Relapse in a Population Based Cohort of Patients with Polymyalgia Rheumatica

HILAL MARADIT KREMERS, MEGAN S. REINALDA, CYNTHIA S. CROWSON, ALAN R. ZINSMEISTER, GENE G. HUNDER, and SHERINE E. GABRIEL

ABSTRACT. ***Objective.*** To determine the incidence and the clinical, laboratory, and treatment related predictors of relapse in polymyalgia rheumatica (PMR).

Methods. Using the population based resources of the Rochester Epidemiology Project, we assembled an incidence cohort of subjects with PMR first diagnosed between January 1, 1970, and December 31, 1999. For inclusion, subjects were required to fulfill 3 criteria: (1) age ≥ 50 years; (2) bilateral aching and morning stiffness in neck, shoulders, or hip girdle regions; and (3) erythrocyte sedimentation rate (ESR) ≥ 40 mm/h. In subjects who fulfilled the first 2 criteria but had a normal ESR, a rapid response to low dose corticosteroids (CS) served as the third criterion. Patients were followed until permanent remission, migration, or a maximum of 5 years after their incidence date. Relapse was defined as an exacerbation of PMR symptoms requiring an adjustment of CS dose (≥ 5 mg) occurring at least 30 days after the incidence date. Time to relapse was modeled using the Kaplan-Meier method. CS treatment patterns were modeled using linear and nonlinear models. Cox regression models were used to evaluate predictors of time to first and subsequent relapses.

Results. The study population included 364 patients with a mean age of 73.4 years and 244 (67%) were women. Among the 284 patients treated with CS, a higher initial CS dose and faster CS tapering rate were significant predictors of future relapses, after adjusting for age, sex, ESR, giant cell arteritis at PMR diagnosis, and the intensity of rheumatologist care. Every 5 mg/day increase in initial CS dose was associated with a 7% increase in the risk of relapse [hazard ratio (HR) 1.07, 95% CI 1.02, 1.13]. The hazard of having a relapse was 4-fold higher when the CS tapering rate was fast (HR 4.27, 95% CI 2.84, 6.44), and 2-fold higher when the CS tapering rate was medium (HR 2.19, 95% CI 1.54, 3.11) compared to slow tapering.

Conclusion. Higher initial CS doses and faster tapering are significant predictors of future relapses. Our results suggest that efforts should be made to minimize initial CS dose and taper CS slowly in order to avoid disease relapses. (J Rheumatol 2005;32:65–73)

Key Indexing Terms:
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Polymyalgia rheumatica (PMR) is a common, nonfatal illness of middle-aged and older individuals characterized by aching and morning stiffness in the proximal regions of the extremities and torso, and elevated markers of inflammation including the erythrocyte sedimentation rate (ESR). The overall age and sex-adjusted annual incidence per 100,000 population aged ≥ 50 years in Olmsted County, Minnesota, is estimated at 58.7 [95% confidence interval (CI) 52.8, 64.7][1]. The management of PMR involves careful titration of the corticosteroid (CS) dose according to the patient's symptoms and the ESR, such that the patient is maintained on the lowest possible dose that controls PMR symptoms and minimizes CS induced complications. There is considerable heterogeneity in patients' clinical course, CS requirements for suppression of symptoms, and the likelihood of relapses[2-5]. Patients with PMR frequently experience disease relapses, which make management of the disease more difficult. Identification of predictors of relapse should lead to optimal treatment strategies aimed at shortening the disease course and minimizing the cumulative CS burden. We investigated the incidence and the clinical, laboratory, and treatment related predictors of relapse in PMR.

From the Division of Epidemiology and Division of Biostatistics, Department of Health Sciences Research, and Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA.

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H. Maradit Kremers, MD, MSc, Division of Epidemiology; M.S. Reinalda, BS; C.S. Crowson, BS; A.R. Zinsmeister, PhD, Division of Biostatistics; G.G. Hunder, MD, Division of Rheumatology; S.E. Gabriel, MD, MSc, Division of Epidemiology, Division of Rheumatology.

Address reprint requests to Dr. S.E. Gabriel, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: gabriel.sherine@mayo.edu

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MATERIALS AND METHODS

Study population. This was a retrospective longitudinal study using the data resources of the Rochester Epidemiology Project (REP). The REP is a diagnostic indexing and medical records linkage system. The potential of this data system for population based research has been described[6,7]. This system assures virtually complete ascertainment of all clinically recognized cases of PMR in a geographically defined community.

Using this data resource, an incidence cohort of all cases of PMR first

diagnosed between January 1, 1970, and December 31, 1999, among Olmsted County residents was identified as described[1]. A trained nurse-abstractor screened the medical records of individuals who had received one or more diagnoses of PMR, giant cell arteritis (GCA), or temporal arteritis (TA). Individuals were included as PMR cases if they fulfilled the following 3 criteria: (1) age 50 years or older; (2) bilateral aching and morning stiffness (lasting ≥ 30 min) persisting for at least 1 month involving 2 of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs; and (3) ESR elevated to more than 40 mm/h (Westergren). Patients with suggestive clinical findings who fulfilled the first 2 of the 3 criteria, and who had a prompt response to low dose CS therapy, were also included. Except for GCA, the presence of another disease that could explain the symptoms, such as active rheumatoid arthritis, was considered an exclusion criterion. If the patient was diagnosed with another rheumatologic disease during the course of followup, then followup for that patient was discontinued, but the patient was not excluded from the study. In cases where the diagnosis was questionable, 3 rheumatologists reviewed all the clinical information and reached consensus on the diagnosis.

