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ISOLATED POLYMYALGIA RHEUMATICA: A CROSS-SECTIONAL, SINGLE-CENTER, RETROSPECTIVE COHORT STUDY

İZOLE POLİMYALJİA ROMATİKA HASTALARININ KLİNİK İZLEMİ: TEK MERKEZLİ, RETROSPEKTİF KOHORT ÇALIŞMASI

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ABSTRACT

Objective: We aimed to review clinical, laboratory findings, disease progression and treatment response in patients with isolated polymyalgia rheumatica (PMR) and to investigate the effect of initial and maintenance corticosteroid dose on the disease progression.

Methods: Nineteen isolated PMR patients were included in the study. Demographic data, anthropometric measurements, comorbidities, initial symptom, physical examination, clinical, laboratory findings, medications, changes in treatment status, cumulative corticosteroid dose were recorded. The medical data of first (1st month), second (4th month), third (7th month) visits were noted.

Results: The initial corticosteroid dose was 21.5±8.9 mg. While the complaints regarding PMR decreased in 52.6% of patients in the first visit, those complaints regressed in 47.4% and 73.7% of patients in the second and third visit, respectively. In the first visit, the mean erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were 21.7±12.3 mm/h and 5.8±5.1 mg/dl. In the second and third visits, while the mean ESR was found as 36.5±27.3 mm/h and 27.3±18.6 mm/h, the mean CRP was 27.2±43.0 mg/dl and 17.6±30.2 mg/dl, respectively. Clinical remission was observed in 47.4% of patients in the second visit and in 31.6% of patients in the third visit. Median cumulative corticosteroid doses were 600 mg in first visit, 960 mg in second visit and 1346 mg in the third visit.

Conclusion: The clinical characteristics and the initial corticosteroid dose were compatible with the literature. Even though cumulative corticosteroid doses were quite high, lower remission rates were observed in these patients.

Keywords: Acute-phase reactants, corticosteroids, polymyalgia rheumatica, remission

ÖZ

Amaç: Bu çalışmada izole polimyaljia romatika (PMR) tanılı hastaların klinik durum, laboratuvar bulguları, hastalık seyri ve tedavi yanıtlarının kısa dönem verilerinin taranması ve kortizon başlangıç ve idame dozunun hastalık progresyonuna etkisinin incelenmesini amaçladık.

Yöntem: On dokuz izole PMR hastası çalışmaya dahil edildi. Hastaların demografik verileri, antropometrik ölçümleri, ek hastalıkları, şikayetleri, fizik muayene bulguları, klinik bulguları, laboratuvar bulguları, tedavileri, tedavi değişiklikleri, kümülatif kortizon dozları kaydedildi. Hastaların 1. ay, 4. ay ve 7. ay poliklinik kontrollerinde elde edilen medikal kayıtları bir olgu formu yardımı ile not edildi.

Bulgular: Hastaların ortalama kortizon başlangıç dozu 21,5±8,9 mg idi. Birinci poliklinik kontrolünde, hastaların %52,6'sının şikayetleri tamamen gerilerken, bu oran 2. ve 3. poliklinik kontrolünde sırası ile %47,4 ve %73,7 idi. Birinci poliklinik kontrolü ortalama eritrosit sedimentasyon hızı (ESH) ve C-reaktif protein (CRP) değerleri sırası ile 21,7±12,3 mm/saat ve 5,8±5,1 mg/dl idi. İkinci ve 3. poliklinik kontrolünde ortalama ESH değerleri sırası ile 36,5±27,3 mm/saat ve 27,3±18,6 mm/saat iken ortalama CRP değerleri sırası ile 27,2±43,0 mg/dl ve 17,6±30,2 mg/dl idi. Hastaların takipleri sırasındaki remisyon oranları ise 2. poliklinik kontrolünde %47,4 ve 3. poliklinik kontrolünde %31,6 olarak bulundu. Median kümülatif kortikosteroid dozları 1. poliklinik kontrolünde 600 mg, 2. poliklinik kontrolünde 960 mg ve 3. poliklinik kontrolünde 1346 mg idi.

