ORIGINAL

Comparison of therapeutic responses between polymyalgia rheumatica and remitting seronegative symmetrical synovitis with pitting edema syndrome

Harutaka Yamaguchi[1], Yoshihiro Okura[2], Kaori Inaba[1,3], Keisuke Inaba[1,3], Ryosuke Takahashi[3], and Kenji Tani[2]

[1]Department of General Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan, [2]General Medicine and Primary Care, Tokushima University Hospital, Tokushima, Japan, [3]Kaifu Tokushima Prefectural Hospital, Tokushima, Japan

Abstract : Polymyalgia rheumatica (PMR) and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome are common inflammatory rheumatic diseases in the elderly. In this study, we investigated the difference of the therapeutic responses between patients with PMR and RS3PE syndrome. Twenty-four patients with PMR and 12 patients with RS3PE syndrome were treated with initial dosages of 10-20 mg per day oral prednisolone, and the dosages were then tapered. Percentages of patients with negative c-reactive protein (CRP) after 8-week treatment were significantly more in RS3PE syndrome than in PMR. Percentages of patients with relapse during one-year treatment were less likely to be in RS3PE syndrome than in PMR. These differences observed between the two disorders were not associated with the level of initial CRP. There was no significant difference in percentages of patients with prednisolone-free remission after two-year treatment between PMR and RS3PE syndrome. These results indicate that the early response to the treatment is greater in RS3PE syndrome than in PMR. J. Med. Invest. 70 : 145-149, February, 2023

Keywords **:** *PMR, RS3PE syndrome, c-reactive protein, prednisolone*

INTRODUCTION

Polymyalgia rheumatica (PMR), was first described by Barber in 1957, is a common inflammatory rheumatic disease (1). It usually has its onset in the elderly individuals aged over 50, and is characterized by pain and morning stiffness in the neck, shoulder, and pelvic girdle with elevated acute phase reactants such as c-reactive protein (CRP) (2). Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, which was described in 1985 by McCarty *et al*. as an original subgroup of seronegative rheumatoid arthritis, is also an elderly onset inflammatory rheumatic disease (3). It occurs usually in people older than 60. The onset of the disease is sudden and it is characterized by a symmetrical polyarthritis associated with pitting edema of the extremities of the upper and lower limbs, elevated acute phase reactants such as CRP and negative rheumatoid factor (4).

The rate of RS3PE syndrome is approximately one-third when compared with PMR in Japan (5). Corticosteroids are used as a standard treatment in both PMR and RS3PE syndrome (4, 6). Typically, the starting dosages are 10-20 mg per day of prednisolone, and gradually tailor tapering. The treatment usually results in rapid resolution of the symptoms in the two disorders, but 30-50% of patients have been shown to experience disease relapse during reducing the drug (5, 7, 8). Thus, there is a considerable heterogeneity in their clinical courses, steroid requirements for suppression of disease activities, and the likelihood of relapse.

PMR and RS3PE syndrome have been shown to share several features in clinical characteristics such as elderly onset and rapid responses to low doses of corticosteroid (9-13), but they appear to be clinically distinctive. However, differences in the response rate to the treatment between PMR and RS3PE syndrome have not been well clarified. The purpose of the present study is to evaluate the differences in the therapeutic response and disease prognosis between PMR and RS3PE syndrome.

Received for publication July 4, 2022 ; accepted October 9, 2022.

Address correspondence and reprint requests to Kenji Tani, M.D., General Medicine and Primary Care, Tokushima University Hospital, 50 Kuramoto-cho 2, Tokushima 770-8503, Japan and Fax : +81-88-633-9687. E-mail : taniken@tokushima-u.ac.jp