Data collection. The complete records of study subjects were reviewed longitudinally starting 30 days prior to incidence date until permanent remission of PMR, migration from Olmsted County, or a maximum of 5 years after their incidence date. Details of all inpatient and outpatient physician encounters (including telephone calls) were abstracted from the medical records. These details included physician specialty (e.g., rheumatology, family medicine, internal medicine), reason for the visit (e.g., PMR diagnosis, routine followup, exacerbation of PMR symptoms, post-hospital followup), result of PMR examination, and therapy information. Patients were considered in permanent remission if they had no PMR symptoms or relapse within 5 years of incidence date while they were no longer undergoing CS therapy, or were taking ≤ 5 mg CS per day, and had normal ESR. Information on the occurrence of GCA and disease relapses was collected for all PMR patients who developed these disorders at any time during the followup period. The diagnosis of GCA was determined according to American College of Rheumatology (ACR) criteria[8].

Statistical methods. The primary outcome in this study was disease relapse. Relapse was defined as an exacerbation of PMR symptoms requiring an increase in CS dose ≥ 5 mg/day occurring at least 30 days after the incidence date. Each patient's total followup period was divided into treatment intervals. The initial treatment interval started on PMR incidence date and ended at first relapse, or the last followup date for those who had no relapses. The subsequent treatment intervals started on the next day following a relapse episode (i.e., the day following an exacerbation of PMR symptoms requiring an increase in CS dose ≥ 5 mg/day) and ended at the date of next relapse, date of remission, or the last followup date. During the initial treatment interval, only such changes occurring at least 30 days after the incidence date (as assessed by the physician and the patient) were considered, while during subsequent intervals, changes at any time were considered. Proportional hazards regression models were used to estimate the influence of all potential predictors on time to first relapse. An extension[9] of these models for multiple events was used to assess predictors of time to relapse considering multiple relapses per patient. Potential predictors of relapse included age, sex, ESR, GCA at diagnosis, rheumatologist care, and specific aspects of CS therapy. The potential predictors considered included "fixed" covariates (e.g., age, sex, GCA at diagnosis) and time-dependent covariates (e.g., number of rheumatologist visits, ESR values). GCA diagnoses during followup were censored. Rheumatologist care was defined as the cumulative number of rheumatologist visits and was included as a time-dependent covariate in regression models. Univariate hazard ratios were computed for each predictor variable and also the hazard ratios for each predictor in multiple-predictor variable models. Since some patients experienced multiple relapses, "robust" variance estimates for the estimated predictor variable coefficients in the multiple-event proportional hazards regression models were obtained using a grouped jackknife approach[9]. P values less than 0.05 were considered significant.

Analyses examining the role of CS therapy were restricted to the subgroup of 284 patients who received CS therapy during the disease course and had at least 4 recorded CS values (Figure 1) for a given interval. Their CS treatment during followup intervals was defined by uninterrupted CS administration during which their daily CS dose during the interval was inferred from their medical care during the interval. An increase in CS dose ≥ 5 mg/day was identified as a relapse, and therefore marked the beginning of another followup interval.

Time to first relapse was summarized using the Kaplan-Meier method. Kaplan-Meier plots were generated for the initial, and separately for tapered and nontapered intervals. Intervals were characterized as "tapered" or "nontapered" based on the form of their cumulative daily dose curves. In analyses restricted to tapered intervals, we examined the role of CS tapering as a potential predictor of relapse in the Cox regression model (time to first relapse) and the multiple-event models (multiple-relapse intervals). The CS tapering rates were categorized as slow, medium, or fast based on the distribution of the estimates of the tapering constant, the parameter "b" in the model described below. In order to estimate CS tapering rates, linear and nonlinear (an exponential growth curve model) models were used to characterize each patient's cumulative daily dose of CS during each followup interval. The goodness of fit was examined using the per-patient interval overall R^2 values for a linear fit versus the nonlinear model. Followup intervals where CS tapering was described better with a linear model (i.e., greater R^2 value) were defined as nontapered intervals. Intervals where a nonlinear model provided a better fit for the data were defined as tapered intervals. Exponential growth curves were used to model each patient's cumulative dose of CS during tapered intervals. This model resulted in an estimate of the tapering rate within each interval, based on the changes in daily doses of CS during the interval. The nonlinear model for the cumulative CS daily dose curves was based on the following formula:

$$\text{cumulative CS dose}_i = \text{maximum cumulative dose of CS} * \{1 - \alpha(e^{-b(\text{time}_i - \text{lag})})\}$$

where:

cumulative CS dose$_i$ = cumulative CS dose at time (day) i;

maximum cumulative CS dose = maximum cumulative CS dose at the time of each relapse. For those who did not relapse, maximum cumulative CS dose at the end of followup (maximum of 5 years since PMR incidence date);

time$_i$ = time from diagnosis, or from previous relapse to the subsequent relapse; and

lag = time from diagnosis (or previous relapse) to first subsequent CS dose.

