

Withdrawal of Glucocorticoid Therapy is Difficult in Women with Polymyalgia Rheumatica: An Observational Study

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Objective: A total of 105 patients (64 women) who were started on glucocorticoid (GC) treatment for polymyalgia rheumatica (PMR) and/or remitting seronegative symmetrical synovitis with pitting edema (RS₃PE) syndrome at Ikeda City Hospital from July 2004 to December 2019 were reviewed (PMR: 81, overlap: 20, pure RS₃PE syndrome: 4). Then, 32 cases that had stopped GC and 17 cases that had continued GC for 7.5 years or longer were evaluated (women:men, stopped GC 12:20, continued GC 13:4, respectively) (PMR:overlap: pure RS₃PE syndrome, stopped GC 26:6:0, continued GC 14:2:1, respectively).

Methods: The GC continuation rate in all patients was examined using the Kaplan–Meier method. The following were compared between the two groups: age at starting GC; sex; erythrocyte sedimentation rate, C-reactive protein, hemoglobin, ferritin, aspartate aminotransferase, and alanine aminotransferase before starting GC; days from the onset of symptoms to GC initiation; GC maximum dose; GC dose half a year after its start; presence of relapse; and existence of concomitant malignant disease.

Results: The GC continuation rate 7.5 years after GC initiation was 52.5%, higher in women (69.2%), than in men (27.1%). The rates then remained unchanged for 15 years. Hemoglobin was high, and relapse was uncommon in the group that stopped GC. There were no differences in other items.

Conclusion: It is difficult to stop GC therapy for PMR in women in Japan, especially in cases with severe anemia.

Keywords: discontinuation of therapy, glucocorticoid, polymyalgia rheumatica, remitting seronegative symmetrical synovitis with pitting edema syndrome, sex difference

Introduction

Polymyalgia rheumatica (PMR) and remitting seronegative symmetrical synovitis with pitting edema syndrome (RS₃PE syndrome) are diseases of unknown etiology that affect elderly persons. They are characterized by pain of sudden onset that continues and elevated erythrocyte sedimentation rate and C-reactive protein levels.¹ Once the symptoms develop, they greatly impair patients' quality of life. With the aging of the population, an increase in the number of such patients has been reported from the UK.² The incidence of PMR has been found to be higher in individuals of Scandinavian background, lower in Southern European countries, and unknown in Japan.^{3,4} Although the symptoms improve markedly with glucocorticoid (GC) treatment, prudent tapering of GC is required.⁵ Although GC could be decreased from the initial dose in all PMR patients, it is difficult to stop

GC treatment, as has been previously reported.⁶ Past studies reported that relapse has been variably associated with female sex, longer duration of morning stiffness, peripheral arthritis, higher erythrocyte sedimentation rate at diagnosis, persistent elevations of C-reactive protein, interleukin-6 levels, and soluble interleukin-6 receptor levels, larger initial doses of prednisone, and a faster rate of tapering.⁷ Furthermore, reports of GC continuation and risk factors for relapse in Japanese PMR patients are few.⁴ To better estimate GC treatment duration, the percentage of patients who could stop GC treatment and the baseline variables associated with inability to withdraw GC after the time when the GC continuation rate stopped decreasing were examined. In particular, sex differences were examined.

Materials and Methods

A total of 105 patients (64 women) who were started on GC treatment for PMR and/or RS₃PE syndrome at Ikeda City Hospital from July 2004 to December 2019 were evaluated. Bird's criteria⁸ were used up to 2014, and the EULAR/ACR polymyalgia rheumatica interim standard of classification⁹ was used between 2015 and 2019 for PMR diagnosis. Patients who showed pitting edema of both hands and both lower extremities and did not fulfill the diagnostic criteria of rheumatoid arthritis,¹⁰ spondyloarthropathy,¹¹ or other diseases were diagnosed as having RS₃PE syndrome. Both PMR and RS₃PE syndrome were diagnosed in patients with PMR who showed pitting edema of both hands and both lower extremities without other cause.

The GC dose was left to the discretion of the attending physician. The initial dose of prednisolone is generally 10 to 16 mg/day, and the aim is to discontinue it by 2–4 years. The dose was actually reduced by 2.5 mg/day every 2–4 weeks in patients treated with >10 mg/day, and by 1 mg/day every 2–4 weeks in patients treated with ≤10 mg/day.⁷ When symptoms returned with GC reduction, the attending physician increased the dose promptly. GC was continued when it was resumed for disease recurrence once it had been stopped.

The days from GC initiation to GC withdrawal were calculated. If GC could not be stopped, the last observation day was used. The GC continuation rate during the observation period was then estimated by the Kaplan–Meier method, creating Kaplan–Meier curves by sex.