PATIENTS AND METHODS

Patients

We retrospectively identified the medical records of 24 patients with PMR and 12 patients with RS3PE syndrome visiting regularly Specialty Outpatient Clinic for Collagen Vascular Diseases at Kaifu prefectural hospital and Toyo hospital as an outpatient between Jan in 2014 and Feb in 2022 over two years after initiation of prednisolone treatment. PMR was diagnosed according to the Bird's criteria ; (a) bilateral shoulder pain or stiffness, or both, (b) onset of illness within 2 weeks, (c) initial ESR>40 mm/h, (d) duration of stiffness > 1 h, (e) age 65 years or older, (f) depression or weight loss, or both, and (g) bilateral upper arm tenderness (14). If any three or more of the seven criteria, a diagnosis of probable PMR was made. None of the patients complicated giant cell arteritis during the follow-up in this study. RS3PE syndrome was diagnosed if patients were older than 50 and satisfied the following diagnostic criteria ; symmetrical polyarthritis, pitting edema of the bilateral hands and foots, serological absence of rheumatoid factor, and a fast response to steroid treatment (12). In this study, since two patients who complicated with malignant diseases (hepatoma and lung cancer) were excluded from this study because malignant diseases might affect the clinical course.

After the diagnosis, all patients were treated with initial dosages of 10-20 mg per day oral prednisolone according to 2015 Recommendations for the management of PMR (15). Current recommendations support a starting dose with prednisolone at 15 mg/day. The dose is then tapered to 12.5 mg/day for an additional 3 weeks, 10 mg/day for 4-6 weeks, then tapering by 1

mg every 4-8 weeks. This schedule results in a total treatment duration of 1-2 year in general. Clinical assessments included the symptom and measurement of serum CRP by standard laboratory methods because elevated levels of CRP are common in patients with PMR and RS3PE syndrome (16-18). Visits were scheduled every 2 to 4 weeks, and at each visit the dosage of prednisolone was tapered when no specific symptoms were complained and the level of CRP was normal or nearly normal. Prednisolone-free remission was defined as the absence of clinical symptoms and normal level of CRP with discontinuation of any drugs which control the diseases including corticosteroids. A relapse was defined as an aggravation or reappearance of clinical symptoms associated with an elevated CRP. If the disease activity relapsed after dose tapering, prednisolone was increased to dosages related to the disease requiring.

This study was conducted in accordance with the Declaration of Helsinki 1975, as revised in 2008 and approved by the Tokushima University Hospital Research Ethics Board (No.2956).

Statistical analysis

Comparison between groups was made using Mann-Whitney U test for continuous variables and Pearson's chi-squared test for categorical variables. Data were mainly presented as median and (25^{th}-75^{th} quarter), count and (percentage), or odds ratio (OR) and 95% confidence interval (CI). The results were regarded as significant when p value was <0.05. All statistical analyses were performed using IBM SPSS statistics version 27 software (Chicago, IL, USA).

RESULTS

Patient baseline characteristics

Table 1 shows baseline clinical and laboratory characteristics of the patients examined in this study. Twenty-four patients with PMR and 12 patients with RS3PE syndrome were included in this study. Patients with PMR consisted of 18 women (75%) and 6 men (25%), and those with RS3PE did of 3 women (25 %) and 9 men (75%), showing significantly more percentages of women in PMR than in RS3PE syndrome. Both disorders consisted of high-aged patients with median age of 75 years. The levels of CRP before initiation of the treatment (initial CRP) were increased in all cases with PMR [8.48 (range ; 2.85-14.12) mg/dl] and RS3PE syndrome [5.94 (range ; 0.57-14.71) mg/dl], but there was no significant difference between the two disorders. The median duration from onset to treatment start was not significantly different in the two disorders (8.0 weeks in PMR and 7. 5 weeks in RS3PE syndrome).

Clinical course

All patients with PMR and RS3PE syndrome were treated with oral prednisolone (median ; 15 mg/day, range ; 10-20). There was no significant difference in the starting doses between the two disorders (Table 2). The clinical responses to the treatment with prednisolone were determined by the change of CRP and the tapering speed of prednisolone, and compared between the two disorders. The percentages of patients whose CRP levels became negative 4 and 8 weeks after initiation of the treatment were significantly higher in RS3PE syndrome than in

Table 1. Baseline characteristics of patients with PMR and RS3PE syndrome

Variables	PMR (n=24)	RS3PE syndrome (n=12)	p value
Women, n (%)	18 (75.0)	3 (25.0)	0.004
Age, years old	75.0 (73.0-82.0)	75.0 (69.3-82.5)	0.737
Initial CRP, mg/dl ; normal range <0.3	8.48 (4.20-10.79)	5.94 (4.14-9.88)	0.392
Time from onset to initiation of treatment, weeks	8.0 (4.0-14.0)	7.5 (3.5-16.8)	0.893

PMR ; polymyalgia rheumatica, RS3PE ; remitting seronegative symmetrical synovitis with pitting edema, CRP ; c-reactive protein. Thirty-six patients were included in this study. Data were presented as counts and (percentage), or median and (interquartile range).