Sonuç: Klinik özellikler ve başlangıç kortikosteroid dozu literatürle uyumluydu. Kümülatif kortikosteroid dozları yüksek olmasına rağmen bu hastalarda daha düşük remisyon oranları gözlendi.

Anahtar Kelimeler: Akut faz yanıtları, DMARD, kortizon, polimyaljia romatika, remisyon

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Introduction

Polymyalgia rheumatica (PMR) is an inflammatory disease characterized mainly by the shoulder and pelvic girdle pain and morning stiffness in individuals over 50 years and may be accompanied by synovitis in extraarticular synovial tissues and proximal joints. Even though PMR may present as an isolated disorder, its association with giant cell arteritis (GCA) is quite common.[1] Initially, PMR and GCA had been assumed to be the same; however, in the following years, they have been identified as different diseases that could accompany each other.[2]

The incidence of PMR has been reported as 58-96/100.000 in the population aged over 50 years. The disease is 2-3 fold more common in females than males, and its incidence increases with age. PMR is the second most common inflammatory autoimmune rheumatic disease in adults following rheumatoid arthritis.[3] Regarding clinical features, pain and stiffness in the shoulder and hip regions are most common; subfebrile fever and constitutional symptoms such as fatigue, loss of appetite, and weight loss may accompany the disease.[4,5] Arthralgia and arthritis may also be present with varying frequencies.[6]

Increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are common laboratory findings in PMR. A study reported CRP as a more accurate indicator of disease activity and ESR as a superior predictor of recurrence.[7] Diagnosing PMR may be a challenge for clinicians due to the absence of a specific diagnostic test and the difficulty in differentiating the underlying reasons for morning stiffness and pelvic girdle pain.

Treatment of PMR relies on low-dose corticosteroids leading to a rapid response after administration. On the other hand, there is no precise consensus on the optimal reduction in corticosteroid dose and the ideal duration of corticosteroid use. In fact, there are various recommendations on PMR treatment; however, some clinical challenges such as elderly PMR patients with different comorbidities may cause not to arrange an appropriate treatment.[4,8-10]

Furthermore, relapses and recurrences may be seen while receiving corticosteroid therapy. Corticosteroid sparing agents are added to the treatment when corticosteroids are ineffective or are attempted to be withdrawn.[11] Accordingly, methotrexate (MTX), the well-known corticosteroid-sparing agent, extensively uses in these patients.[12]

Despite a growing literature on PMR, the data on the clinical presentation and response to treatment in patients with isolated PMR is limited. Therefore, we aimed to compile the sociodemographic data, clinical parameters, and laboratory results of patients with isolated PMR, and we presented short-term data on the response of corticosteroid treatment to disease progression in these patients.

Methods

Study Design and Study Population

The study was designed as retrospective, cohort study. Ethical approval was obtained from the Local Ethics Committee of Kocaeli University (March 2021; no. 2021/06.21). The patients fulfilled Chuang and Colleagues-2 criteria and followed up regularly in our clinic were included in the study.[13] The exclusion criteria was defined as following; i) those with concomitant GCA disease, ii) those with malignities, and iii) those with a disease requiring corticosteroid therapy. Thirty-nine patients were screened and 19 eligible patients were included in the study.

Data Collection and Definition

Demographic data (gender, age, age of diagnosis), anthropometric measures (height, weight, body mass index), comorbidities, complaints at admission to the clinic, and physical examination were recorded. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were obtained from database. Treatments, treatment changes, and cumulative corticosteroids doses were noted. The cumulative corticosteroid dose was converted to an equivalent dose of prednisolone and calculated for each patient based on medical records. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) used by patients were either MTX or leflunomide (LEF). Definition of remission in PMR was dissussed by many authors so far. According to Kremers et al., in the current study, remission was accepted as the absence of clinical symptoms with normal ESR and CRP values under treatment with corticosteroids of 5 mg or less.[14,15] We used this definition in this study. All clinical data were collected at baseline, at 1st, 4th, and 7th months.

