseline demographics, misclassified patients (eg, patients initially diagnosed with GCA or later develop-

ing GCA or other inflammatory conditions), patients lost to follow-up, follow-up duration, and treatment-related adverse effects. All data were reviewed and confirmed by one of us (J.H.-R.).

Various proposed definition criteria for PMR (**Table 1**)⁸⁻¹¹ and the authors' own criteria are noted when used. In studies including patients initially diagnosed with GCA, only those patients with isolated PMR were analyzed when possible. In studies with patients initially considered to have PMR alone who later developed symptoms suggestive of GCA, confirmed or not by temporal artery biopsy, the number of patients with isolated PMR at the end of the study was specified.

Methodologic quality was evaluated independently by 3 of us (J.H.-R., X.B., and G.E.-F.). Observational studies were evaluated according to the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement."¹² Quality and susceptibility to bias in observational studies were appraised using the criteria recommended by Sanderson et al.¹³ The quality of randomized trials was assessed using the scale proposed by Jadad et al.¹⁴ Disagreements on data and the quality of selected studies were resolved by discussion among all authors.

DATA SYNTHESIS AND ANALYSIS

According to the type of medication used to treat PMR, we analyzed glucocorticoids, glucocorticoid-sparing agents, and NSAIDs. Treatments for initial remission induction and maintenance phases were examined separately.

RESULTS

SEARCH RESULTS

We identified 784 citations. After retrieving 163 articles, 133 were excluded. We finally analyzed 30 studies with ≥ 20 patients (13 randomized trials 17 and observational studies) (**Figure 1**). No meta-analyses or systematic reviews were found. Of the 2220 patients initially included, 153 (6.9%) were either initially diagnosed with GCA or developed GCA during follow-up, and 2161 (97.3%) were finally analyzed.

Prednisone or prednisolone alone was investigated in 14 observational studies¹⁵⁻²⁸ and 2 random-

ized trials.^{29,30} Observational studies included 8 case series (5 retrospective¹⁵⁻¹⁹ and 3 prospective²⁰⁻²²), 3 retrospective case-control trials,²³⁻²⁵ and 3 prospective cohort studies²⁶⁻²⁸ (**Table 2** and **Table 3**). Deflazacort was analyzed in 1 prospective case series³¹ and 3 randomized trials.³²⁻³⁴ Methylprednisolone³⁵ and 6-methylprednisolone³⁶ were investigated in 1 randomized trial each. Eight studies used glucocorticoid-sparing agents; 5 used methotrexate (3 randomized trials,³⁷⁻³⁹ 1 retrospective case-control trial,⁴⁰ and 1 prospective cohort study⁴¹); and 2 randomized studies (1 each) tested azathioprine⁴² and infliximab⁴³ (**Table 4** and **Table 5**). Three studies analyzed NSAIDs.^{19,23,44}

QUALITY AND HETEROGENEITY OF THE STUDIES

All studies used different diagnostic PMR criteria (Table 1), outcome definitions (eg, relapse, recurrence, and disease remission) (**Table 6**), scoring systems, medications and routes of administration, initial dosages, tapering schedules, and length of follow-up. Most studies were observational, and only 2 randomized trials could be considered confirmatory studies with an appropriate sample size calculation.^{38,43} This heterogeneity did not allow a pooled estimator to be calculated or statistical heterogeneity to be tested. Study designs were therefore considered in the following order (listed from lowest to highest evidence quality): case series, case-control studies, cohort studies, and randomized trials.

MEDICATIONS USED FOR POLYMYALGIA RHEUMATICA

Glucocorticoids

Most studies evaluating the use of glucocorticoids alone for remission induction or maintenance in PMR were observational (Table 2 and Table 3).

Initial Treatment (Induction of Remission). In 1 study, patients with PMR who were treated with a dose

Table 1. Most Frequent Diagnostic Criteria Used for Polymyalgia Rheumatica

Criteria	Source			
	Bird et al, ⁸ 1979	Jones and Hazleman, ⁹ 1981	Chuang et al, ¹⁰ 1982	Healey, ¹¹ 1984
Age, y	>65	NR	≥50	>50
Clinical involvement	Bilateral shoulder pain and/or stiffness, bilateral upper arm tenderness	Shoulder and pelvic girdle pain, primarily muscular, in the absence of true muscle weakness	Bilateral aching and stiffness involving 2 of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs; movements of involved joint areas accentuate the pain	Pain involving 2 of the following areas: neck, shoulders, and pelvic girdle
Duration of morning stiffness	>1 h	Only presence required; duration not specified	≥30 Minutes (or after periods of inactivity)	>1 h
Duration of symptoms until PMR diagnosis	<2 wk	At least 2 mo	At least 1 mo	At least 1 mo
ESR, mm/h	≥40	>30	>40	>40
CRP, mg/L	NR	6	NR	NR
Exclusion of other diseases	NR	Absence of objective signs of muscle disease, rheumatoid or inflammatory arthritis, or malignant disease	Absence of other diseases that could explain the symptoms (except GCA), such as active rheumatoid arthritis, lupus erythematosus, polymyositis, chronic infection, multiple myeloma, and Parkinson disease	Absence of other diseases capable of causing the musculoskeletal symptoms
Response to glucocorticoids	NR	Prompt and dramatic response to systemic glucocorticoids (no dose specified, although in the study, prednisone doses of 10 to 15 mg/d were prescribed for PMR)	Considered a supporting diagnosis in some cases	Rapid response to prednisone, ≤20 mg/d
Other	Depression and/or loss of weight	NR	In cases with typical musculoskeletal findings but borderline ESR elevation, the authors considered ESR before and after the illness for comparison or for other evidence to support the diagnosis, such as a rapid response to low-dose glucocorticoids or history of GCA	NR
Conditions for meeting diagnostic criteria	3 or more features required for diagnosis of PMR (sensitivity 92% and specificity 80%)	All criteria required for diagnosis of PMR	All findings required for diagnosis of PMR	All findings required for diagnosis of PMR

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; NR, not reported; PMR, polymyalgia rheumatica. SI conversion factor: To convert CRP to nanomoles per liter, multiply by 9.524.

of 10 mg/d of prednisolone required fewer dose increases than those taking less than 10 mg/d, although no patient treated with more than 10 mg/d required dose modification.²⁷ When initial prednisolone doses of 15 mg/d or lower were

compared with doses higher than 15 mg/d, the daily maintenance dose was higher in patients initially treated with more than 15 mg/d after the first and second year of treatment, although the initial dose did not influence relapses or treatment

discontinuation.²⁸ A case series using prednisolone at initial doses of 15 mg/d found that fewer than 1% of patients required doses higher than 15 mg/d to control symptoms.²¹ In the only randomized trial in which a prednisolone regimen was started at

