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Polymyalgia rheumatica: inflammation suppression with low dose of methylprednisolone or modified-release prednisone

M. BENUCCI, B. OLIVITO[1], M. MANFREDI[1], F. MEACCI[1], M. INFANTINO[1], F. LI GOBBI, P. SARZI-PUTTINI[2], C. MARCASSA[3], F. ATZENI[2]

Rheumatology Unit, S. Giovanni di Dio Hospital, Florence, Italy
[1]Immunology and Allergology Laboratory Unit, S. Giovanni di Dio Hospital, Florence, Italy
[2]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy
[3]S Maugeri Foundation, Veruno, Novara, Italy

Abstract. – OBJECTIVE: Polymyalgia rheumatica (PMR) is an inflammatory disease that affects people aged > 50 years, and is characterised by pain and morning stiffness in the shoulder and pelvic girdle with synovitis of the proximal joints and extra-articular synovial structures. It is currently mainly treated with glucocorticoids (GCs). The aim of the study was to evaluate changes in inflammatory markers and their correlations with cortisol levels after treatment with 6-methylprednisolone (6-MP) or modified-release prednisone (MR-P) in patients with "early" PMR.

PATIENTS AND METHODS: The study involved 81 GC-naïve with "early" PMR diagnosed on the basis of the 2012 EULAR/ACR criteria: 38 treated with 6-MP at a starting dose of 12 mg at 8.00 a.m, gradually tapered to 8, 4 and 2 mg/day, and 43 treated with MR-P at a starting dose of 10 mg at 10 p.m, tapered to 7, 5, 3, 2 and 1 mg. The markers of inflammation (ESR mm/h, CRP mg/dL and fibrinogen mg/dL), the circulating serum levels of cytokines (TNFα and IL-6), and morning serum cortisol levels were evaluated at baseline and during GC treatment.

RESULTS: There were significant differences between baseline and the end of treatment in the serum levels of IL-6 (5.3 ± 9.3 vs 2.8 ± 3.3 pg/mL; $p < 0.05$) and CRP (2.1 ± 3.3 vs 0.9 ± 1.7 mg/dL; $p < 0.01$) in the patients treated with MR-P, and in serum cortisol levels (15.8±6.4 vs 13.6+5.6 µg/dL; $p < 0.01$) in the patients treated with 6-MP. After the first month of treatment, 76.7% of the patients treated with MR-P had IL6 levels at or below the upper normal limit, whereas 52.6% of those treated with 6-MP had normal IL6 levels ($p < 0.05$). There was also a significant difference in the percentage of patients in whom the daily GC dose was tapered within eight months (6.7% in the MR-P group vs 25% in the 6-MP group; $p < 0.001$) and, by the end of the study, respectively 59.5% vs 35.1% patients were receiving a low GC dose or had discontinued treatment altogether (OR 2.7, 95% CI 1.0-6.77; $p < 0.001$). After six and 12 months, respectively 10.3% and 14.3% of the patients had discontinued MR-P, as against none of the patients treated with 6-MP ($p < 0.05$).

CONCLUSIONS: In this prospective observational study of PMR patients receiving low-dose GCs, the changes in inflammatory markers were similar in those treated with 6-MP or MR-P, whereas morning cortisol levels remained unchanged only in the MR-P group. During the first month of treatment, MR-P chronotherapy given at bedtime significantly decreased IL-6 levels. The percentage of patients stopping GC treatment was higher in the MR-P group than in the 6-MP group.

Key Words:
Polymyalgia rheumatica, Modified-release prednisone, 6-methylprednisolone.

Introduction

Polymyalgia rheumatica (PMR) is an inflammatory disease that affects people aged > 50 years. It may be 'isolated' or associated with giant cell arteritis (GCA), and is characterized by pain and morning stiffness in the shoulder and pelvic girdle with synovitis of the proximal joints and extra-articular synovial structures. The first case was described in 1888[1], but the term "polymyalgia rheumatica" was proposed by Barber in 1957[2].