Statistical Analysis

The statistical analysis of the present study was performed by using the IBM SPSS Statistics version 20.0. Descriptive statistics were performed. The normality of the data was checked by Kolmogorov-Smirnov normality test. The values with parametric distribution were presented as mean±standard deviation while the values with non-parametric distribution were presented as median (Q1-Q3). Friedman test was used to assess the differences in clinical parameters throughout the clinical visits. The meaningful statistical results after Friedman test were analyzed by a post hoc analysis using Wilcoxon signed ranks test. The Bonferroni correction was used for the adjustment of multiple comparisons. Spearman correlation analysis was performed to explore the associations between cumulative corticosteroid dose and acute phase reactants. The results were regarded as “statistically significant” when the p values were below 0.05.

Results

Nineteen PMR patients (16 females and three males) were included in the study. The mean age of patients was 68±8 years. In addition, 42.1% (n=8) of the patients had initially presented with weight loss. In their first examination, the mean body mass index (BMI) was 27.4±5.1 kg/m^2. The medical history revealed diabetes mellitus in eight (42.1%), hypertension in ten (52.6%), cardiovascular disorders in five (26.3%), and thyroid pathologies in six (31.6%) patients. The complaints at the time of diagnosis are summarized in Table 1. While 28.6% (n=2) of the patients with morning stiffness experienced stiffness for less than 30 minutes, 71.4% (n=5) had stiffness for 30 minutes or more. The median ESR and CRP values were 75.0 mm/hour and 61.0 mg/dl, respectively. The mean initial corticosteroid dose was 21.5±8.9 mg.

Table 1. Clinical presentation of patients with isolated polymyalgia rheumatica

	n (%)
Arthralgia	19 (100)
Shoulder girdle and neck pain	18 (94.7)
Pelvic girdle pain	14 (73.7)
Arthritis	9 (47.4)
Myalgia	9 (47.4)
Weight loss	8 (42.1)
Morning stiffness	7 (36.8)
Jaw claudication	4 (21.1)

The changes in symptoms, remission rates, acute phase responses, the treatments, and cumulative corticosteroids dose of patients are presented in Table 2. Accordingly, the median cumulative corticosteroid dose was 600 mg at first visit while it was 960 mg at second visit. In the last visit, the median cumulative dose at the end of the seventh month was calculated as 1346 mg. Apart from that, at 1st month visit, morning stiffness on the initial evaluation completely regressed in three of seven patients (42.9%) while this symptom partially ameliorated in three patients (42.9%). One patient declared that this symptom was the same as at the beginning of complaint. Nine patients with inadequate clinical response to morning stiffness after using corticosteroids started to use LEF 20 mg/day (n=1) and MTX 7.5 mg/week (n=8).

In the second outpatient evaluation (4th month), the symptoms of four (50%) out of eight patients with morning stiffness completely receded. One patient stated that there was no difference compared to the 1st month evaluation. In addition, morning stiffness of one patient increased. Two patients who never expressed morning stiffness developed morning stiffness. One of these patients had discontinued corticosteroids himself. In another patient, the dose of csDMARD was increased. 31.6% (n=6) of the patients were in remission with no drugs. In these patients in remission, corticosteroids were tapered and then discontinued until ensuing follow-up examination. While 36.8% (n=7) of the patients continued the csDMARD treatment with the same doses, 10.5% (n=2) increased the csDMARD dose. 21.1% (n=4) patients started to use MTX because remission was still not achieved even though they used corticosteroid. Acute phase reactants were 3 times higher in two patients due to discontinuation of corticosteroid therapy without informing the physician.