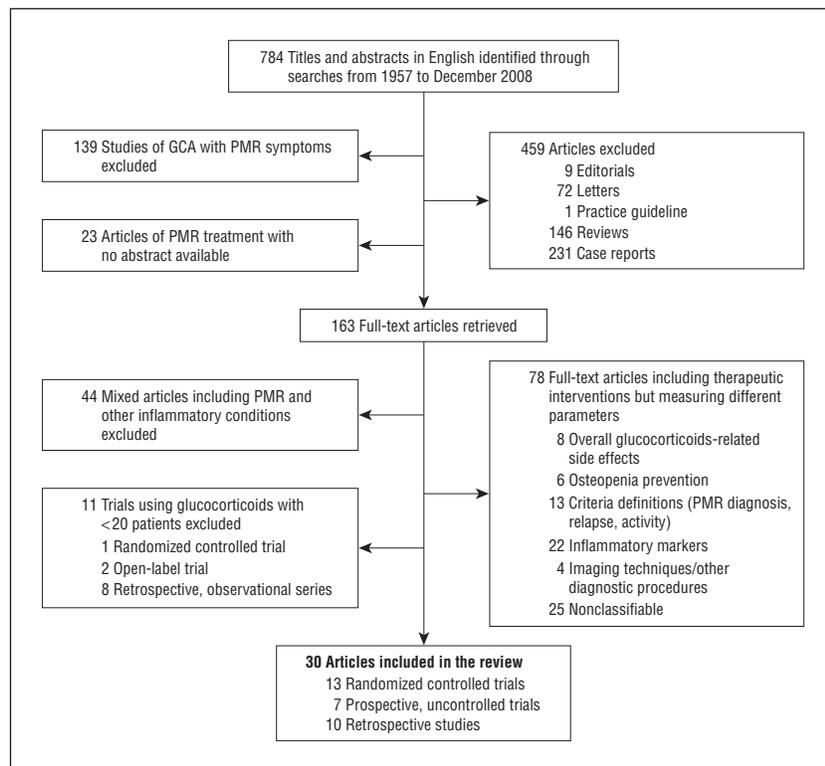


Figure 1. Study flow diagram. GCA indicates giant cell arteritis; PMR, polymyalgia rheumatica.

10 mg/d or 20 mg/d for 4 weeks with rapid tapering in 2 months, patients initially receiving 20 mg/d had fewer relapses than those receiving 10 mg/d, and 30% of patients taking 10 mg/d had to increase to 15 to 20 mg/d to control symptoms.²⁹

Based on these results, fewer than 1% of patients with PMR initially treated with prednisolone at 15 mg/d required higher doses to control their symptoms. Prednisolone doses of 10 mg/d or higher seemed to control initial PMR more efficiently than lower doses, and doses of 15 mg/d or lower appeared to be as effective as higher doses. Therefore, the best available evidence seems to indicate that 15 mg/d of prednisone as a starting dose could be effective in most patients with PMR.

Dose Tapering During the Maintenance Phase. Glucocorticoid regimens are usually tapered according to clinical and laboratory responses (generally ESR and CRP levels).^{16,31,34} González-Gay et al¹⁵ found that a tapering rate of less than 1 mg/mo was associated with fewer relapses than reductions greater than 1 mg/mo after initial prednisone doses of 10 to 20 mg/d. Similar re-

sults have been found by other authors.^{17,21,35} Two studies used prednisolone at 15 mg/d followed by gradual tapering until maintenance doses of 8 mg/d²¹ and 10 mg/d³⁵ were reached, with subsequent reductions of 1 mg every 2 months until treatment discontinuation. Both of these studies showed optimal control of disease activity during the study period.^{21,35} Conversely, faster reduction regimens were associated with poorer results.^{27,30} These findings would indicate that once a stable prednisone daily dose of 10 mg is achieved after initial remission, further dose reductions should be smaller than 1 mg/mo (eg, 1 mg every 2 months).

Long-term Impact of Initial Treatment (Therapy Discontinuation and Relapse Rates). For prednisone regimens initiated at 10 to 20 mg/d, discontinuation rates have been reported to be 41% to 50% after 2 years,^{16,24,25} 70% after 3 years, 82% after 4 years,¹⁶ and 91% after 11 years.¹⁵ When regimens started at 10 mg/d or lower or 12.5 mg/d or lower, 70% of patients discontinued therapy after 4 years of follow-up.^{18,20} In a study of a starting prednisone dose

of 20 mg/d, 33% of patients discontinued treatment in less than 1 year.²⁶

Several studies have compared the effect of different initial glucocorticoid doses on treatment duration and/or relapse rate.²³⁻²⁵ When compared with prednisone doses lower than 15 mg/d, doses of 15 mg/d or higher did not show differences in any outcomes.²⁵ Prednisone treatment discontinuation rates were similar when initial doses of 10 mg/d or lower were compared with initial doses of 15 to 20 mg/d²³ and when initial doses of 10 mg/d (range, 7-12 mg/d) were compared with initial doses of 24 mg/d (range, 15-30 mg/d).²⁴ However, patients taking 10 mg/d tended to have more relapses than patients taking higher initial doses.²⁴ Starting doses of greater than 15 mg/d were associated with a higher risk of glucocorticoid-related adverse effects and no additional benefit.^{19,24}

Relapses usually occurred in 23% to 29% of patients during the entire follow-up period^{15,16} and, depending on the study, in 33% of patients during the first year.²¹ A higher relapse rate (55%) was reported by a retrospective study using prednisone at wide dose ranges (1-100 mg/d; median dose, 15 mg/d).¹⁷

The only study assessing sex-related differences in newly diagnosed PMR cases found that women had more relapses, received higher cumulative doses, and had more glucocorticoid-related adverse effects than men.²²

Despite the differing starting doses and tapering regimens, prednisone doses between 10 and 20 mg/d seemed to control disease activity at PMR onset and, overall, allowed glucocorticoid treatment cessation in about 50% of patients at 2 years.