In this model, b and α are the estimated parameters for each subject and interval. The parameter b reflects the rate of increasing CS dose (i.e., tapering constant). It is a measure of the rate that the dose is approaching the maximum cumulative CS dose, i.e., the tapering rate. The parameter α reflects the instantaneous remaining proportion of the maximum cumulative CS dose.

RESULTS

A total of 378 incident cases of PMR who were Olmsted County residents aged ≥ 50 years and who first fulfilled the diagnostic criteria for PMR between 1970 and 2000 had been identified[1] (Figure 1). Of the 378 incident cases, 364 were eligible for this analysis; 14 were excluded because they either subsequently denied research authorization or they had a serious comorbid disease (e.g., cancer) that dominated their medical care.

Two hundred forty-four (67%) of the 364 patients were women and the mean age at PMR incidence was 73.4 years (Table 1). Median pretreatment ESR was 52.0 mm/h (mini-

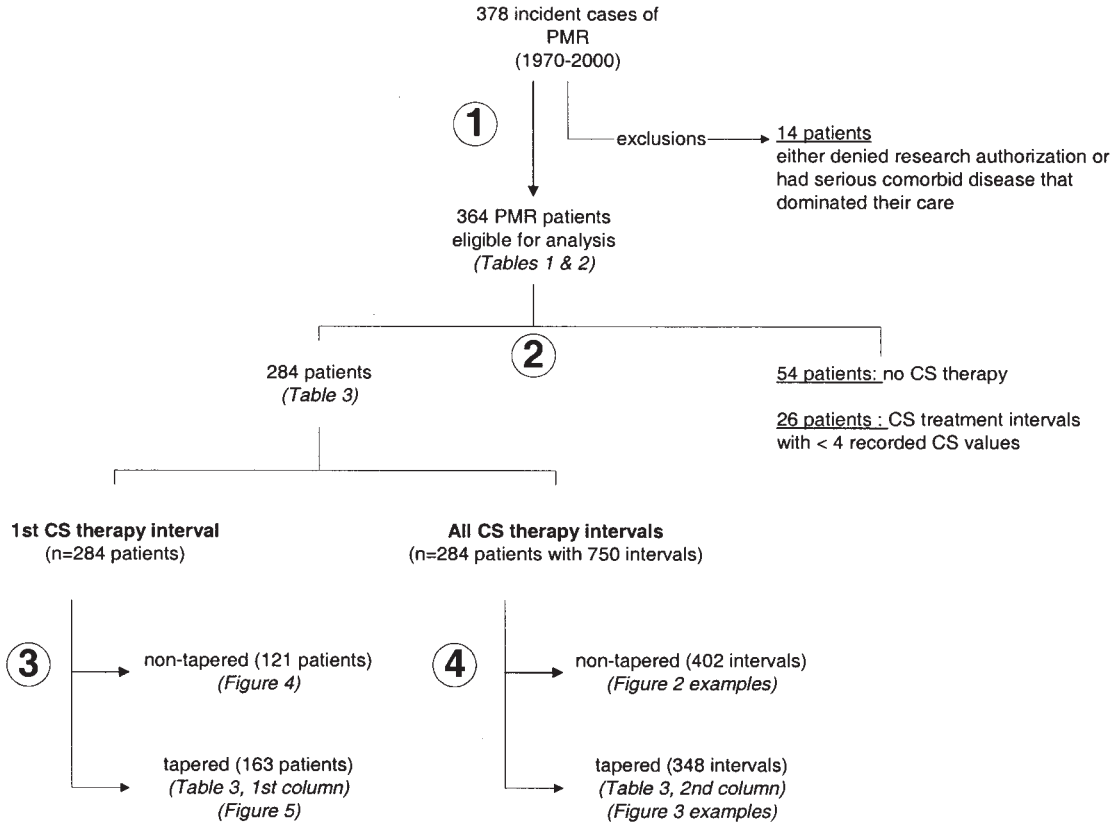

Figure 1. Patient disposition. 1. Of the total 378 incident cases of PMR that first fulfilled the diagnostic criteria for PMR between 1970 and 2000, 14 subjects either subsequently declined to participate or had a serious comorbid disease that dominated their medical care. 2. Of the 364 PMR patients, 54 never received CS during the disease course. In 26 CS-treated patients, the number of recorded CS values was less than 4 during a given CS treatment interval. Therefore these 80 patients (54 + 26) were excluded from analyses examining the effect of CS therapy on relapses. 3. During the first CS treatment interval following PMR diagnosis, CS dose was not tapered in 121 and was tapered in 163 of the 284 patients. Figure 4 shows the cumulative rate of relapse according to daily CS dose during 121 nontaper intervals; Figure 5 shows the cumulative rate of relapse by tapering rates during 163 CS tapering intervals. 4. During the entire CS treatment duration of the 284 patients, there were 750 treatment intervals. Of these 750 CS treatment intervals, CS dose was not tapered in 402 intervals and was tapered in 348. Figure 2 displays selected examples of the 402 treatment intervals when CS were not tapered. Figure 3 displays selected examples of the 348 treatment intervals when CS were tapered.

mum 2, maximum 136). Patients were followed for a median of 5.1 years (minimum 0.12, maximum 5.1), during which 310 (85%) patients received CS with or without nonsteroidal antiinflammatory drugs (NSAID). Overall, initial median CS dose was 15 mg (minimum 1, maximum 100) and the median duration of CS therapy was 1.83 years (minimum 0, maximum 4.97).