In the third outpatient follow-up evaluation (7th month), morning stiffness was determined to continue in only one patient. On the other hand, the morning stiffness of other patients with stiffness complaints in previous follow-up examinations regressed. Even though 31.6% (n=6) of the patients were symptom-free with no drugs, half of these patients were not in remission clinically. 68.4% (n=13) of the patients were continuing their csDMARDs. 31.6% (n=6) of these patients were in remission regarding their clinical and laboratory evaluations. Eight (68.4%) of 13 patients who were not in remission were asymptomatic. No significant associations were determined between remission status and other clinical variables. The changes in ESR and CRP of 19 patients over time are presented in Figures 1 and 2.

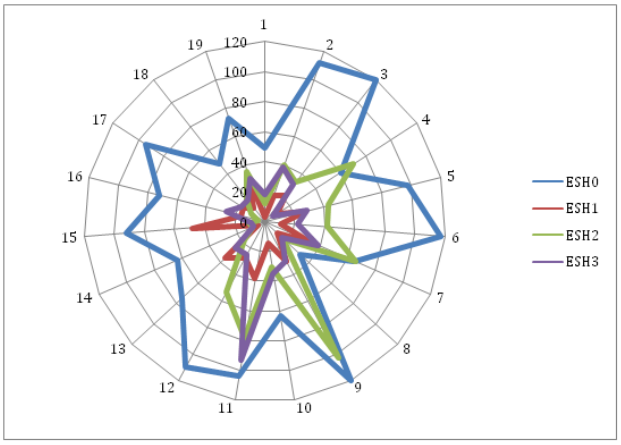

Figure 1. Changes in erythrocyte sedimentation rate (ESR) over time in nineteen PMR patients

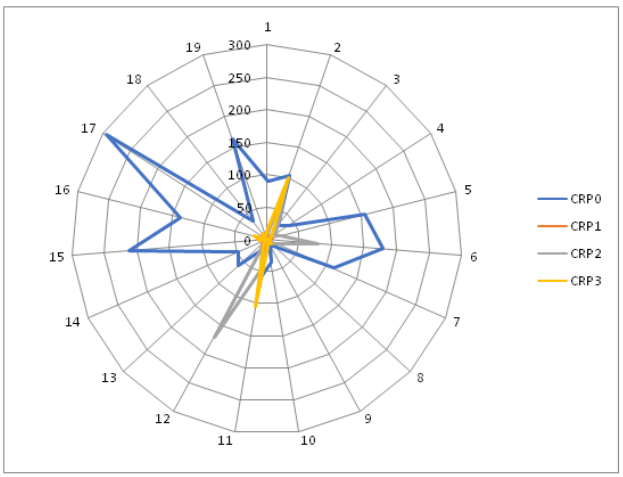

Figure 2. Changes in C-reactive protein (CRP) over time in nineteen PMR patients

When the temporal alterations of acute-phase reactants were evaluated, changes in both ESR and CRP were statistically significant (p<0.001, and p<0.001, respectively). The results of the post-hoc analysis performed to determine which measure caused significance are presented in Table 3. Regarding correlation analysis between acute-phase responses and cumulative corticosteroid doses, only a negative correlation was found in the second follow-up evaluation between ESR and cumulative corticosteroid dose (rs=-0.460, p=0.048).

Table 2. Clinical parameters followed over time

	V1	V2	V3
Symptoms			
No Change	–	2 (10.5)	3 (15.8)
Progression	–	6 (31.6)	1 (5.3)
Regression	9 (47.4)	2 (10.5)	1 (5.3)
No symptoms	10 (52.6)	9 (47.4)	14 (73.7)
Remission	8 (42.1)	9 (47.4)	6 (31.6)
ESR (mm/h)	19.0 (11–33)	33.0 (12–53)	26.0 (18–31)
CRP (mg/dl)	3.8 (2–9)	8.0 (4.0-29.6)	8.3 (3.4–12)
Cumulative corticosteroid dose (mg)	600 (480–720)	960 (852–1546)	1346 (1212–1906)
csDMARDs	9 (47.4)	6 (31.6)	13 (68.4)

Values are given as median (Q1-Q3) and n (%)
V1: First visit-1st month, V2: Second visit-4th month, V3: Third visit-7th month, ESR: erythrocyte sedimentation rate (mm/h), CRP: C-reactive protein (mg/dl), csDMARDs: conventional synthetic disease-modifying antirheumatic drugs