Deflazacort and Methylprednisolone in PMR. Three randomized trials compared deflazacort with other glucocorticoids in terms of efficacy at controlling disease activity during a 12-month or shorter follow-up period.³²⁻³⁴ When used at the same doses, deflazacort was found to have a lower potency than prednisone,³² prednisolone,³⁴ and 6-methylprednisolone.³³ Although deflazacort treatment initiated at

Table 2. Studies Using Prednisone or Prednisolone as Starting Treatment for Polymyalgia Rheumatica (Part 1)

Source ^a	Study Type	End Point(s)	Patients Included/ Finally Analyzed, No.	Sex, F/M, No.	Age, y ^b	Patients With Initial/ Later-Developing GCA, No.
González-Gay et al, ¹⁵ 1999 ^c	Retro case series	Frequency of relapses in PMR	134/134	85/49	70 (7.5)	0/0
Narváez et al, ¹⁶ 1999 ^c	Retro case series	Therapy duration and relapses in PMR	69/69	41/28	71 (8)	0/0
Kremers et al, ¹⁷ 2005	Retro case series	Predictors of relapse in PMR	284/284	67% F	73 (51-96)	~ 41/0
Fauchald et al, ¹⁸ 1972	Retro case series	PMR and GCA descriptive study	29/29	18/9	65 (47-82)	4/0
Gabriel et al, ¹⁹ 1997 ^d	Retro case series	Long-term outcome of therapy (GC and NSAIDs) in PMR	232/232	163/69	73 (52-96)	0/30
Spiera and Davison, ²⁰ 1978	Pro case series	PDN cessation and need to increase initial dose in PMR	56/48	39/17	NR (60-80)	1/1 (+8) ^e
Hutchings et al, ²¹ 2007	Pro case series	Impact of PMR on clinical outcomes and quality of life	129/129	77/52	71 (52-92)	0/5 (+7) ^e
Cimmino et al, ²² 2006	Pro case series	Sex-related difference in disease activity in PMR	80/76	52/28	69 (8)	0/4
Mowat and Camp, ²³ 1971 ^d	Retro case-control	PMR descriptive study	23/21	15/8	64.8 (43-77)	2/0
Delecoeuillerie et al, ²⁴ 1988 ^c	Retro case-control	Relapses, PDN discontinuation, and adverse events in PMR	132/132	91/41	72 (9)	8/9
Ayoub et al, ²⁵ 1985	Retro case-control	Duration of GC, GC requirements, and relapses in PMR	76/75	42/34	68 (50-84)	0/0 (+1) ^e
Weyand et al, ²⁶ 1999 ^f	Pro cohort	Clinical and laboratory markers of response to PDN treatment in PMR	27/27	NR	NR	0/0
Behn et al, ²⁷ 1983 ^c	Pro cohort	PDL cessation and relapses in PMR and GCA	114/108	NR	NR	11/0 (+6) ^e
Myklebust and Gran, ²⁸ 2001 ^c	Pro cohort	Maintenance PDL dose and annual cessation rate during the first 2 y in PMR and GCA	217/217	141/76	71, mean	0/0
Kyle and Hazleman, ²⁹ 1989 ^c	Pro randomized	Relapses and need to increase dose of PDL in PMR and GCA during the first 2 mo	39/39	NR	71.4, mean	0/6
Kyle and Hazleman, ³⁰ 1993 ^c	Pro randomized	Relapses during the disease course in PMR and GCA treated with PDL	39/39	NR	71.4, mean	0/8

Abbreviations: GC, glucocorticoid therapy; GCA, giant cell arteritis; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; PDL, prednisolone therapy; PDN, prednisone therapy; PMR, polymyalgia rheumatica; pro, prospective; retro, retrospective.

^aDefinition criteria for PMR used in these studies were those from Chuang et al¹⁰ in González-Gay et al,¹⁵ Narváez et al,¹⁶ Kremers et al,¹⁷ Gabriel et al,¹⁹ and Cimmino et al²²; from Bird et al⁶ in Myklebust and Gran²⁸; from Jones and Hazleman⁹ in Hutchings et al²¹ and Kyle and Hazleman^{29,30}; and from the respective authors' own criteria in Fauchald et al,¹⁸ Spiera and Davison,²⁰ Mowat and Camp,²³ Delecoeuillerie et al,²⁴ Ayoub et al,²⁵ Weyand et al,²⁶ and Behn et al.²⁷

^bUnless otherwise indicated, data are reported as mean (SD) or median (range).

^cAlthough the study initially included patients with GCA and PMR, only patients with isolated PMR were finally analyzed.

^dThis study used NSAIDs alone or in combination with GC to treat PMR.

^eIn Spiera and Davison,²⁰ 8 patients died during follow-up (none of the patients examined had arteritis); in Hutchings et al²¹ 122 of 129 patients finished the study at month 12; in Ayoub et al,²⁵ 1 of 76 patients with isolated PMR was treated with NSAIDs only and was lost to follow-up after 5 months; in Behn et al,²⁷ 6 of 114 patients were treated with NSAIDs.

^fIn Weyand et al,²⁶ patients were categorized into 3 groups according to response to treatment: group A (n=8; 30%) included patients with a short disease course, rapid PDN tapering (duration of PDN, <1 year), and few relapses; group B (n=12; 44%) included patients who had less rapid GC tapering (duration of GC, >1 year) and more relapses when GC was tapered to doses lower than 10 mg/d; group C (n=7; 26%) included patients requiring GC for more than 1 year, early evidence of more resistant disease, and incomplete initial response to doses of 20 mg/d at 4 weeks.

doses higher than 20 mg/d seemed to be effective in newly diagnosed PMR cases,³¹ these results are mainly based on a single observational study.

Two randomized, double-blind, placebo-controlled trials analyzed the efficacy and safety of intramuscular (IM) methylprednisolone treatment³⁵ and methylprednisolone administered via local shoulder injections³⁶ in the treatment of PMR. A 1-year study compared a depot preparation of IM methyl-

prednisolone acetate (120 mg every 2 weeks for 12 weeks followed by monthly injections with dose reductions of 20 mg every 3 months) with an oral prednisolone regimen (15 mg/d gradually reduced to 10 mg/d) in newly diagnosed PMR cases. Prednisolone dose reductions below 10 mg/d were made at 1 mg every 8 weeks. Although both glucocorticoids induced and maintained disease remission, prednisolone tended to control symptoms more rapidly

and consistently and also showed higher glucocorticoid treatment discontinuation rates than IM methylprednisolone. However, patients taking prednisolone received higher cumulative doses and had more glucocorticoid-related adverse effects.³⁵

One study³⁶ evaluated 6-methylprednisolone treatment given as bilateral shoulder injections every 4 weeks in newly diagnosed PMR cases limited to the shoulder girdle. Shoulder discomfort and

Table 3. Studies Using Prednisone or Prednisolone as Starting Treatment for Polymyalgia Rheumatica (Part 2)