PMR is currently mainly treated with glucocorticoids (GCs), which is the gold standard treatment as it reduces symptoms and suppresses inflammation within a few weeks. GCs such as prednisone inhibit the circadian release of pro-inflammatory cytokines such as IL6, and hence reduce the duration of morning stiffness, and a

Corresponding Author: Maurizio Benucci, MD; e-mail: maubenucci@tiscali.it

short course of treatment at a dose of > 10 mg/day is associated with fewer relapses than lower doses[3]. However, immediate-release prednisone is taken upon waking, which is too late to have an impact on morning symptoms and the inflammatory effects of IL-6[4,5], and the more appropriate timing of drug administration or the use of modified-release prednisone (MR-P) preparations may lead to an improvement in the duration of morning stiffness.

The circadian administration of prednisone in patients with rheumatoid arthritis (RA) as in the CAPRA-1 and -2 studies showed that the optimised administration of low-dose MR-P (designed to be released at 3.00 a.m. in order to control increasing IL-6 levels) improves the risk/benefit ratio of long-term GC treatment[4,5]. An MR-P formulation developed on the basis of biological rhythms (chronotherapy) delivers prednisone at the most physiologically efficient time in order to relieve the morning symptoms of RA, and has no adverse impact on the hypothalamic-pituitary-adrenal axis.

The aim of this study was to evaluate the changes in inflammation markers and their correlations with cortisol levels after treatment with 6-methylprednisolone (6-MP) or MR-P in patients with "early" PMR.

Patients and Methods

The study involved 81 GC-naïve with "early" PMR diagnosed on the basis of the 2012 EULAR/ACR criteria: 38 treated with 6-MP at a starting dose of 12 mg at 8.00 a.m, gradually tapered to 8, 4 and 2 mg/day, and 43 treated with MR-P at a starting dose of 10 mg at 10 p.m, tapered to 7, 5, 3, 2 and 1 mg. Blood was drawn between 8.00 a.m and 9.00 a.m. when the patients visited the outpatient clinic at baseline, and every month during GC treatment. The blood was immediately centrifuged and the serum was stored at –80°C. Written informed consent was obtained from all patients and the study was approved by the Ethics Committee of San Giovanni Di Dio Hospital, Florence, Italy.

The evaluated inflammation markers were the erythrocyte sedimentation rate (ESR, mm/h), and the levels of C-reactive protein (CRP, mg/dL) and fibrinogen (mg/dL). Circulating interleukin-6 levels (IL-6, upper normal limit [UNL] < 3.0 pg/mL) were determined by means of a human IL6 instant enzyme-linked immunosorbent assay (ELISA) (eBioscience, Bender MedSystem GmbH, Vienna, Austria), and circulating tumour necrosis factor-alpha levels (TNFα, UNL < 15.6 pg/mL) by means of a quantitative sandwich enzyme immunoassay technique (Human TNF-alpha Quantikine Immunoassay, RD System Inc., Minneapolis, MN, USA). Morning serum cortisol levels (μg/dL) were assessed at baseline and every month during GC treatment by means of an electrochemiluminiscence immunoassay (ECLIA, Roche, Mannheim, Germany).

Statistical Analysis

The continuous variables are expressed as mean values and standard deviation, and were compared within and between the groups using the non parametric Mann-Whitney U test (paired and two- sample independent tests) at the different times of follow-up. The categorical variables are expressed as frequencies and percentages, and were compared using the Cochrane Q test. Odds ratios (OR) were calculated to compare the groups on different daily doses at the end of the follow-up.

Results

Table I shows the patients' demographic characteristics and baseline laboratory parameters: there were significant differences between the MR-P and 6-MP groups in the levels of cortisol (11.5 ± 6.7 *vs* 15.8±6.4 μg/mL; $p < 0.01$) and IL-6 (5.3 ± 9.3 *vs* 1.9±1.3 pg/mL; $p < 0.05$).