Furthermore, cases that had stopped GC (withdrawal group) and cases that had continued GC for ≥7.5 years

(continuation group) were identified, and the following were compared between them: Age at time of starting GC treatment; sex; type (PMR and/or RS₃PE syndrome); erythrocyte sedimentation rate, C-reactive protein, hemoglobin, ferritin, aspartate aminotransferase, and alanine aminotransferase levels before starting GC; days from onset of symptoms to GC initiation; GC maximum dose; GC dose half a year after it was started; presence of relapse (GC restarting or increasing due to deterioration of symptoms); and the presence of concomitant malignant disease. Cases belonging to neither the withdrawal group nor the continuation group constituted the intermediate group. Patients with malignant diseases were counted when they were diagnosed with them within 6 months since GC was started for PMR or RS₃PE syndrome. It was thought that cases in the intermediate group included cases that would be reclassified to the withdrawal group or the continuation group if they were observed for a longer time. It was expected that the parameters associated with GC continuation in the intermediate group would be between those of the withdrawal group and the continuation group and totaled the parameters in the intermediate group.

This survey was based on a chart review, but a telephone poll of patients whose charts could not be reviewed was conducted.

Statistical analyses were performed with IBM SPSS Statistics, version 27. Kaplan–Meier curves were compared using the Log rank test. Comparisons between the withdrawal group and the continuation group were made with Student's *t*-test for independent continuous variables, and the chi-squared test was used to compare categorical data between groups.

Ethics Approval

This investigation protocol adopted the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ikeda City Hospital Ethics Committee (approval number A20010). The data accessed from the medical records were de-identified in this report. Because this report contains no individual person's data, and this investigation was observational and noninterventional, the Ikeda City Hospital Ethics Committee waived the need for patient consent.

Results

There were 58 cases diagnosed by Bird's criteria, 43 cases diagnosed by the EULAR/ACR polymyalgia rheumatica interim standard of classification, and 4 cases with pure

RS₃PE syndrome. There were 32 cases in the withdrawal group and 17 cases in the continuation group.

The dose of GC could be reduced from the initial dose in all patients.

The duration from the onset of symptoms to GC therapy starting was 79.5 ± 79.6 days (mean \pm SD) in all patients.

The GC continuation rate 7.5 years after starting GC was 52.5% in all patients, 69.2% in women, and 27.1% in men. The rates remained unchanged for 15 years (Figures 1 and 2). The GC continuation rate was significantly higher in women (Log rank test). No patients were prescribed immunosuppressants.

P values by Student's *t*-test or the chi-squared test are shown in the table for the other survey items, including numbers of cases, with data displayed as mean \pm standard deviation (Table 1). Since there was a case with suspected temporal arteritis at the beginning in the withdrawal group that was treated with prednisolone 50 mg/day, this case was excluded as an abnormal value for the GC maximum dose and the GC dose half a year after its initiation. In the withdrawal group, there were few women ($P=0.016$). In all patients, hemoglobin levels (mean \pm SD) before starting GC were lower (10.5 ± 1.6 g/dL) in women than in men (11.4 ± 1.8 g/dL) ($P=0.014$). In the withdrawal group, they were 10.9 ± 1.5 g/dL in women and 11.9 ± 1.6 g/dL in men. In the continuation group, they were 10.4 ± 1.9 g/dL in women and 10.0 ± 2.8 g/dL in men. Relapses were fewer

in the withdrawal group than in the continuation group ($P=0.0003$).

Discussion

In this study, the duration of GC treatment for PMR and RS₃PE syndrome in Japanese patients was longer than in previous reports in English.¹² GC treatment was needed for a longer time in women than in previous reports, and it was difficult to stop GC treatment in cases with severe anemia.

Although it has been reported that female sex is a risk factor for long-term GC treatment by Narváez et al¹³ and Cimmino et al,¹⁴ there has been no English-language report from Japan. Aoki et al reported the GC treatment duration of Japanese PMR patients, and they found no difference between men and women.¹² They classified their patients into two groups by whether they had stopped GC therapy as of 24 months. Therefore, their observation period was shorter than in the present study. Two important factors causing sex-based disparities are genetics and sex hormones.¹⁵ Estrogen enhances B cell differentiation and immunoglobulin production.¹⁶ Several studies reported an immunosuppressive role of testosterone on different components of the immune system.¹⁵ Furthermore, the small number of GC receptors or low GC receptor affinity in woman may have an effect.¹⁴