Source ^a	GC Starting Doses and Tapering Regimens ^b	Duration of Therapy/Follow-Up ^b	GC Cessation, %	Time to Stop GC, y	Relapses	GC Cessation and GC Daily or Cumulative Dose
González-Gay et al, ¹⁵ 1999 ^c	PDN, 14.5 (3.5) mg/d; speed of tapering (mg/mo) was analyzed	20.2 (11.4) mo/ up to 11 y	91	11	23.1%; PDN was tapered faster in relapsers than in nonrelapsers (1.2 vs 0.9 mg/mo; <i>P</i> < .05)	NR
Narváez et al, ¹⁶ 1999 ^c	PDN, 10-20 mg/d; subsequent reductions made according to disease activity and ESR	23 (7-24) mo/ up to 10 y (11 mo after PDN cessation)	50 70 82	2 3 4	29%, mean time, 48 wk	PDN, MDD 6.1 (1.6); cumulative, 3.9 (1.6) g
Kremers et al, ¹⁷ 2005	PDN, 15 (1-100) mg/d; 2 tapering regimens: at different visits, 57% tapered; 43% not tapered	Median, 1.8 y/ 4.2 (0.12-5.1) y	NR	NR	55%, more relapses in patients with faster PDN tapering than in those with slower (70% vs 10%; <i>P</i> = .001)	NR
Fauchald et al, ¹⁸ 1972	PDN, 40 to 60 mg/d; reduction to 5.0-12.5 mg/d over 1-4 wk	At least 2 y/ 4.1 (0.7-8) y (2.8 y after PDN cessation)	70	4	18%	Maintenance dose, 7.5-10 mg/d
Gabriel et al, ¹⁹ 1997 ^d	GC, 28 (5-100) mg/d; GC alone, 53%; GC + NSAIDs, 22%	2.4 (0.1-19.4) y/ mean, 8 y	NR	NR	NR	No differences in daily and cumulative GC doses or GC duration
Spiers and Davison, ²⁰ 1978	PDN, ≤10 mg/d, followed by slow tapering	Follow-up, 4 to 9 y	73	4-9	Initially, 4% of patients required 15 mg/d to control symptoms	NR
Hutchings et al, ²¹ 2007	PDL, 15 mg/d; gradual reduction to 8 mg/d in 9 mo; subsequent reductions, 1 mg every 2 mo	At least 2 y/1 y	NR	NR	33%, 59% within 2 wk and 41% within 12 mo of a dose reduction; <1% required >15 mg/d	NR
Cimmino et al, ²² 2006	PDN, 15.5 (5-40) mg/d	30 (14) mo/ 15 (4-68) mo	NR	NR	Women had more relapses than men (0.7 [1.0] vs 0.3 [0.4]; <i>P</i> = .02)	Women received higher cumulative doses than men
Mowat and Camp, ²³ 1971 ^d	PDL, 15-20 mg/d (n=8), ≤10 mg/d (n=8), and NSAIDs (n=5)	15 (8) mo/ 21 (15) mo	44 70 82	1.4 3 4	NR	No differences in PDN cessation (50% vs 38%)
Delecoeuillerie et al, ²⁴ 1988 ^c	PDN, group 1 (74%), 10.2 (7-12) mg/d; group 2 (26%), 24.2 (15-30) mg/d	At least 2.1 y/ 3.6 y after GC cessation	49	2	10.5% (13.1% in group 1 vs 3.9% in group 2, the difference was not significant)	NR
Ayoub et al, ²⁵ 1985	PDN, ≥15 mg/d (67%), <15 mg/d (33%)	3.1 y (mean)/ 6 mo to 4.5 y	31 53 74 84	1 2 3 4	56%	No differences in duration of therapy; MDD during tapering, 15.8 mg (month 1); 12.7 mg (month 3); and 8 mg (>12 mo)

(continued)

systemic symptoms resolved initially in all patients, and this effect was sustained after 14 months in 50% of patients.

These limited results and the need for repeated invasive procedures suggest that routine methylprednisolone injections (IM or shoulder) do not represent a practical PMR treatment and should only be considered for patients at high risk of glucocorticoid-related adverse events (IM injections) and in cases of shoulder-limited PMR (shoulder injections).

Glucocorticoid-Sparing Agents

Initial Treatment. Three randomized studies have investigated methotrexate regimens in newly diagnosed PMR cases (Table 4 and Table 5).³⁷⁻³⁹ Oral methotrexate

doses of 7.5 mg/wk plus 20 mg/d of prednisone offered no greater benefits than prednisone alone in all outcomes measured after 2 years of follow-up.³⁷ However, these results may be misleading because (1) methotrexate doses of 7.5 mg/wk may be insufficient to exert glucocorticoid-sparing effects and (2) 15% of patients included had GCA, which usually requires higher prednisone doses to control disease activity. Oral³⁸ and IM³⁹ methotrexate at a dose of 10 mg/wk, when added to a prednisone regimen, showed glucocorticoid-sparing effects compared with a prednisone regimen alone regarding relapse rates, prednisone treatment discontinuation rates, duration of prednisone therapy, and cumulative prednisone dose.^{38,39} Intramuscular methotrexate treatment was discontinued at 18 months

by all patients who had stopped prednisone therapy 6 months before.³⁹ Overall glucocorticoid-related adverse effects and a significant decrease in bone mass density were observed only in patients receiving prednisone alone.³⁹

A randomized, double-blind, placebo-controlled study tested the efficacy of infliximab as a glucocorticoid-sparing agent in newly diagnosed PMR cases⁴³ (Table 4 and Table 5). No differences were observed between groups in (1) the proportion of patients without relapses through week 52 (primary end point), (2) the number of relapses, (3) the duration and cumulative dose of prednisone, or (4) prednisone treatment discontinuation rates. Thus, while infliximab cannot be considered a useful glucocorticoid-sparing agent in pa-

Table 3. Studies Using Prednisone or Prednisolone as Starting Treatment for Polymyalgia Rheumatica (Part 2) (continued)

Source ^a	GC Starting Doses and Tapering Regimens ^b	Duration of Therapy/Follow-Up ^b	GC Cessation, %	Time to Stop GC, y	Relapses	GC Cessation and GC Daily or Cumulative Dose
Weyand et al, ²⁶ 1999 ^e	PDN, 20 mg/d for 4 wk and then tapered by 2.5 mg every 2 wk as symptoms remained improved	At least 18 wk/2.7 y (mean)	33	2	Higher relapse rate in patients with more GC requirements; higher risk of relapse when reductions <10 mg/d	Higher PDN MDD at first flare occurrence in resistant patients
Behn et al, ²⁷ 1983 ^c	PDL (3 groups), <10 mg/d (62%); 10 mg/d (31%); and >10 mg/d (7%), followed by tapering by 1 mg/mo	2.6 y/12 y	16	2	17%, dose increase required more frequently by patients taking 5 to 9 mg/d than by those taking 10 mg/d (33% vs 12%; <i>P</i> <.025); none taking >10 mg/d needed changes	NR
Myklebust and Gran, ²⁸ 2001 ^c	PDL, 21.5 (5-80) mg/d; 2 groups, ≤15 mg/d (69%) and >15 mg/d (31%)	<1 to >2 y/2 y (6 mo after PDL cessation)	10 24	1 2	No differences in relapses; 3% and 13% of patients taking >15 and ≤15 mg/d, respectively, required an increase of the initial dose	No differences in PDL cessation; PDL effective MDD during the first and second years, 5.7 and 4.3 mg, respectively
Kyle and Hazleman, ²⁹ 1989 ^c	PDL (2 groups), 10 mg/d for 4 wk, then reductions every 2 wk to 7.5 and 5 mg/d (n=20); and 20 mg/d for 4 wk, then reductions every 2 wk to 15 and 10 mg/d	2 mo for both treatment and follow-up	NR	NR	11% of patients taking 20 mg/d (all in reductions from 15 to 10 mg/d); 65% of patients taking 10 mg/d (30% of them required doses of 15-20 mg/d)	NR
Kyle and Hazleman, ³⁰ 1993 ^c	Same patients as in Kyle and Hazleman ²⁹ ; after the first 2 mo, PDL reductions of 2.5 mg/mo (month 2-4), 1 mg/mo (month 4-12), and then 1 mg every 2 to 3 mo	60 wk (median)/up to 3 y	24	2	61% (52% and 69% occurred within 6 and 12 mo, respectively; 50% of relapses occurred when reductions were <10 mg/d)	PDL, MDD after year 1 (n=25), 7.1 mg/d; year 2 (n=9), 6.9 mg/d; and year 3 (n=3), 7.5 mg/d