Each patient's cumulative dose of CS over time was modeled using linear and exponential growth curve models. Of the 364 patients, 54 were excluded because they did not receive CS during the disease course, and 26 CS treated patients were excluded because they had < 4 recorded CS values for a given CS treatment interval (Figure 1). Therefore, these analyses were restricted to 284 patients. The CS treatment duration of these 284 patients was divided into a total of 750 treatment intervals. During the first CS treatment interval following PMR diagnosis, CS dose was tapered in 163 of the 284 patients (Figure 1). Out of 750 CS treatment intervals over the entire followup of these 284 patients, CS dose was tapered in 348 intervals and not tapered in 402 (Figure 1).

Figure 2 displays examples of treatment intervals when CS were not tapered, indicating that the patient was either taking a stable CS dose or the dose changes were < 5 mg/day from one day to the next. These nontaper treatment intervals were further classified as "high dose" (> 10 mg/day), "medium dose" (5–10 mg/day), and "low dose" (≤ 5 mg/day), depending on the slope of the linear model, which approximates the average daily CS dose during that interval. Figure 3 displays examples of treatment intervals where exponential growth curves provided a better fit for the data, indicating that the CS dose was tapered during that treatment interval, and a tapering rate could be estimated using the "tapering constant" (b) from the exponential growth curve formula (see Materials and Methods). These tapering treatment intervals were further classified as "slow," "medi-

Table 1. Demographic and clinical characteristics of 364 Olmsted County residents (≥ 50 years of age) who first fulfilled the diagnostic criteria for PMR between 1970 and 2000.

Characteristic	n = 364
Age at PMR diagnosis, yrs	
Mean, median	73.4, 74.1
Minimum, maximum	50.8, 95.5
Female, n (%)	244 (67.0)
Length of followup, yrs	
Mean, median	4.2, 5.1
Minimum, maximum	0.12, 5.1
ESR at diagnosis, mm/h	
Mean, median	55.2, 52.0
Minimum, maximum	2, 136
Treatment, n (%)	
NSAID alone	54 (14.8)
Corticosteroid (CS) alone	110 (30.2)
NSAID + corticosteroids	200 (55.0)
Initial CS dose, mg (n = 310)	
Mean, median	19.2, 15.0
Minimum, maximum	1, 100
Patients with relapses, n (%)	200 (55.0)
Patients with GCA, n (%)	53 (14.6)
Patients with any CS complication*, n (%)	216 (59.3)

* At least one CS complication following PMR diagnosis. Includes diabetes mellitus, vertebral fractures, Colles' fracture of the wrist, proximal femur fracture, aseptic necrosis of the femoral head, posterior subcapsular cataract, bacteremia, sepsis, pneumonitis, other infections, upper gastrointestinal bleeding, essential hypertension, myopathy.

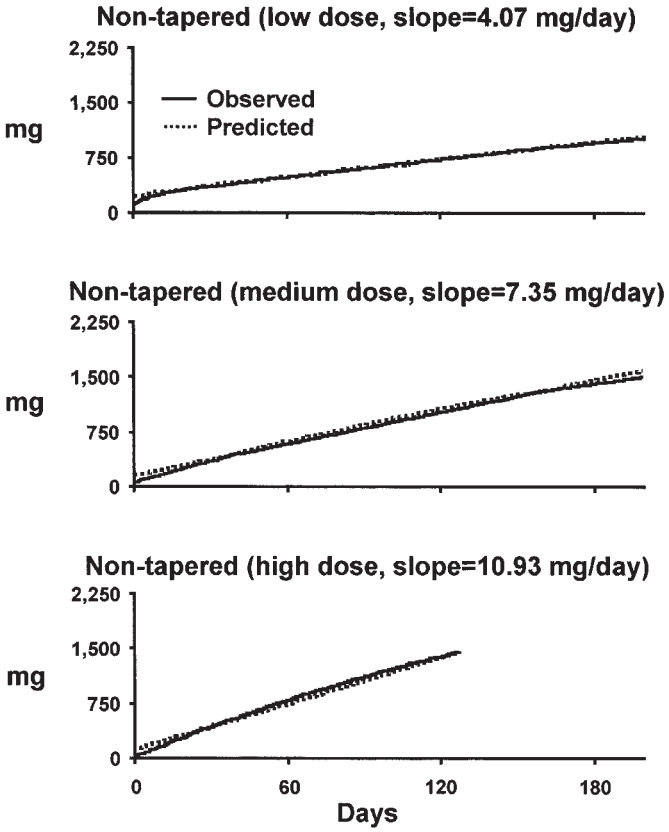

Figure 2. Selected examples of observed and predicted cumulative CS dose over time during treatment intervals when CS were not tapered.

um," or "fast" using the distribution of the tapering constant. Lower values (Figure 3A) indicated slow CS tapering rates, whereas higher values (Figure 3C) indicated fast CS tapering rates.