Table II shows the changes in inflammation markers, cytokine and cortisol levels between baseline and the last visit. There were significant changes in the levels of IL-6 (5.3±9.3 *vs* 2.8±3.3 pg/mL, $p < 0.05$) and CRP (2.1±3.3 *vs* 0.9±1.7 mg/dL; $p < 0.01$) in the patients treated with MR-P, and in serum cortisol levels (15.8±6.4 *vs* 13.6+5.6 μg/dL; $p < 0.01$) in the patients treated with 6-MP. Figure 1 shows IL-6 levels in both groups: after the first month of GC treatment; 76.7% of the MR-P patients had IL-6 levels ≤ UNL, whereas 52.6% of those treated with 6-MP had normal IL6 levels ($p < 0.05$) (Figure 2). The tapering of the daily GC dose was significantly different between the two groups ($p < 0.001$; Figure 3). There was also a significant difference in the percentage of daily of GC dose tapered within eight months (6.7% in the MR-P group *vs* 25% in the 6-MP group; $p < 0.001$) (Figure 4) and, by the end of the study, respectively 59.5% *vs* 35.1% patients were receiving a low GC

Table I. Demographic characteristics and laboratory parameters at baseline.

	MR-P	6-MP	*p* value
No. of patients	43	38	ns
Age, years	73.9 ± 8.5	74.0 ± 8.2	ns
No. of males (%)	20 (47%)	14 (37%)	ns
No. of females (%)	23 (53%)	24 (63%)	ns
ESR, mm/h	33.6 ± 20.9	31.2 ± 17.3	ns
CRP, mg/dL	2.1 ± 3.3	1.5 ± 1.7	ns
Fibrinogen mg/dL	464 ± 143	487 ± 168	ns
Serum cortisol, µg/dL	11.5 ± 0.7	15.8 ± 6.4	< 0.01
Serum TNFα, pg/mL (× UNL)	1.12 ± 6.7	1.1 ± 0.3	ns
Serum IL6, pg/mL (No. of with patients > UNL)	16	21	ns
Serum IL6, pg/mL (× UNL)	5.3 ± 9.3	1.9 ± 1.3	< 0.05

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TNF: tumour necrosis factor-alpha; IL-6: interleukin-6; UNL: upper normal limit.

Table II. Inflammation markers, cytokine levels and glucocorticosteroid dose.

	MR-P Baseline	MR-P Last visit	6-MP Baseline	6-MP Last visit
ESR, mm/h	33.6 ± 20.9	27.5 ± 20.6	31.2 ± 17.3	25.5 ± 19.0
CRP, mg/dL	2.1 ± 3.3	0.9 ± 1.7°°	1.5 ± 1.7	1.1± 1.1
Fibrinogen, mg/dL	464 ± 143	426 ± 112	487 ± 168	455 ± 93
Serum cortisol, µg/dL	11.5 ± 6.7	12.0 ± 4.1	15.8 ± 6.4**	13.6 ± 5.6
Serum TNFα, pg/mL (× UNL)	1.1 ± 0.6	2.3 ± 8.2	1.1 ± 0.3	2.5 ± 6.3
Serum IL6, pg/mL (× UNL	5.3 ± 9.3	2.8 ± 3.3*	1.9 ± 1.3*	2.0 ± 2.9
Daily dose, mg	10	3.0 ± 1.9	12	3.4 ± 1.2
% of starting dose		29 ± 20		28 ± 11
Follow-up, days		179 ± 70		150 ± 58

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TNF: tumour necrosis factor; IL-6: interleukin-6; UNL: upper normal limit. **$p < 0.1$ vs baseline MR-P; *$p < 0.05$ vs baseline MR-P; °°$p < 0.01$ vs baseline.