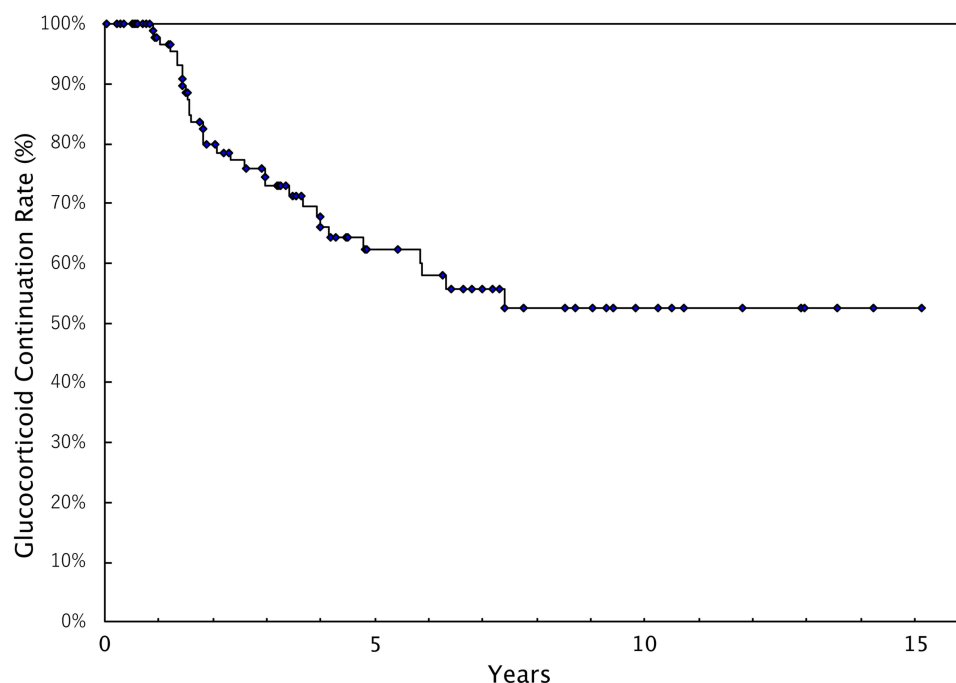


Figure 1 Glucocorticoid continuation rate of all cases (Kaplan–Meier method).

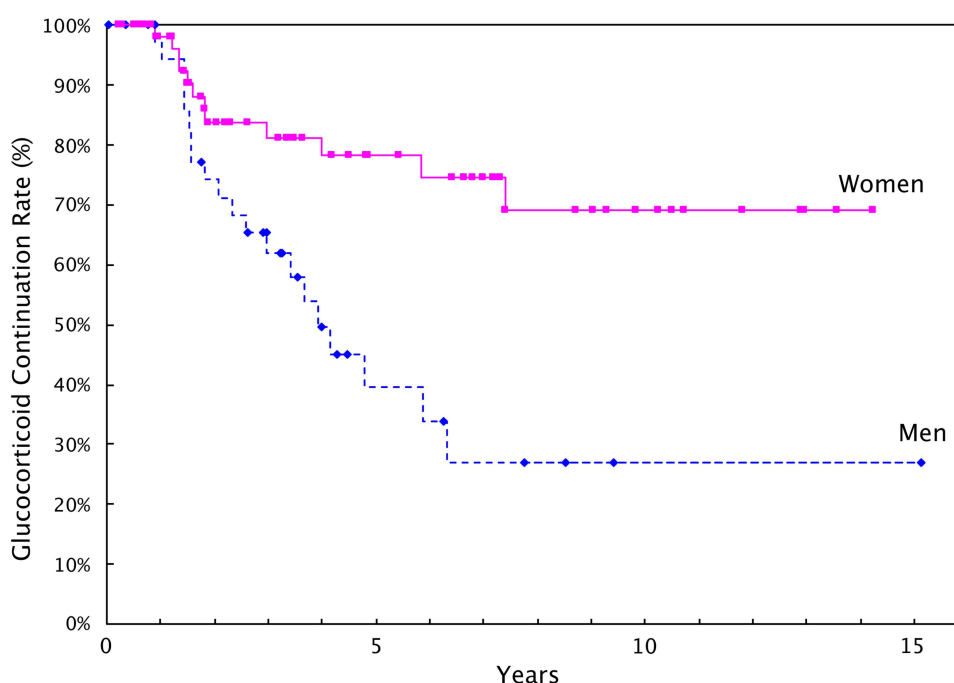


Figure 2 Glucocorticoid continuation rate by sex (Kaplan–Meier method). The glucocorticoid continuation rate is higher in women ($P=0.020$).

In the present study, although the GC continuation rate fell to 55.6% at 7 years and 5 months, it did not fall further. The necessity for continuing GC differed among reports. Aoki et al reported that the median time of remission was 16 months.¹² Cimmino et al reported that about 26% of the patients required GC treatment for 6 years or more.¹⁴ Shbeeb et al reported that the median GC treatment period was 5.95 years.¹⁷ Although the present study found a longer GC treatment period than previous reports, a prudent approach to GC dose reduction may have been one reason, given the report of a certain rate of disease recurrence in the report by Aoki et al.¹² In 17 patients in the continuation group, three patients have not relapsed. This may show that our treatment is sometimes passive with respect to reducing the GC dose. Although there may have been a bias among certain institutions for longer GC treatment, the bias among institutions cannot explain the sex difference. There sometimes were newly suspected patients who received no GC treatment while waiting for spontaneous resolution. This study included no spontaneously resolved patients. The duration from the onset of symptoms to the start of GC therapy in all patients was over 2 months. This might be one reason for the long GC continuation in this study, and it might be a characteristic of Japanese/Asian people.