Table 2. Comparison of clinical data between patients with PMR and RS3PE syndrome

Variables	PMR (n=24)	RS3PE syndrome (n=12)	p value
Starting dose of prednisolone per day, mg/day	15 (10-15)	15 (10-15)	0.262
Becoming negative CRP after 4 weeks, n (%)	9 (37.5)	9 (75.0)	0.034
Becoming negative CRP after 8 weeks, n (%)	11 (45.8)	11 (91.7)	0.008
Time from initiation of treatment to negative CRP, weeks	8.5 (3.0-16.3)	4.0 (2.0-5.0)	0.006
CRP after 1 year, mg/dl	0.11 (0.06-0.53)	0.12 (0.05-0.62)	0.724
Relapse during 1 year, n (%)	6 (25.0)	0 (0)	0.058
Dose of prednisolone after 1 year, mg/day	4.0 (3.0-5.0)	4.5 (3.3-7.1)	0.465
Prednisolone-free remission after 1 year, n (%)	1 (4.2)	0 (0)	0.473
Relapse during 2 years, n (%)	8 (33.3)	3 (25.0)	0.609
Dose of prednisolone after 2 years, mg/day	2.0 (0-4.0)	3.0 (0.5-4.8)	0.546
Prednisolone-free remission after 2 years, n (%)	10 (41.7)	3 (25.0)	0.326

PMR ; polymyalgia rheumatica, RS3PE ; remitting seronegative symmetrical synovitis with pitting edema, CRP ; c-reactive protein. Data were presented as counts and (percentage), or median and (interquartile range).

PMR (Figure 1). Time from initiation of treatment to negative CRP was significantly shorter in patients with RS3PE syndrome (4.0 weeks) than in those with PMR (8.5 weeks) (Figure 2). These results suggest that a greater early response to prednisolone is observed in patients with RS3PE syndrome than in those with PMR. Moreover, no patients with RS3PE syndrome and 6 patients (25%) with PMR were in disease relapse during one-year treatment though not statistically significant. We next compared the level of CRP, the dosage of prednisolone, and the remission rate, after one- and two-year treatment between PMR and RS3PE syndrome (Table 2). After one- or two-year treatment, the level of CRP was not significantly different between the two disorders. The dosage of prednisolone or the percentage of patients with prednisolone-free remission was not significantly different after one- or two-year treatment between the two disorders.

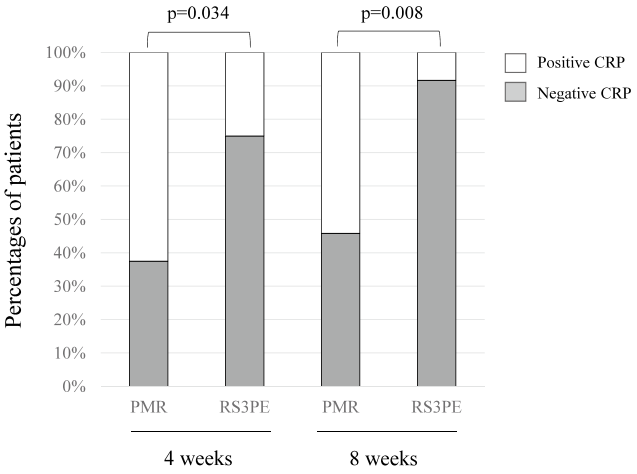

Figure 1. The comparison of percentages of patients with positive and negative CRP between PMR and RS3PE syndrome 4 and 8 weeks after initiation of the treatment. Twenty-four patients with PMR and 12 patients with RS3PE syndrome were treated with oral prednisolone, and the patients were divided into two groups by the level of CRP ; positive and negative CRP. PMR ; polymyalgia rheumatica, RS3PE ; remitting seronegative symmetrical synovitis with pitting edema.