Table 3. The comparisons of acute phase reactants within groups and post hoc analysis

	V0	V1	V2	V3	pt		z	p
ESH	75.0 (63–110)	19.0 (11–33)	33.0 (12–53)	26.0 (18–31)	**<0.001**	ESH 0 vs. ESH 1	-3.823	**<0.001***
						ESH 0 vs. ESH 2	-3.703	**<0.001***
						ESH 0 vs. ESH 3	-3.823	**<0.001***
						ESH 1 vs. ESH 2	-2.254	0.024
						ESH 1 vs. ESH 3	-1.961	0.050
						ESH 2 vs. ESH 3	-1.229	0.219
CRP	61.0 (35–154)	3.8 (2–9)	8.0 (4-29.6)	8.3 (3.4–12)	**<0.001**	CRP 0 vs. CRP 1	-3.724	**<0.001***
						CRP 0 vs. CRP 2	-3.139	**0.002***
						CRP 0 vs. CRP 3	-3.461	**0.001***
						CRP 1 vs. CRP 2	-2.657	**0.008***
						CRP 1 vs. CRP 3	-1.811	0.070
						CRP 2 vs. CRP 3	-0.327	0.744

p_{time} (p_t): p value for the comparison of within-group, Friedman Test
Values are given as median (Q1-Q3)
V0: Baseline evaluation, V1: First visit-1st month, V2: Second visit-4th month, V3: Third visit-7th month, ESR: erythrocyte sedimentation rate (mm/h), CRP: C-reactive protein (mg/dl)
*Statistical significance is accepted as p<0.017

Discussion

The present study screened the patients with isolated PMR, and the data at baseline, 1st, 4th, and 7th months of patients were recorded. The acute phase responses were significantly decreased over time compared to the initial values. Also, the comparisons of acute phase responses between visits were found statistically significant. The clinical symptoms regressed over time, but the remission rates of follow-up periods were similar. Furthermore, the rate of csDMARD use increased over time.

PMR typically affects individuals aged 50 years and over, and its incidence peaks at ages 70-80 years. Similarly, the mean age was 68±7.7 years in our study population, and we had only one patient with an age below 50. Moreover, our female patient ratio was higher than males, consistent with the literature.[4]

There are studies related to the comorbidities accompanying PMR in the literature. The most commonly investigated association was between PMR and thyroid disorders. Even though Bowness et al. reported an increased hypothyroidism risk, the study conducted by Juchet et al. did not determine a significant relationship.[16,17] Both PMR and hypothyroidism are common in females. Even though there is no evidence of autoimmune PMR pathogenesis, similar mechanisms have been suggested to play roles in both diseases. For this reason, although the PMR-hypothyroidism association is common, the relationship between these two disorders has not been proven yet.[18] In our study, 31.6% of the patients had a thyroid disorder; hypothyroidism was present in only one patient, whereas the other five patients had a toxic multinodular goiter.

The most essential and first-line drug in PMR treatment is corticosteroids. The guidelines provide various recommendations about the initial dose, duration, and cessation of treatment; however, the therapeutic approaches may differ from physician to physician. According to the 2015 PMR treatment recommendations of the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR), prednisolone at a dose of 12.5-25 mg/day or its equivalent corticosteroid was suggested to be used for 4-8 weeks as the initial treatment. An initial dose of under 7.5 mg/day or over 30 mg/day was not recommended. It was recommended to taper 1 mg/day in prednisolone dose or its equivalent corticosteroid once every four weeks. The duration of treatment was suggested as 12 months; however, a definite interpretation about the duration of treatment could not be made.[8] In a retrospective study involving 218 patients, the cumulative end-of-4-weeks corticosteroid dose was 460 mg in patients <60 years of age, and 420 mg in those aged >60 years, whereas the doses calculated at the 86th week were 1153 mg in patients aged <60 years, and 1050 mg in those aged >60 years.[19] In our study, the mean initial dose of corticosteroid was 21.5±8.9 mg, which is compatible with the literature. On the other hand, cumulative corticosteroid doses were found to be higher in this study than in the above-mentioned study.