Univariate results from the Cox proportional hazards regression analyses indicated that age at diagnosis of PMR, sex, and the number of rheumatologist visits during the initial treatment interval were not associated with time to first relapse (Table 2). Higher ESR values [hazard ratio (HR) per 10 mm/h increase 1.07, 95% CI 1.02, 1.13] and CS therapy during the first 30 days following diagnosis (HR 4.07, 95% CI 2.48, 6.71) were significantly associated with a shorter time to first relapse (Table 2). These estimates remained unchanged in multivariable analysis after adjustment for age, sex, GCA at PMR diagnosis, and the number of rheumatologist visits. Subjects who were diagnosed with GCA at around the time of PMR incidence had a lower likelihood of experiencing a relapse (HR 0.25, 95% CI 0.08, 0.77), but this was no longer significant after adjustments for age, sex, number of rheumatologist visits, and CS therapy (Table 2). In supplementary analyses, we examined the effect of initial CS dose on time to first relapse. A higher initial CS dose was a significant predictor of relapse in both univariate and multivariable models. Every 5 mg/day increase in initial CS dose (i.e., at the beginning of CS therapy) corresponded to a 10% increase in the risk of relapse (multivariable HR per 5 mg/day increase 1.11, 95% CI 1.07, 1.16). Patients who received > 10 mg/day had a much higher likelihood of relapses compared to those who received 5–10 mg/day or ≤ 5 mg/day (p = 0.012; Figure 4).

We then examined the predictors of time to first relapse among 163 patients (Figure 1) whose CS doses were tapered during the first treatment interval following incidence (Table 3, first column). Higher ESR values (HR per 10 mm/h increase 1.16, 95% CI 1.06, 1.25), higher initial CS doses (HR per 5 mg/day 1.07, 95% CI 1.00, 1.13), and CS tapering rates were significant predictors of time to first relapse, after adjusting for age, sex, GCA at PMR diagnosis, and the number of rheumatologist visits. Compared to slow CS tapering (reference group), the hazard of having a first relapse was 2.4 times higher when tapering was medium (HR 2.39, 95% CI 1.33, 4.29) and 5.3 times higher when tapering was fast (HR 5.27, 95% CI 2.99, 9.28), after adjustment for age, sex, ESR, GCA at PMR diagnosis, number of rheumatologist visits, and the initial CS dose (Table 3, first column).

The observed associations in time to first relapse remained essentially unchanged when the analysis was extended to include all relapses during the 348 CS tapering

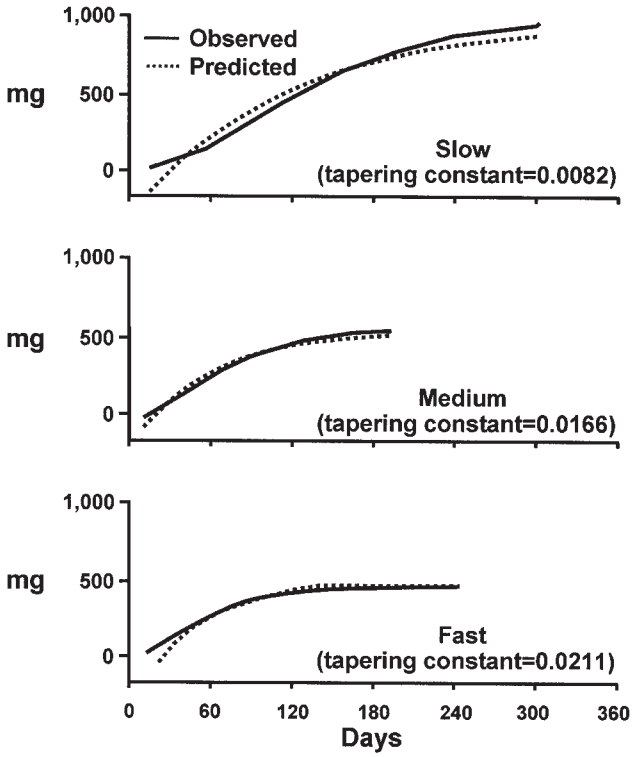

Figure 3. Selected examples of observed and predicted cumulative CS dose over time during treatment intervals when CS were tapered.

intervals of 284 patients (Table 3, second column). In addition, the number of previous relapses was a significant predictor of future relapses. Each additional relapse resulted in a 14% increase in the risk of a subsequent relapse (HR 1.14, 95% CI 1.05, 1.23). The number of rheumatologist visits and any rheumatologist care during the preceding 6 month period had no effect on the likelihood of relapses (Table 3). Figure 5 shows the cumulative rate of relapses by categories of tapering rates (i.e., tapering constant) during CS tapering intervals. A significant association was observed between tapering rate and time to relapse. By the end of the first year of the disease, almost 70% of the patients experienced at least one disease relapse if the CS dose was tapered fast, compared to only 10% of patients if the CS dose was tapered slowly (p = 0.001; Figure 5).

The tapering rates are illustrated with an example in Table 4. A patient who started CS therapy with 20 mg/day would fall into the slow tapering category if CS therapy was maintained for at least a year, into the medium category if CS therapy was discontinued after 9 months of therapy, and into the fast category if CS therapy was discontinued after 3 months of therapy.