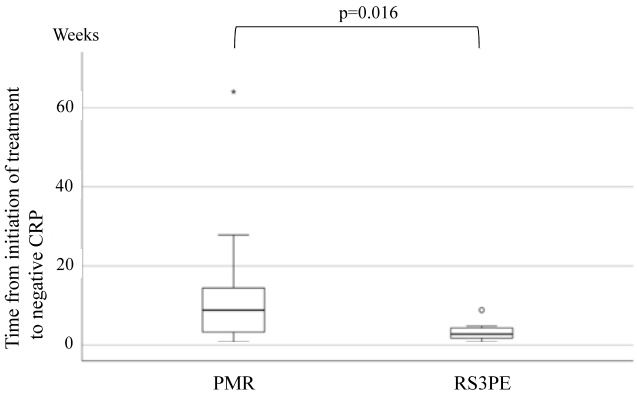

Figure 2. The comparison of time from initiation of treatment to negative CRP in patients with PMR and RS3PE syndrome. Twenty-four patients with PMR and 12 patients with RS3PE syndrome were treated with oral prednisolone, and time from initiation of treatment to negative CRP was recorded. PMR ; polymyalgia rheumatica, RS3PE ; remitting seronegative symmetrical synovitis with pitting edema.

DISCUSSION

In this study, we compared clinical findings during the treatment between patients with PMR and RS3PE syndrome. The level of CRP was more rapidly decreased to be negative by the corticosteroid treatment in patients with RS3PE syndrome than in those with PMR. There is a previous paper which compared the clinical characteristics between PMR and RS3PE syndrome, showing that initial doses of steroids and response rate to them in patients with RS3PE syndrome are similar to those with PMR, but the rate of relapse is fewer in patients with RS3PE syndrome than in those with PMR though not statistically significant (19). To our knowledge, this is the first report which shows the early good responses to corticosteroids in patients with RS3PE syndrome when compared with those with PMR.

This study showed that the percentages of patients with negative CRP during 8-week treatment was more in RS3PE syndrome than in PMR. The percentages of patients with relapse after one-year treatment were less likely to be in patients with RS3PE syndrome though not statistically significant. On the other hand, there was no significant difference between the two disorders in the levels of initial CRP. These results suggest that the levels of initial CRP are not likely to correspond to the subsequent CRP levels. Some previous studies, which showed initial levels of CRP do not affect the clinical response of PMR patients to corticosteroids (8, 14), have supported our findings. In contrast, other reports have demonstrated the significant relation between initial CRP levels and the subsequent therapeutic responses in PMR patients (2, 12, 15). Lee *et al*. showed that PMR patients with an initial CRP >2.5mg/dl have a greater possibility of relapse (2). Longer durations of steroid treatment are required in those who have higher baseline inflammatory markers in PMR (12, 15). Further studies are needed to clarify the discrepancies in the relation between the initial CRP levels and the subsequent therapeutic responses in PMR and RS3PE syndrome.

This study showed that patients with RS3PE syndrome were more likely to be men than those with PMR, which is consistent to previous reports (5, 7). However, there was no difference between men and women in the percentages of patients with negative CRP after 8-week treatment when examined separately in patients with PMR or RS3PE syndrome (data not shown). Some previous reports showed poor prognosis in women of PMR (17, 18). The number of relapses during steroid treatment in patients with PMR is more in women (17). The continuation rate of corticosteroids at 7.5 years after the treatment for PMR patients is higher in women than in men in Japan (18). Thus, gender may modulate the response to corticosteroids in PMR patients, but it is not clear whether women with PMR have more inflammation and a worse prognosis in comparison with men. In contrast, Aoki *et al*. showed no difference between men and women in the treatment duration with corticosteroids which was determined at 2 years after the treatment (20) in agreement with our study. The longer follow-up periods would be helpful to clarify differences in the later prognosis between men and women.