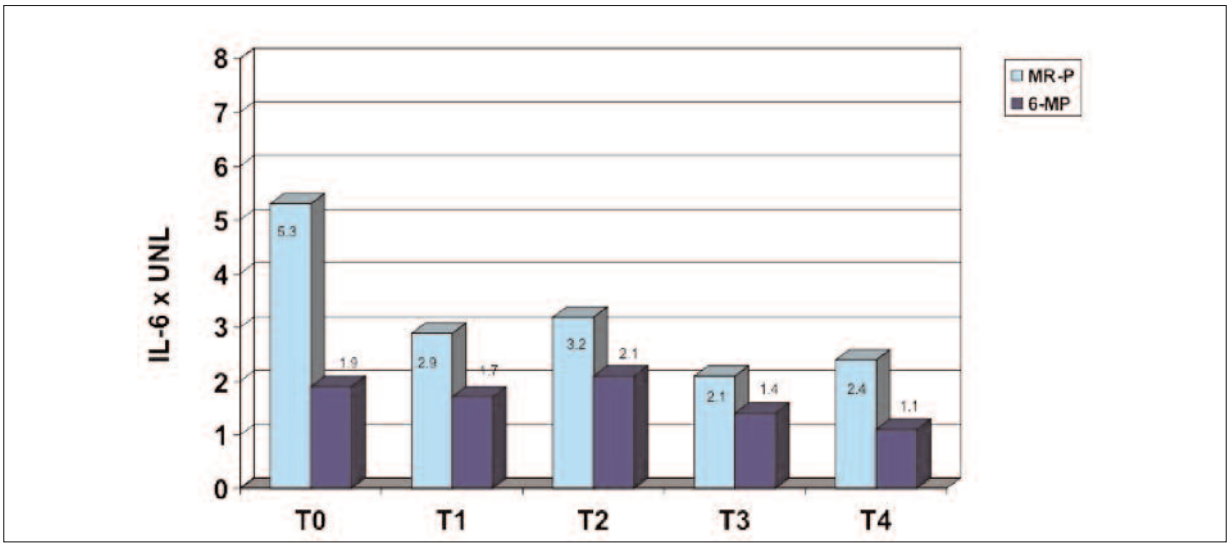

Figure 1. IL-6 levels from baseline to month four.

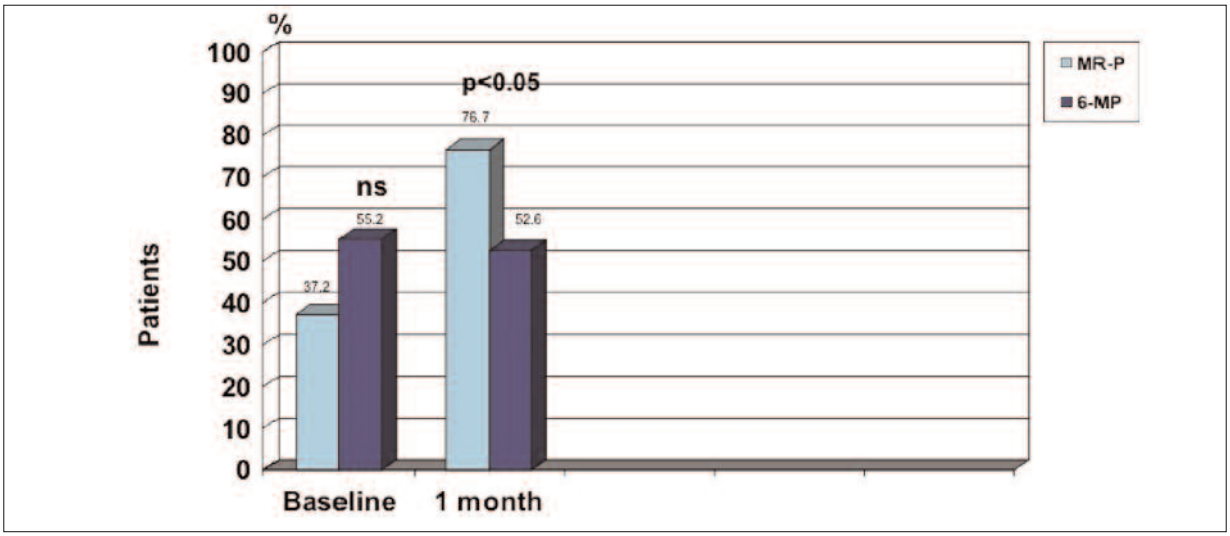

Figure 2. Percentage of patients with IL-6 levels ≤ UNL.

dose or had discontinued treatment altogether (OR 2.7, 95% CI 1.0-6.77; $p < 0.001$) (Figure 5). After six and 12 months, respectively 10.3% and 14.3% of the patients had discontinued MR-P, as against none of the patients treated with 6-MP ($p < 0.05$) (Figure 6).