Abbreviations: ESR, erythrocyte sedimentation rate; GC, glucocorticoid therapy; GCA, giant cell arteritis; MDD, mean (SD) or median (range) daily dose; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; PDL, prednisolone therapy; PDN, prednisone therapy.

^aDefinition criteria for PMR used in these studies were those from Chuang et al¹⁰ in González-Gay et al,¹⁵ Narváez et al,¹⁶ Kremers et al,¹⁷ Gabriel et al,¹⁹ and Cimmino et al²²; from Bird et al¹⁸ in Myklebust and Gran²⁸; from Jones and Hazleman⁹ in Hutchings et al²¹ and Kyle and Hazleman^{29,30}; and from the respective authors' own criteria in Fauchald et al,¹⁸ Spiera and Davison,²⁰ Mowat and Camp,²³ Delecoeuillierie et al,²⁴ Ayoub et al,²⁵ Weyand et al,²⁶ and Behn et al.²⁷

^bUnless otherwise indicated, data are reported as mean (SD) or median (range).

^cAlthough the study initially included patients with GCA and PMR, only patients with isolated PMR were finally analyzed.

^dThis study used NSAIDs alone or in combination with GC to treat PMR.

^eIn Weyand et al,²⁶ patients were categorized into 3 groups according to response to treatment: group A (n=8; 30%) included patients with a short disease course, rapid PDN tapering (duration of PDN, <1 year), and few relapses; group B (n=12; 44%) included patients who had less rapid GC tapering (duration of GC, >1 year) and more relapses when GC was tapered to doses lower than 10 mg/d; group C (n=7; 26%) included patients requiring GC for more than 1 year, early evidence of more resistant disease, and incomplete initial response to doses of 20 mg/d at 4 weeks.

tients with newly diagnosed PMR. the addition of oral or IM methotrexate to the regimen at 10 mg/wk or higher seemed to reduce relapses, prednisone requirements, and prednisone-related adverse effects.

Maintenance Phase. Oral methotrexate doses of 7.5 mg/wk (increased to 10.0-12.5 mg/wk, according to clinical response) used as cotreatment for remission maintenance in patients with PMR previously receiving prednisone (most requiring ≥20 mg/d) for ≥3 months did not show clinical or biochemical benefit after 9 months of follow-up.⁴¹ However, the inefficacy of methotrexate in this subset of patients requiring unusually high glucocorticoid doses may not be generalizable to the larger PMR population.

Long-term effects of oral methotrexate were retrospectively ana-

lyzed⁴⁰ in a cohort that had earlier been studied in a randomized clinical trial.³⁸ At 59 months after therapy initiation, a modest effect of methotrexate was maintained in that the number of flare-ups per patient was reduced, but no differences in other disease outcomes were found.⁴⁰

The only study (randomized, double-blind, placebo-controlled) using azathioprine (150 mg/d) during the maintenance phase in PMR showed a high frequency of medication-related adverse effects, and 35% of patients withdrew (44% in the azathioprine group and 27% in the placebo group).⁴² After 52 weeks, patients receiving azathioprine required lower cumulative prednisolone doses than those taking placebo. The small number of completers and high proportion of included patients with GCA (29%) make the results difficult to interpret.

Nonsteroidal Anti-inflammatory Drugs

The addition of NSAIDs to glucocorticoid regimens for the treatment of patients with PMR has shown no advantage over glucocorticoids alone in duration of therapy or daily or cumulative prednisone doses, and it produced more adverse events.¹⁹ However, some patients with PMR may achieve sustained remission with NSAIDs.²³ Anecdotally, the effects of tenidap, an unlicensed NSAID, were investigated during the maintenance phase in PMR, and a high toxic profile was found without glucocorticoid-sparing effects.⁴⁴ Although these conclusions were based on low-quality evidence, it is safe to say that treatment with NSAIDs alone may relieve symptoms in a minority of patients with PMR, but it may also have undesirable adverse ef-

Table 4. Clinical Trials Using Glucocorticoid-Sparing Agents in Polymyalgia Rheumatica (Part 1)

Source ^a	Study Type	End Point(s)	Patients Included/ Finally Analyzed, No.	Sex, F/M, No.	Age, y ^b	Patients With Initial/Later Developing GCA, No.
Initial Treatment With GCs (MTX and IFX)						
van der Veen et al, ³⁷ 1996	Randomized, double-blind, placebo-controlled	GC-sparing effect of MTX in PMR and GCA	40/40	30/10	71 (53-84)	6/0
Ferraccioli et al, ³⁹ 1996	Randomized	GC-sparing effect of MTX used early in PMR	24/24	22/2	67.5 (7)	0/0
Caporali et al, ³⁸ 2004	Randomized, double-blind, placebo-controlled	Efficacy and safety of MTX as GC-sparing agent in PMR	72/62	48/24	72.5 (8)	0/0 (+10) ^c
Salvarani et al, ⁴³ 2007	Randomized, double-blind, placebo-controlled	Efficacy of IFX as GC-sparing agent in PMR (percentage of patients without relapse at week 52)	51/47	31/20	71 (7)	0/0 (+4) ^c
Cotreatment for Remission Maintenance (MTX and AZA)						
Feinberg et al, ⁴¹ 1996	Observational, prospective cohort	Efficacy of MTX in PMR resistant patients	43/43	32/11	70 (59-88)	0/0
Cimmino et al, ⁴⁰ 2008	Retrospective case-control study	Long-term effects of MTX in PMR	57/43	37/20	78 (7)	0/3 (+4 + 5) ^c
De Silva and Hazleman ⁴² 1986	Randomized, double-blind, placebo-controlled	GC-sparing effects of AZA during maintenance phase in PMR/GCA	31/20	24/7	70 (57-80)	9/0 (+11) ^c

Abbreviations: AZA, azathioprine therapy; GC, glucocorticoid; GCA, giant cell arteritis; IFX, infliximab therapy; MTX, methotrexate; PMR, polymyalgia rheumatica.