DISCUSSION

PMR is a challenging disease, in terms of both diagnosis and the longterm management. Corticosteroids are currently the standard therapy in patients with PMR. Although CS therapy successfully controls disease symptoms, CS-associated adverse events are common. Despite these difficulties, there is no consensus on what the optimal initial CS dose should be and how it should be tapered during the long disease course. Management is further complicated by frequent relapses in a substantial proportion (55%) of the patients. In this community based cohort of PMR patients, we were able to effectively assess the patterns and predictors of disease relapses because of the availability of detailed encounter-specific followup information on CS therapy and disease relapses. First, acknowledging that the reductions of the daily CS dose were not always linear over time, we successfully developed a mathematical model that accurately described CS tapering according to an exponential function, where CS dose reduction was measured proportional to the patients' current CS dose. Second, we found that patients who received a higher initial CS dose and whose CS were tapered fast were significantly more likely to experience relapses, after adjusting for demographics and various disease characteristics. Third, the presence or intensity of rheumatologist care had no influence on the likelihood of relapses, but was significantly associated with a lower initial CS dose and slower tapering rates. These results indicate that PMR relapses may be reduced through careful monitor-

Table 2. Predictors of time to first relapse among 364 Olmsted County residents ≥ 50 years of age who first fulfilled the diagnostic criteria for PMR between 1970 and 2000.

	Univariate HR (95% CI)*	Multivariate HR (95% CI)**
Age (per 10 year increase)	1.08 (0.92, 1.27)	1.03 (0.88, 1.21)
Sex (male vs female)	0.91 (0.68, 1.22)	0.96 (0.71, 1.30)
ESR (per 10 mm/h)	**1.07 (1.02, 1.13)**	**1.11 (1.06, 1.17)**
Giant cell arteritis at PMR diagnosis	**0.25 (0.08, 0.77)**	0.42 (0.13, 1.33)
No. of rheumatologist visits	1.01 (0.94, 1.08)	1.03 (0.96, 1.10)
Treatment with CS during the 30 days following incidence (yes/no)	**4.07 (2.48, 6.71)**	**4.27 (2.57, 7.10)**

* Hazard ratios and 95% confidence intervals derived from univariate Cox regression models. ** Hazard ratios and 95% confidence intervals derived from multiple predictor variable Cox regression model. Significant differences are in bold type.

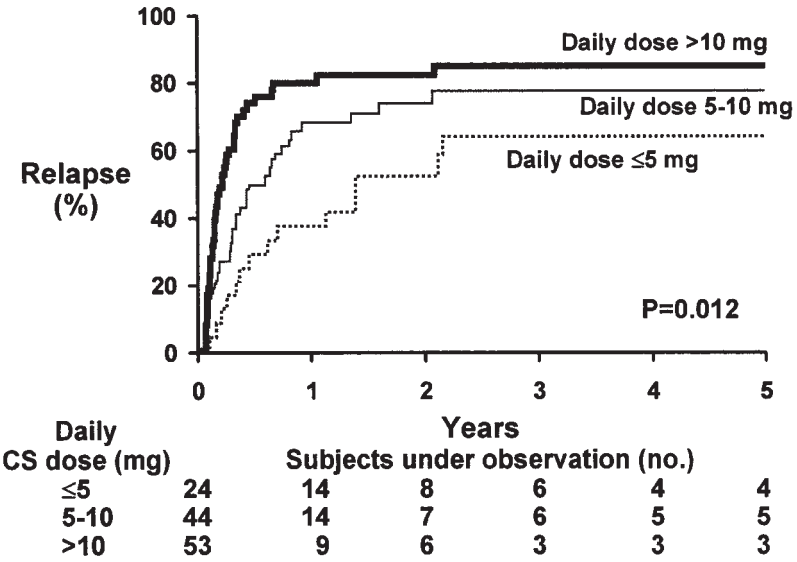

Figure 4. Cumulative rate of relapse by daily CS dose during treatment intervals when CS were not tapered.

Table 3. Predictors of time to relapse among 284 patients whose corticosteroid doses were tapered*.

	First CS Treatment Interval HR (95% CI)**	All CS Treatment Intervals HR (95% CI)***
Age (per 10 year increase)	1.07 (0.82, 138)	1.13 (0.91, 1.39)
Sex (male vs female)	0.74 (0.45, 1.20)	0.84 (0.58, 1.21)
ESR (per 10 mm/h)	**1.16 (1.06, 1.25)**	**1.14 (1.06, 1.22)**
Giant cell arteritis at PMR diagnosis	1.19 (0.35, 4.06)	0.99 (0.57, 1.74)
No. of previous relapses	—	**1.14 (1.05, 1.23)**
Rheumatologist care		
No. of rheumatologist visits	1.08 (0.97, 1.20)	1.00 (0.97, 1.04)
Rheumatologist care during previous 6 mo	—	1.15 (0.78, 1.69)
Corticosteroid therapy		
CS dose at beginning of interval (per 5 mg)	**1.07 (1.00, 1.13)**	**1.07 (1.02, 1.13)**
CS tapering rate		
Slow	**1**	**1**
Medium	**2.39 (1.33, 4.29)**	**2.19 (1.54, 3.11)**
Fast	**5.27 (2.99, 9.28)**	**4.27 (2.84, 6.44)**