Rapidly reducing the corticosteroid dose increases the recurrence risk. Therefore, the patients should continue their treatments at the lowest dose to minimize the side effects. Female gender, ESR>40mm/hour, and peripheral arthritis are the significant risk factors for recurrence and long-term treatment requirements.[20] In a study conducted by Cimmino et al. on 60 PMR patients, treatment was initiated with prednisolone 12.5 mg/day, and 47 patients had achieved remission. Accordingly, the authors showed that patients with heavier weight did not achieve remission. Therefore, the best determinant for response to treatment was reported as calculating the corticosteroid dose according to the bodyweight (0.2 mg/kg/day prednisolone).[21] In the current study, there was no significant link between remission status and other clinical variables. We may not have found a relationship between these parameters due to the small sample size.

In the literature, MTX is recommended as a corticosteroid-sparing agent to decrease the risk of recurrence. In addition, this agent is preferred in patients with a high risk of developing side effects after using corticosteroids. A study involving 42 patients reported that the response to treatment and remission rate was lower in patients aged under 60 years, necessitating high-dose corticosteroid and MTX treatments.[12] Another randomized controlled study found that adding MTX (10 mg/week) to corticosteroid reduced the corticosteroid dose, shortened the time of discontinuation of corticosteroid, and decreased the recurrence rate and cumulative corticosteroid dose.[22] A study conducted in Japan followed 93 PMR patients for up to 97 months. According to this study, the authors showed that the history of relapse till 6 months played an important role in predicting long-term corticosteroid use and MTX should be added to the treatment regimen of these patients. Furthermore, high CRP values at the time of diagnosis were another significant factor leading to the long-term corticosteroid treatment.[23] Even though MTX is the most reliable and valid corticosteroid-sparing agent in PMR patients, LEF is also regarded as effective as MTX to reduce the corticosteroid dose.[24] In our study, nine patients started using csDMARDs (MTX n=8, LEFn=1) at month 1 while four patients were added MTX at month 4. In the last visit, 68.4% of our patients received csDMARD (MTX n=12, LEFn=1).

ESR is a basic laboratory test used in the follow-up of PMR patients. Therefore, it is commonly used for assessing the treatment response. In the literature, ESR values regressed rapidly to the normal range with corticosteroid treatment in 40-72.7% of patients.[25] A retrospective study conducted in Turkey with a one-year follow-up of 41 patients, reported that 80.5% of patients responded well to corticosteroid treatment at the 3rd-week outpatient follow-up evaluation.[26] Our study determined that while approximately half of the patients were in remission at the first and second outpatient follow-up evaluations, this rate decreased at the third evaluation. At the final outpatient follow-up evaluation, the goal of remission was achieved in approximately one-third of the

patients. We assumed that the most important reason for this situation was the non-adherence of the patients to the treatment.

The study has some limitations. First, the small number of patients prevented us from generalizing the results. Second, the retrospective study design caused patients selection bias. Last but not least, the short follow-up duration and the retrospective design made large-scale data difficult. On the other hand, the strength of the present study was the limited number of publications in the literature on isolated PMR.

In conclusion, the clinical characteristics and initial corticosteroid doses of the study population were consistent with the literature. The decline in acute phase response over time was a valuable parameter for monitoring treatment response. The low remission rates of our study could be related to the non-compliance of our patients with treatment. Cumulative corticosteroid doses were higher than previously published studies. Longitudinal studies are needed to find the influence of initial corticosteroid dose regimes and different maintenance treatment approaches on the clinical parameters of patients with isolated PMR.

Compliance with Ethical Standards

Ethical approval was obtained from the Local Ethics Committee of Kocaeli University (March 2021; no. 2021/06.21).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

Authors contributed equally to this work.

Financial Disclosure

Financial disclosure none.

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