^aThe study by Littman et al⁴⁴ evaluating tenidap as a GC-sparing agent is not illustrated in this table since tenidap is not currently approved by the US Food and Drug Administration. Definition criteria for PMR used in these studies were those from Chuang et al¹⁰ in van der Veen et al,³⁷ Caporali et al,³⁸ and Cimmino et al⁴⁰; from Healey¹¹ in Salvarani et al⁴³; from Jones and Hazleman⁹ in De Silva and Hazleman⁴²; and from the authors' criteria in Ferraccioli et al³⁹ and Feinberg et al.⁴¹

^bData reported as mean (SD) or median (range).

^cIn Caporali et al,³⁸ Salvarani et al,⁴³ and De Silva and Hazleman,⁴² 10, 4, and 11 patients, respectively, did not complete the treatment protocol and were not included in the final analysis. In Cimmino et al,⁴⁰ 3 patients developed GCA; 1, rheumatoid arthritis; and 3, other inflammatory conditions for which PDN was administered at the end of the study; moreover, 2 of 29 and 3 of 28 patients died during the follow-up in the MTX and placebo groups, respectively.

fects when administered long term with glucocorticoids.

COMMENT

Although studies evaluating treatment of PMR not associated with GCA have significant clinical and methodologic variations, and the quality of evidence does not allow specific therapeutic recommendations, the best available evidence suggests that prednisone or its equivalent, at a starting dose of 15 mg/d, may control disease activity in most patients. However, 0% to 13% of patients may still require higher initial doses to control symptoms.^{21,27-29}

Initial prednisone dose reductions of 2.5 mg monthly or every 2 weeks until the dose of 10 mg/d is reached have been used.^{1,21,35} Subsequent reductions may be attempted at 1 mg/mo or less (eg, 1 mg every 6-8 weeks) until discontinuation.^{15,17,21,35} Since relapses usually occur when the prednisone dose is reduced to below 10 mg/d^{26,30} or 5 mg/d,^{15,16} near the time of,^{21,25} or within the first 3 months of,¹⁸ dose

reduction, control visits every 3 months are reasonable, especially when the dose was reduced at the previous visit.

No studies have addressed the management of refractory or relapsing disease. Our own experience is based on maintaining the minimum prednisone dose that controls disease activity. Continuing treatment with glucocorticoids only or adding an agent with glucocorticoid-saving properties should be decided after considering the risks and benefits of long-term glucocorticoid therapy and contraindications to adjuvant therapy.

Of the glucocorticoid-sparing agents tested, oral³⁸ or IM³⁹ methotrexate at a dose of at least 10 mg/wk seems to be useful in new-onset PMR. However, relapsing cases or those treated with long-term prednisone doses of 10 mg/d or higher may require higher methotrexate doses. The initial addition of methotrexate to a prednisone regimen might benefit patients at high risk of glucocorticoid-related adverse effects: the combination treatment

regimen has shown fewer adverse effects than prednisone alone.³⁹ The increased benefit and lower adverse-event profile of IM and subcutaneous methotrexate treatment compared with oral methotrexate in the treatment of rheumatoid arthritis^{45,46} suggests that subcutaneous methotrexate might also be considered for the treatment of PMR. Methotrexate therapy discontinuation could be tentatively attempted 6 to 12 months after glucocorticoid treatment cessation.³⁹

From the findings of the present review, we have designed an algorithm for treating PMR (**Figure 2**). Osteoporosis prophylaxis with bisphosphonates, oral calcium, and vitamin D supplementation are broadly recommended¹ because glucocorticoid-related adverse effects are reported in widely divergent percentages of patients with PMR: one group of studies concludes the range to be 3.6% to 27%^{15,20,25,27,35} of patients with PMR, while another group reports it to range from 58% to 91%.^{19,21,39} Adverse effects can be detected after 1 year of treat-

Table 5. Clinical Trials Using Glucocorticoid-Sparing Agents in Polymyalgia Rheumatica (Part 2)

Source ^a	Baseline Situation and Drug Starting Doses	Drug Modifications	Duration of Therapy/Follow-up	Relapses	GC Cessation and GC Daily or Cumulative Dose
Initial Treatment With GCs (MTX and IFX)					
van der Veen et al, ³⁷ 1996	At PMR diagnosis, randomization to PDN + placebo (n = 20) or PDN and oral MTX, 7.5 mg/wk (n = 20) (all PDN doses, 20 mg/d)	PDN tapered 2.5 mg every 3 wk until 7.5 mg/d, then by 2.5 mg every 6 wk; after PDN cessation, 3 blinded pills every 2 wk	47.5 wk (median)/at least 2 y or 1 y after PDN cessation	Similar relapse rates, MTX, 25%, vs placebo, 23%	No differences in cumulative PDN doses at the first and second years of follow-up in either time to remission or duration of remission
Ferraccioli et al, ³⁹ 1996	After failure of NSAIDs to control PMR, randomization to PDN alone, 15 mg/d for 3 months (n = 12) or IM MTX, 10 mg/wk + PDN, 25 mg/d for 1 mo (n = 12)	PDN alone, 10, 5, and 2.5 mg/d (1 mo each); IM MTX, 10 mg/wk + PDN, 12.5, 10, 6.25, 5, and 2.5 mg/d (1 mo each)	PDN, 6 mo; MTX, 12-18 mo/1 y, extension of 6 mo	More relapses in patients treated with PDN alone vs PDN + MTX (100% vs 50%)	At months 6 and 12, 50% of the MTX patients stopped PDN, while all PDN-alone patients continued PDN; at month 18, 100% of patients not taking PDN stopped MTX, and no PDN-alone patients stopped PDN; at 12 mo, PDN-alone group had higher PDN mean DD (1.9 vs 5.1 mg; <i>P</i> = .001) and cumulative dose (1.8 vs 3.2 g; <i>P</i> < .001)
Caporali et al, ³⁸ 2004	At PMR diagnosis, randomization to PDN, 25 mg/d + oral MTX, 10 mg/wk (n = 36) or PDN, 25 mg/d + placebo (n = 36); all PDN was administered for 4 wk	PDN tapered to 0 in 24 wk in both groups (subsequent doses, 17.5, 12.5, 7.5, 5, and 2.5 mg/d for 4-wk periods each)	24 wk/76 wk	Occurrence of ≥1 relapses or recurrences at week 76 lower in MTX than in placebo (47% vs 73%; <i>P</i> = .04); total episodes, 27 vs 50 (<i>P</i> = .009)	At 76 wk, PDN cessation higher in MTX than in placebo group (88% vs 53%; <i>P</i> = .003); median duration of PDN, 30 vs 56 wk (<i>P</i> = .007); PDN mean DD lower in MTX than in placebo group (2.1 vs 3.0 mg/d; <i>P</i> = .03); no differences in the cumulative PDN dose
Salvarani et al, ⁴³ 2007	At PMR diagnosis, randomization to PDN + IFX (n = 23) or PDN + placebo (n = 28). All PDN doses were 15 mg/d for 4 wk; all IFX doses were 3 mg/kg given at week 0, 2, 6, 14, and 22	PDN tapered to 10, 5, and 2.5 mg/d for 4-wk periods each, and stopped if indicated by patient's clinical condition	1 y for both treatment and follow-up	At wk 52, no differences in total No. of flare-ups (30% IFX vs 37% placebo) or the number of patients free of them	At week 52, no differences were found in patients who could discontinue PDN (50% IFX vs 54% placebo), in median PDN duration (26 wk, IFX vs 22 wk, placebo), or in median cumulative PDN dose (17.1 g, IFX vs 12.2 g, placebo)
Cotreatment for Remission Maintenance (MTX and AZA)					
Feinberg et al, ⁴¹ 1996	All patients initially taking PDN, 10 mg/d (79% required ≥20 mg/d), treated with PDN + oral MTX; MTX doses started at 7.5 mg/wk for at least 3 mo	MTX was increased to 10 to 12.5 mg/wk if no response	9 mo for both treatment and follow-up	No decrease in ESR levels for any MTX dose. In some patients, ESR decrease not accompanied by clinical improvement	Disease control not achieved in any patient, and PDN could not be reduced
Cimmino et al, ⁴⁰ 2008	Retrospective review of patients with PMR from Caporali et al ³⁸ in 2 groups, 29 treated with MTX and 28 with placebo	Not described during the follow-up	Mean (SD) 59 (11), mo for both treatment and follow-up	MTX lower No. of flare-ups/patient than placebo (1.2 vs 1.9; <i>P</i> = .05). No differences in percentage of patients having flare-ups	64.9% stopped PDN after a mean of 6.5 y; no differences in patients continuing PDN 5 y after completing the study (31%, MTX vs 39%, placebo) in cumulative PDN dose or in medication-related adverse effects
De Silva and Hazleman, ⁴² 1986	After a remission period of ≥3 mo (mean, 2.4 y) while being treated with PDL, ≥5 mg/d, randomization to PDL + AZA (50 mg/8 h) (n = 16) or PDL + placebo (n = 15)	AZA was adjusted according to tolerance	9 mo to 1 y/1 y		At week 36 and 52, 71% and 65% of patients completed treatment, respectively; at week 52, AZA patients had lower cumulative PDL dose than placebo patients (1.9 vs 4.2 mg; <i>P</i> < .05)