This study showed that there were more patients with negative CRP after 8-week treatment and fewer patients with relapse after one-year treatment in RS3PE syndrome than in PMR. However, there was no significant difference in percentages of patients with prednisolone-free remission after two-year treatment between the two disorders. The differences between PMR and RS3PE syndrome in long-term prognosis have been unknown (21-23). The reasons why the early better treatment responses shown in patients with RS3PE syndrome do not lead to the long-term prognosis are unknown.

Our study has several limitations. First, this was a

retrospective study. The further prospective studies are required to confirm these results in the future. Second, only a small number of patients with PMR and PS3PE syndrome were available for this study. Since the numbers were small and thus inconclusive, larger studies are necessary to elucidate differences in the therapeutic responses between PMR and RS3PE syndrome.

In conclusion, this study has investigated the clinical differences between PMR and RS3PE syndrome, and demonstrates that more patients with the early response to the treatment and fewer patients with relapse during one-year treatment are observed in RS3PE syndrome than PMR. The early good response observed in RS3PE syndrome may result in reducing corticosteroid with faster tapering speed which can reduce corticosteroid-related adverse events. However, further studies are needed to clarify adequate therapeutic strategies such as the difference in starting dosage and dose tapering speed of corticosteroid not to cause relapse or long-term treatment in PMR and RS3PE syndrome.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest to declare.

ACKNOWLEDGEMENTS

The authors thank Ms. Yayoi Tagawa for her valuable secretarial support.