There are many more female than male patients. In Ikeda City, in which our hospital is located, the population aged 60 years and over as of March 31, 2020, included

18,880 women and 14,506 men.¹⁸ Therefore, it cannot be said that the incidence is higher among women than men.

Since PMR and the RS₃PE syndrome often merged, they were considered together in one group.^{1,19} Since there are few pure RS₃PE syndrome cases, whether there are differences between PMR and RS₃PE syndrome in GC continuation and by sex is unknown. Aoki et al observed peripheral edema in 41 of 93 PMR patients.¹² Such cases would be considered combined PMR and RS₃PE syndrome cases according to the definition used in the present study.

Origuchi et al reported that GC dose and CRP 1 year after starting therapy were high in men with RS₃PE syndrome.²⁰ In the report by Origuchi et al, the observation period was 1 year, shorter than in other reports.²⁰ In the present study, the women's continuation rate was also not high until 1.4 years after starting.

The present data showed severe anemia in the GC continuation group. Narváez et al reported that hemoglobin levels were low in women with PMR.¹³ They considered that anemia reflects intense inflammation. The range of ferritin was large for every case, and the difference between the withdrawal group and the continuation group was not clear. Ferritin levels were high in all groups, reflecting the impaired iron utilization in these diseases.

As a limitation of the present investigation, the number of patients was insufficient for a multivariable statistical

Table I Clinical Features of the 105 Patients

Characteristic	Reference Range, Adults	Withdrawal Group (N=32)	Intermediate Group (N=56)	Continuation Group (N=17)	P-value* (Withdrawal Group versus Continuation Group)
GC starting age, years		73.1±7.0	76.9±9.2	71.6±6.2	0.449
Female sex, no. (%)		12 (37.5)	39 (69.6)	13 (76.5)	0.016
Type, no.					
PMR		26	41	14	
PMR and RS ₃ PE syndrome		6	12	2	
Pure RS ₃ PE syndrome		0	3	1	
Duration from the onset of symptoms to GC therapy starting, days		78.6±68.9	75.9±76.5	93.0±107.4	0.591
Erythrocyte sedimentation rate, mm/hr	3–15	100.7±27.1	103.1±24.5	107.5±16.8	0.382
C-reactive protein, mg/liter	<4.0	70.0±51.0	87.2±63.5	81.4±55.3	0.475
Hemoglobin, g/dL	12.0–16.0	11.5±1.6	10.7±1.5	10.3±2.0	0.034
Ferritin, ng/mL (median) ^{††}	10–200	379.2±446.7 (268)	1047.3±4351.8 (213)	419.3±398.3 (289)	0.772
Aspartate aminotransferase, IU/liter	10–40	20.6±11.4	23.5±4.5	23.1±10.4	0.452
Alanine aminotransferase, IU/liter	8–40	24.3±26.8	20.3±14.9	20.4±13.6	0.572
Dosage of GC (converted to prednisolone)					
Maximum dosage, mg/day		14.4±4.2 [‡]	14.8±2.9	14.2±3.6	0.800
Dosage at 6 months after GC therapy starting, mg/day		6.9±2.1 [‡]	7.8±3.1	8.1±3.3	0.144
Presence of relapse, no.					
No relapse		24	21	3	
Presence		5	18	10	
Unknown		3	17	4	
Malignancies, no.		2	4	1	

Notes: Plus-minus values are mean±SD. *Comparisons between groups were made using Student's *t*-test and chi-square test. ^{††}Because several cases show outliers, medians are shown in parentheses. [‡]One case with initial diagnosis of giant cell arteritis was excluded.

Abbreviations: GC, glucocorticoid; PMR, polymyalgia rheumatica; RS₃PE, remitting seronegative symmetrical synovitis with pitting edema.

analysis of the GC continuation rate and anemia. In addition, because some of the patients were interviewed by telephone, recall bias may have occurred. Because this study was retrospective, sex hormone levels were not measured before treatment; it is a future task to measure them in order to identify causes of the sex difference.

When considering the future treatment strategy for PMR and RS₃PE syndrome in Japan, it is important to note that it is difficult to stop GC treatment for women and for those with severe anemia.

Conclusions

It is difficult to stop GC for PMR and/or RS₃PE syndrome in women in Japan, especially in cases with severe anemia.

Disclosure

All authors have no conflicts of interest that should be declared. All authors take full responsibility for the content of this paper.

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