Discussion

In this non-randomized, prospective observational study of PMR patients receiving low-dose GCs, the changes in inflammatory markers were similar in those treated with 6-MP or MR-P, whereas morning cortisol levels remained unchanged only in the MR-P group. An MR-P induced improvement in morning stiffness was observed after 9-12 months during the open-label extension of the CAPRA-1 study[4], and this finding is in line with those of observational studies of adult RA patients. The evening administration of MR-P for up to 12 months is tolerated as well as the evening administration of placebo or morning immediate-release prednisone, and longer-term treatment with the evening administration of MR-P improves morning stiffness in RA patients[7]. In the 9-month extension phase of CAPRA-1, the dura-

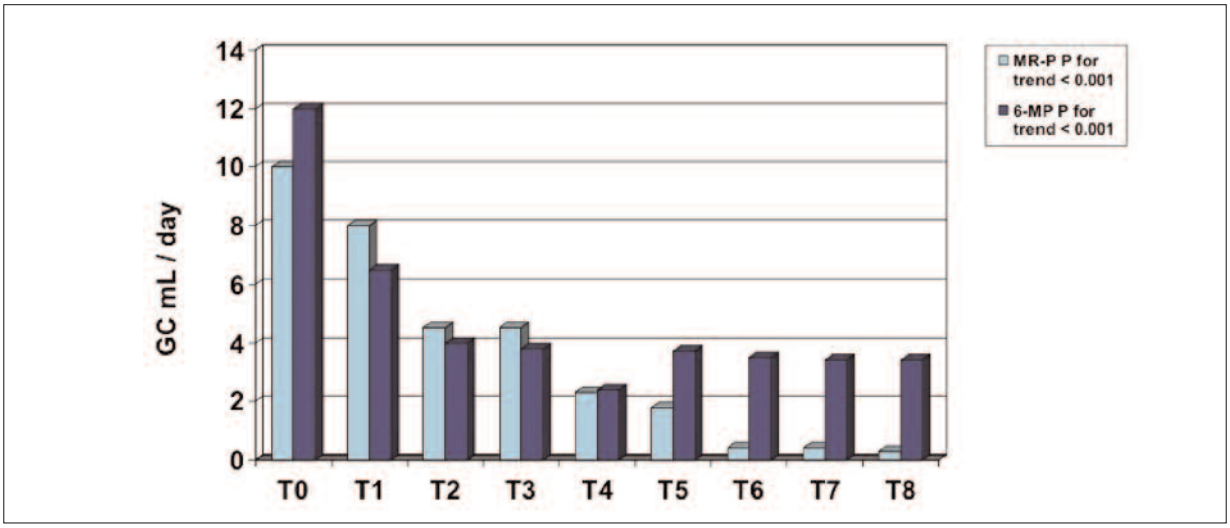

Figure 3. Tapering of daily of GC dose (absolute values).

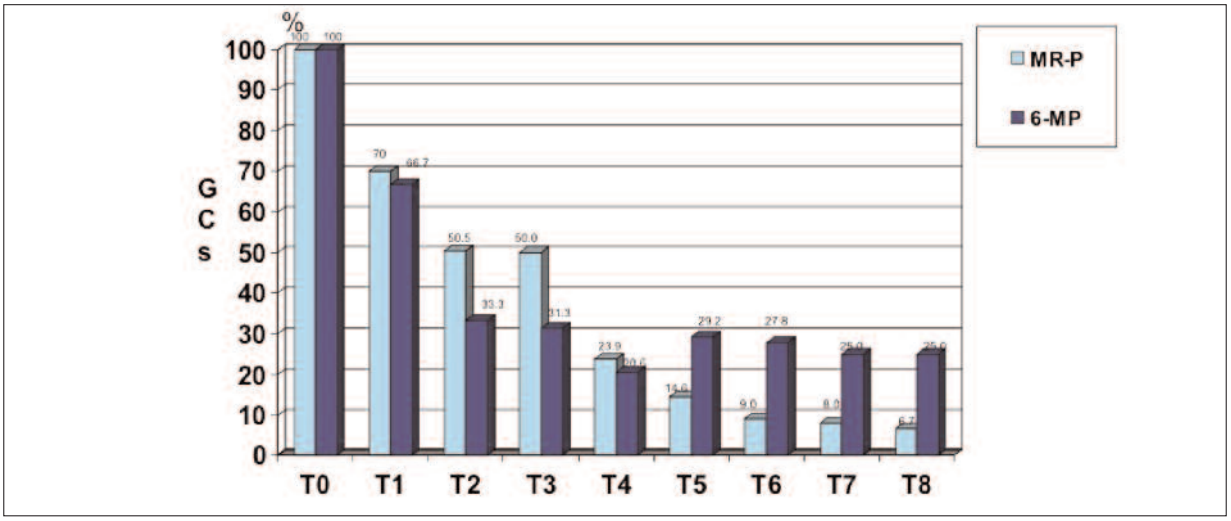

Figure 4. Tapering of GC dose (reduction from starting dose).