Abbreviations: AZA, azathioprine therapy; DD, daily dose; GC, glucocorticoid; GCA, giant cell arteritis; IFX, infliximab therapy; IM, intramuscular; MTX, methotrexate therapy; NSAID, nonsteroidal anti-inflammatory drug; PDL, prednisolone therapy; PDN, prednisone treatment; PMR, polymyalgia rheumatica.
^aThe study by Littman et al⁴⁴ evaluating tenidap as a GC-sparing agent is not illustrated in this table since tenidap is not currently approved by the US Food and Drug Administration. Definition criteria for PMR used in these studies were those from Chuang et al¹⁰ in van der Veen et al,³⁷ Caporali et al,³⁸ and Cimmino et al⁴⁰; from Healey¹¹ in Salvarani et al⁴³; from Jones and Hazleman⁹ in De Silva and Hazleman⁴²; and from the authors' own criteria in Ferraccioli et al³⁹ and Feinberg et al.⁴¹

ment^{19,21} and are more frequent in patients experiencing more disease relapses¹⁵ and those receiving higher glucocorticoid doses and for longer periods.^{15,19,24,25,27}

It is challenging to identify patients with PMR who have more

resistant disease and who may benefit from a tailored treatment strategy. Elevated ESR^{16,17,26,28,48,49} and CRP⁴⁸ and interleukin 6^{26,48} levels at the time of diagnosis correlate with an increased risk of relapse^{17,26,48,49} or higher glucocorti-

coid requirements,^{16,28} especially if abnormalities persist during treatment.^{26,48} High hemoglobin levels and low ESR values are associated with a better response to glucocorticoid therapy in PMR.²⁸ Sex seems to influence the course of PMR:

Table 6. Different Outcome Definitions Reviewed Sources

Source	Conditions Required to Define a PMR Relapse				Remission Definition		
	Return of Symptoms, Signs, or Both	Increase in ESR and/or CRP Values	Timing of Appearance	Improvement After Reinstitution of Previous or Higher GC Dose	Recurrence Definition (Timing of Relapse)	Clinical	Laboratory
Ayoub et al, ²⁵ 1985	Signs or symptoms	NR	While receiving GC	Yes	After GC discontinuation	Absence of symptoms	NR
Behn et al, ²⁷ 1983	Original symptoms	ESR (NSV) but not necessarily required	NR	NR	NR	Absence of symptoms	NR
Caporali et al, ³⁸ 2004 and Cimmino et al, ⁴⁰ 2008	Signs and symptoms ^a	ESR >30 mm/h or CRP >5 mg/L or both	During GC tapering	NR	After GC withdrawal	NR	NR
Cimmino et al, ²² 2006	Both	ESR >30 mm/h and/or CRP >5 mg/L	During the GC tapering	NR	During the GC withdrawal	NR	NR
Cimmino et al, ³¹ 1994	Signs or symptoms	NR	After GC discontinuation	Yes	During GC therapy	NR	NR
Dasgupta et al, ³⁵ 1998	Symptoms	NR	NR	NR	NR	Morning stiffness <30 min, a reduction in VAS from baseline ≥50%	ESR <20 mm/h and Hb >12 g/dL
Di Munno et al, ³³ 1995	NR	NR	NR	NR	NR	80% Reduction in pain and morning stiffness	ESR <15 mm/h or CRP <5 mg/L
Fauchald et al, ¹⁸ 1972	Symptoms	ESR (NSV)	NR	NR	NR	Regression of the symptoms	Normal ESR (NSV)
Ferraccioli et al, ³⁹ 1996	Return of myalgia	Increase of ESR and/or CRP at levels 100% higher than in the previous assessment	NR	NR	NR	No symptoms	Normal ESR and CRP values (NSV)
González-Gay et al, ¹⁵ 1999	Symptoms	ESR (NSV) but not necessarily required	NR	Yes	After 1 y since GC discontinuation	NR	NR
Hutchings et al, ²¹ 2007	Symptoms	NR	NR	Yes	NR	No pain or >50% improvement in pain in shoulder and pelvic girdle on a VAS; morning stiffness ≤30 min	ESR <30 mm/h and CRP <10 mg/L
Kremers et al, ¹⁷ 2005	Symptoms	NR	At least 30 d after the incidence date (symptoms)	Yes. An increase in GC dose ≥5 mg/d had to be required	NR	No symptoms within 5 y from the last relapse without GC or taking ≤5 mg/d	Normal ESR (NSV)
Kyle and Hazleman, ³⁰ 1993	Signs and symptoms ^a	NR	NR	Yes	NR	No significant signs or symptoms	NR
Narváez et al, ¹⁶ 1999	Original symptoms or signs	ESR (NSV)	During the PDN tapering or during the first month after discontinuation	Yes	≥1 mo after treatment discontinuation	Permanent GC cessation	NR
Salvarani et al, ⁴³ 2007	Signs and symptoms ^a	ESR >30 mm/h or CRP >5 mg/L or both	During GC tapering	Yes	>1 mo after discontinuation of therapy of PMR	No signs or symptoms of PMR	Normal ESR (<30 mm/h)
van der Veen et al, ³⁷ 1996	Original symptoms	An increase of 100% in ESR or CRP	Still receiving GC	NR	After stopping GC and other trial drug treatment	NR	NR

Abbreviations: CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; Hb, hemoglobin level; NR, not reported; NSV, no stated value; PDN, prednisone treatment; PMR, polymyalgia rheumatica; VAS, visual analog scale.