* These analyses are restricted to 284 PMR patients who received corticosteroids (CS), and had at least 4 recorded CS values (see Figure 1). ** Among 163 patients whose CS dose was tapered during the first therapy interval following incidence date (see Figure 1). Hazard ratios and confidence intervals are calculated from a multivariable Cox regression model adjusted for all covariates included in the table. *** Among 284 patients who received CS, had at least 4 recorded CS values and 348 treatment intervals where CS dose was tapered (see Figure 1). Hazard ratios and confidence intervals are calculated from a multivariable Anderson-Gill model examining predictors of multiple relapses per patient during the 348 tapered intervals, adjusted for all covariates included in the table. Significant differences are in bold type.

ing of CS therapy, and that rheumatologists may be more experienced than generalists in management of chronic CS therapy.

Previous studies have reported considerable heterogeneity in clinical course of PMR, outcomes, and CS requirements[3-5,10-12]. Studies of optimal therapeutic strategies in PMR date from the 1970s, but the findings are not easily comparable due to differences in definition of outcomes. Some studies used relapse as an outcome, whereas others examined the duration of CS therapy or time to remission as a surrogate for relapses. When relapse was examined as an outcome, patient characteristics such as age and sex do not appear to be helpful in identifying patients who are more likely to relapse[4,11]. In a series of 104 PMR patients from Spain, increasing age at diagnosis, female sex, higher ESR values, and lower daily CS dose were significantly associat-

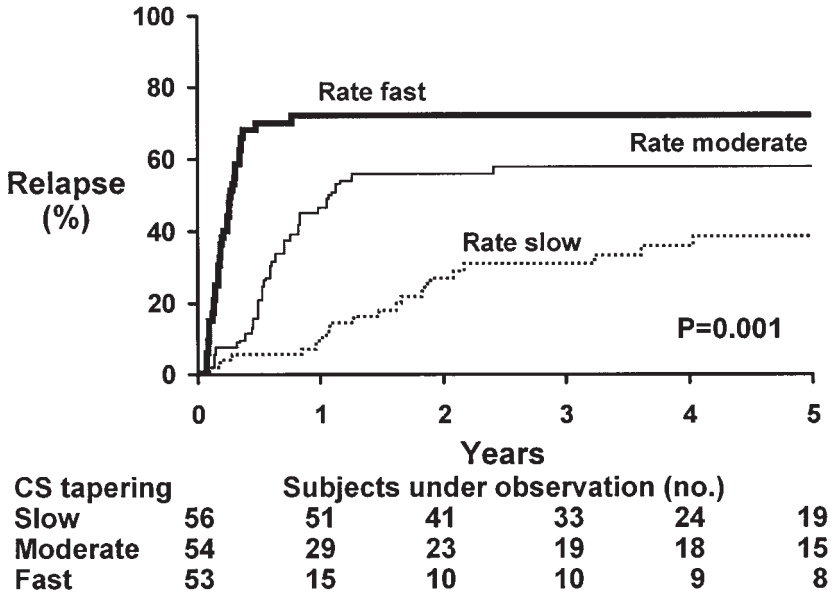

Figure 5. Cumulative rate of relapse by rate of decreasing CS dose during treatment intervals when CS were tapered. Slow: tapering constant (b) < 0.009. Moderate: tapering constant (b) 0.009 to < 0.021. Fast: tapering constant (b) ≥ 0.021.

Table 4. Tapering example for a patient who received 20 mg/day CS at the time of PMR diagnosis*.

Weeks	Dosage (mg/day) According to Tapering Rate*		
	Slow	Medium	Fast
First day	20	20	20
1st week	17	18	19
4 weeks (1 mo)	15	14	8
8 weeks (2 mo)	13	9	3
13 weeks (3 mo)	11	6	1
26 weeks (6 mo)	7	2	0
39 weeks (9 mo)	4	1	0
52 weeks (1 year)	3	0	0

* Estimates derived from the regression models.

ed with a longer duration of therapy, but none of these predicted the likelihood of relapses[11]. Although high pretreatment ESR was frequently implicated as an indicator of more severe and longer disease course[13-15], evidence is scanty on its predictive role in disease relapses. Similarly, C-reactive protein (CRP), interleukin 6 (IL-6) concentrations, and early response to low dose CS therapy[5,10,15,16] were reported to be important in differentiating the course of the disease, but not necessarily the likelihood of relapses. Our findings are consistent with these earlier observations. We examined the role of age, sex, and GCA, and none of these was associated with the likelihood of relapses. However, ESR was a significant predictor of relapses in our study. Although we were unable to examine the role of CRP, ESR and CRP values correlate closely, in general.