REFERENCES

1. Barber HS : Myalgic syndrome with constitutional effects ; polymyalgia rheumatica. Ann Rheum Dis 16 : 230-237, 1957
2. Lee JH, Choi ST, Kim JS, Yoon BY, Kwok SK, Kim HS, Kim YS, Song JS, Lee SH, Kim HR : Clinical characteristics and prognostic factors for relapse in patients with polymyalgia rheumatica (PMR). Rheumatol Int 33 : 1475-1480, 2013
3. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB : Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. JAMA 254 : 2763-2767, 1985
4. Origuchi T, Arima K, Umeda M, Kawashiri SY, Tamai M, Nakamura H, Tsukada T, Miyashita T, Iwanaga N, Izumi Y, Furuyama M, Tanaka F, Kawabe Y, Aramaki T, Ueki Y, Eguchi K, Fukuda T, Kawakami A : Clinical outcomes in the first year of remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome. Mod Rheumatol 27 : 150-154, 2017
5. Okumura T, Tanno S, Ohhira M, Nozu T : The rate of polymyalgia rheumatica (PMR) and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome in a clinic where primary care physicians are working in Japan. Rheumatol Int 32 : 1695-1699, 2012
6. Schirmer M, Dejaco C, Dasgupta B, Matteson EL : Polymyalgia rheumatica : strategies for efficient practice and quality assurance. Rheumatol Int 35 : 1781-1789, 2015
7. Origuchi T, Arima K, Kawashiri SY, Tamai M, Yamasaki S, Nakamura H, Tsukada T, Aramaki T, Furuyama M, Miyashita T, Kawabe Y, Iwanaga N, Terada K, Ueki Y, Fukuda T, Eguchi K, Kawakami A : High serum matrix metalloproteinase 3 is characteristic of patients with paraneoplastic remitting seronegative symmetrical synovitis with pitting edema syndrome. Mod Rheumatol 22 : 584-588, 2012
8. Hutchings A, Hollywood J, Lamping DL, Pease CT, Chakravarty K, Silverman B, Choy EH, Scott DG, Hazleman BL, Bourke B, Gendi N, Dasgupta B : Clinical outcomes, quality of life, and diagnostic uncertainty in the first year of polymyalgia rheumatica. Arthritis Rheum 57 : 803-809, 2007
9. Tani K, Kawaminami S, Okura Y, Tabata R, Yuasa S, Nakanishi Y, Kawahito K, Inaba K, Inaba K, Kondo K, Umetani K, Suzuki Y, Yamaguchi H : Predictive factors associated with the therapeutic response in patients with polymyalgia rheumatica and remitting seronegative symmetrical synovitis with pitting edema syndrome. J Med Invest 66 (1, 2) : 112-118, 2019
10. Cleuziou C, Binard A, De Bandt M, Berthelot JM, Saraux A : Contribution of the polymyalgia rheumatica activity score to glucocorticoid dosage adjustment in everyday practice. J Rheumatol 39 : 310-313, 2012
11. Salvarani C, Cantini F, Niccoli L, Macchioni P, Consonni D, Bajocchi G : Acute-phase reactants and the risk of relapse/recurrence in polymyalgia rheumatica : a prospective follow-up study. Arthritis Rheum 53 : 33-38, 2005
12. Olive A, del Blanco J, Pons M, Vaquero M, Tena X : The clinical spectrum of remitting seronegative symmetrical synovitis with pitting edema. The Catalan Group for the Study of RS3PE. J Rheumatol 24 : 333-336, 1997
13. Mackie SL, Hensor EM, Haugeberg G, Bhakta B, Pease CT : Can the prognosis of polymyalgia rheumatica be predicted at disease onset? Results from a 5-year prospective study. Rheumatology (Oxford) 49 : 716-722, 2010
14. Bird HA, Esselinckx W, Dixon AS, Mowat AG, Wood PH : An evaluation of criteria for polymyalgia rheumatica. Ann Rheum Dis 38 : 434-439, 1979
15. Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, Abril A, Bachta A, Balint P, Barraclough K, Bianconi L, Buttgereit F, Carsons S, Ching D, Cid M, Cimmino M, Diamantopoulos A, Docken W, Duftner C, Fashanu B, Gilbert K, Hildreth P, Hollywood J, Jayne D, Lima M, Maharaj A, Mallen C, Martinez-Taboada V, Maz M, Merry S, Miller J, Mori S, Neill L, Nordborg E, Nott J, Padbury H, Pease C, Salvarani C, Schirmer M, Schmidt W, Spiera R, Tronnier D, Wagner A, Whitlock M, Matteson EL, Dasgupta B : European League Against Rheumatism ; American College of Rheumatology. 2015 Recommendations for the management of polymyalgia rheumatica : a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis 74 : 1799-1807, 2015
16. Dejaco C, Duftner C, Cimmino MA, Dasgupta B, Salvarani C, Crowson CS, Maradit-Kremers H, Hutchings A, Matteson EL, Schirmer M : Definition of remission and relapse in polymyalgia rheumatica : Data from a literature search compared with a Delphi-based expert consensus. Ann Rheum Dis 70 : 447-453, 2011
17. Cimmino MA, Parodi M, Caporali R, Montecucco C : Is the course of steroid-treated polymyalgia rheumatica more severe in women? Ann N Y Acad Sci 1069 : 315-321, 2006
18. Aoki D, Kajiwara N, Irishio K, Kato Y, Suezaki S, Kageyama M, Misago M, Tamai D, Nakao S, Ueoka T, Ito M, Murakami S : Withdrawal of glucocorticoid therapy is difficult in women with polymyalgia rheumatica : An observational study. Int J General Med 14 : 6417-6422, 2021
19. Kimura M, Tokuda Y, Oshiawa H, Yoshida K, Utsunomiya M, Kobayashi T : Clinical characteristics of patients with remitting seronegative symmetrical synovitis with pitting edema compared to patients with pure polymyalgia

rheumatica. J Rheumatol 39 : 148-153, 2012
20. Aoki A, Kobayashi H, Yamaguchi Y : Predictors of long-term therapy with glucocorticoid in polymyalgia rheumatica. Mod Rheumatol 31 : 417-420, 2021.
21. Narvaez J, Nolla-Sole JM, Clavaguera MT, Valverde-Garcia J, Roig-Escofet D : Longterm treatment in polymyalgia rheumatica : effect of coexistent temporal arteritis. J Rheumatol 26 : 1945-1952, 1999
22. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B : Polymyalgia rheumatica and giant cell arteritis : A systematic review. JAMA 315 : 2442-2458, 2016
23. Li H, Altman RD, Yao Q : RS3PE : Clinical and research development. Curr Rheumatol Rep 17 : 49-55, 2015