SI conversion factors: To convert CRP to nanomoles per liter, multiply by 9.524; to convert Hb to grams per liter, multiply by 10.

^aSigns and symptoms of PMR defined as pain and stiffness in the shoulder, hip girdle, or both.

compared with men, women seem to have more resistant disease, more relapses,²² a need for greater cumulative amounts of glucocorticoids,²² more glucocorticoid-related adverse effects,^{19,22,25,35} and a need for longer-duration glucocorticoid treatment.^{16,25}

The limitations of this review are mainly due to the lack of controlled intervention studies on PMR treatment. In addition, there was significant variation between studies, including different diagnostic PMR criteria, outcome definitions, initial dosages, tapering schedules, and fol-

low-up periods. Specifically, the indistinct use of nonvalidated PMR classification criteria⁸⁻¹¹ weakens the inclusion criteria. However, a recent consensus study by 27 international experts⁴⁷ established 7 potential PMR classification criteria that are awaiting prospective validation. We have

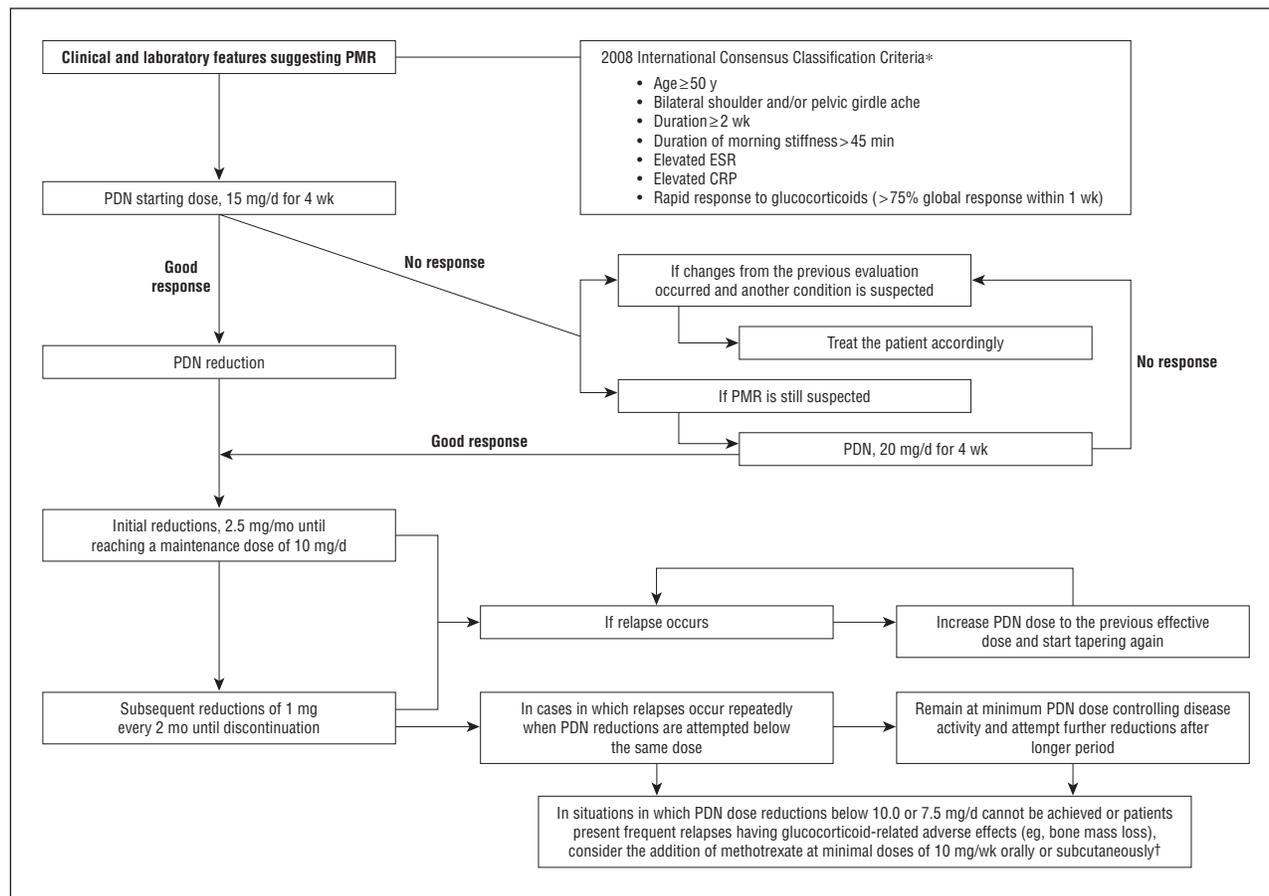


Figure 2. Proposed therapeutic algorithm for the treatment of polymyalgia rheumatica (PMR). PDN indicates prednisone. *The 2008 International Consensus Classification Criteria⁴⁷ are awaiting prospective validation. †This recommendation is not based on the data analyzed in the present review; rather, it relies on evidence that methotrexate administered at PMR onset can reduce glucocorticoid-related adverse effects, especially bone mass loss,³⁹ and suggestions and reports from experienced investigators.^{2,38} Glucocorticoid-related adverse effects, including bone mass loss, should be managed according to local policies and guidelines. CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate.

based the therapeutic algorithm on these classification criteria (Figure 2). Other multicenter studies have addressed PMR activity scoring systems for defining remission thresholds and developing response criteria for treatment monitoring.^{50,51}

In conclusion, although with limited evidence-based information, the available data suggest a starting prednisone dose of 15 mg/d followed by a slow tapering regimen as appropriate treatment for most PMR cases. Although methotrexate has shown glucocorticoid-saving properties, the efficacy of all adjuvant medications included in this review and new biologic and nonbiologic glucocorticoid-sparing agents remains to be determined in larger randomized controlled trials, especially in patients with PMR who are glucocorticoid dependent.

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