The influence of the rate of CS tapering in avoiding disease relapses has been suggested previously[4,11,17-19]. In a cohort of 74 PMR patients who were on a fixed CS regime, 54% of the relapses occurred after CS dose reduction, usually at a dose of around 10 mg/day[4]. The authors suggested that clinicians should monitor patients more closely when CS dose reduction is below 10 mg/day. In a more recent study from Spain, most relapses occurred when CS dose was tapered below 7.5 mg/day[19]. Similarly to these 2 studies, Narvaez and colleagues identified average daily CS dose as a significant predictor of relapses in a cohort where most relapses occurred when the CS dose was reduced from 7.5 to 5 mg/day[11]. These studies seem to suggest a threshold at around 7.5–10 mg/day below which the risk of relapses increases substantially. However, all these studies included relatively small and selected cohorts of PMR patients with limited followup data, and none of them considered the nonlinear nature of tapering rate over time. In our cohort, the median CS dose at the time of first relapse was 9.0 mg/day, very similar to previous observations, but the daily doses ranged between 0.5 mg and 80 mg. Clearly, relapses can

occur at both very high and very low CS doses. Having successfully modeled CS dose reductions over time in a nonlinear model, we were able to demonstrate for the first time that the CS tapering rate is indeed strongly associated with the likelihood of relapses, irrespective of the current CS dose.

The role of the presence of GCA on CS therapy duration and outcome has also been investigated extensively[10,11,20]. Most studies grouped patients according to the presence or absence of GCA, despite the fact that only a limited number of subjects had GCA diagnosed at around the time of PMR diagnosis. Indeed, in our study, of all the 53 PMR patients who had GCA, only 16 (30%) were diagnosed with GCA at the time of PMR diagnosis. Therefore, the remaining 37 patients who were diagnosed with GCA later in the disease course were treated for PMR until the diagnosis of GCA. We did not exclude the patients with GCA, but instead examined the effect of GCA on disease relapses, and observed that GCA at diagnosis of PMR was not associated with a higher likelihood of relapses. Patients diagnosed with GCA later in the disease course were censored in regression analyses. Clearly, patients with GCA typically require higher daily doses of CS for a longer time than patients with PMR only[11], but these patients do not seem to have a higher likelihood of relapses.

Another area of uncertainty in dealing with PMR is the lack of guidelines to define remissions or disease relapses. All the previous studies used a relatively subjective definition of relapse. In addition, the duration of followup was substantially different in each study. Consequently, there is wide variation in the reported rates of relapses[2,4,11,15,18,21-24]. Our definition of relapse was based on both increase in clinical symptoms and increase in CS dose, rather than the ESR values. This is important because some PMR patients may have a low ESR at diagnosis and even during relapses[25-27]. Exclusion of ESR changes from the definition of relapse also allowed us to examine the effect of ESR on the occurrence of relapses. We considered changes in ESR values throughout the followup by including ESR as a time-dependent covariate in regression models, and observed that every 10 mm/h increase in ESR corresponded to a 10–15% higher risk of relapse.

Only one study so far has attempted to propose CS therapy guidelines in PMR[5]. In a small case series of patients treated with a standard schedule of CS, pretreatment ESR and nonresponsiveness of IL-6 to CS therapy were helpful to subdivide patients into groups with different therapeutic requirements[5]. Based on these observations, the authors proposed preliminary CS treatment guidelines for each subset of patients. Although very practical and useful, these guidelines were based on findings from a relatively small case series.

The strengths of this study include its population based design, diagnostic accuracy using a standardized systematic approach for case ascertainment, inclusion of all cases of PMR irrespective of disease severity, complete and detailed data collection through a complete review of medical records including all inpatient and outpatient encounters by all healthcare providers and telephone calls, detailed review of CS therapy, including all dose changes over time, and the use of novel statistical analysis techniques to examine CS tapering rates. Assessing therapy characteristics at each physician-patient encounter, including telephone calls, allowed a more accurate assessment of compliance with the prescribed regimens. This is the largest reported population based cohort of PMR patients with longterm and comprehensive followup data on CS therapy and clinical events.

However, some potential limitations are worth noting. First, confounding by indication is a potential limitation of our findings. This is an observational study, and therefore treatment assignment is not random. For example, ESR is used as an indicator of disease severity in PMR patients. ESR values change throughout the followup period, and this is not only a predictor of relapses but also influences CS dose decisions (and therefore predicts CS dose). Although we adjusted for changes in ESR values throughout the followup using ESR as a time-dependent covariate, it is likely that some residual confounding exists and cannot be accounted for with the data collected in our study. Second, we did not take into account various laboratory measures (i.e., CRP, IL-6) shown to be important markers of disease activity and response to therapy. It is possible that monitoring the levels of these markers throughout the disease course could substantially add to the prognostic information provided by disease and therapy characteristics examined in this study. However, unlike ESR, these were not routinely used in clinical practice over the years of the study. Third, our findings may not be generalizable to non-white individuals because the Rochester population during the calendar years under investigation was > 90% white. However, with the exception of a higher proportion of the working population employed in the healthcare industry and correspondingly higher education levels, the sociodemographic characteristics of Olmsted County residents resemble those of the US white population[7]. Moreover, the epidemiology of PMR in our study resembles that for other white populations[28].

Our findings suggest that management of CS therapy influences disease relapses in PMR. Although there is no single dosing regimen that can be applied to all patients with PMR because of the variable nature of this syndrome, a low initial dose and a slow tapering regimen will likely minimize disease relapses. Additional research is warranted to elucidate the association between CS doses and tapering rates with disease relapses to provide insight into the pathogenesis of the disease, and to develop therapeutic guidelines that consider the entire duration of the disease. Rheumatologists may be more experienced than generalists in careful monitoring of longterm CS therapy.

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