tion of morning stiffness was reduced by 55% from the baseline of the double-blind phase in all of the patients after the first three months of treatment (i.e. after a total of six months of prednisone treatment), regardless of the prednisone formulation received, and prolonged MR-P treatment led to 45-61% reduction after six and nine months (i.e. after a total of nine and 12 months of prednisone treatment)[7].

In our study of low-dose GCs, one month of MR-P chronotherapy given at bedtime induced a greater decrease in IL-6 levels. RA patients experience a circadian increase in endogenous cortisol levels during the evening[8], but this is not sufficient to counter the increase in IL-6 levels[9]. However, two randomized trials of 12 weeks' treatment with evening MR-P in RA patients (3-10 mg[4] or an equivalent of 5 mg[5]) found a significant reduction in IL-6 levels (a marker of inflammatory disease activity)[10] in comparison with placebo[5] or the morning administration of immediate-release prednisone[4]. In the placebo-controlled trial, the geometric mean IL-6 titre ratio was 0.8 (95% CI 0.7-0.9) in favour of MR-P (baseline 5 pg/mL)[5]; in the trial comparing MR-P with immediate-release prednisone, MR-P led to a 28.6% reduction in IL-

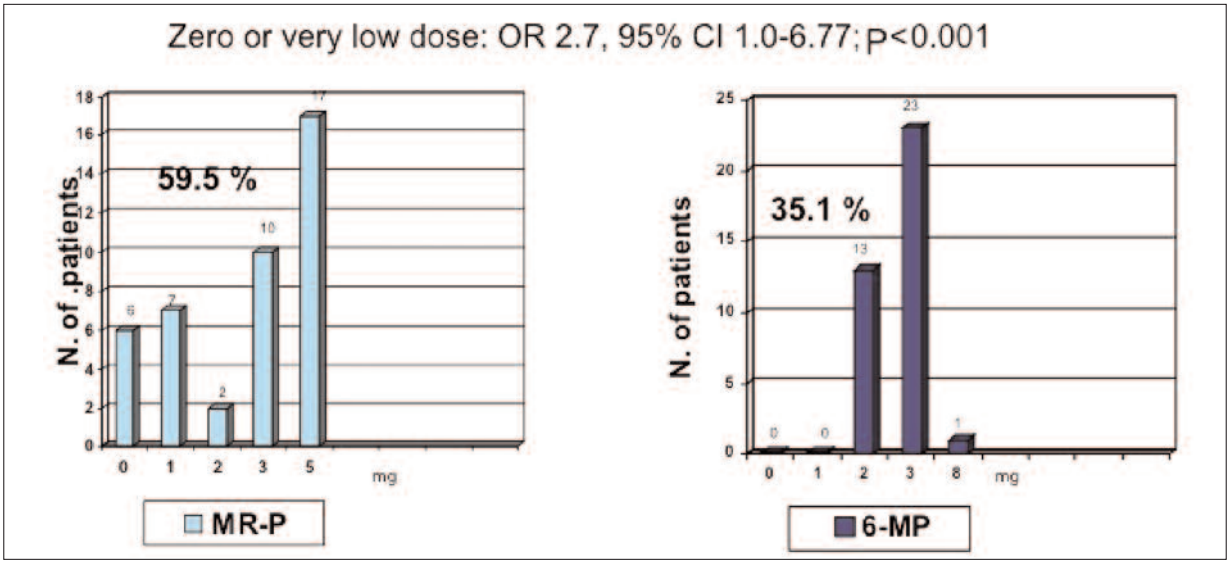

Figure 5. Daily GC dose at last follow-up.

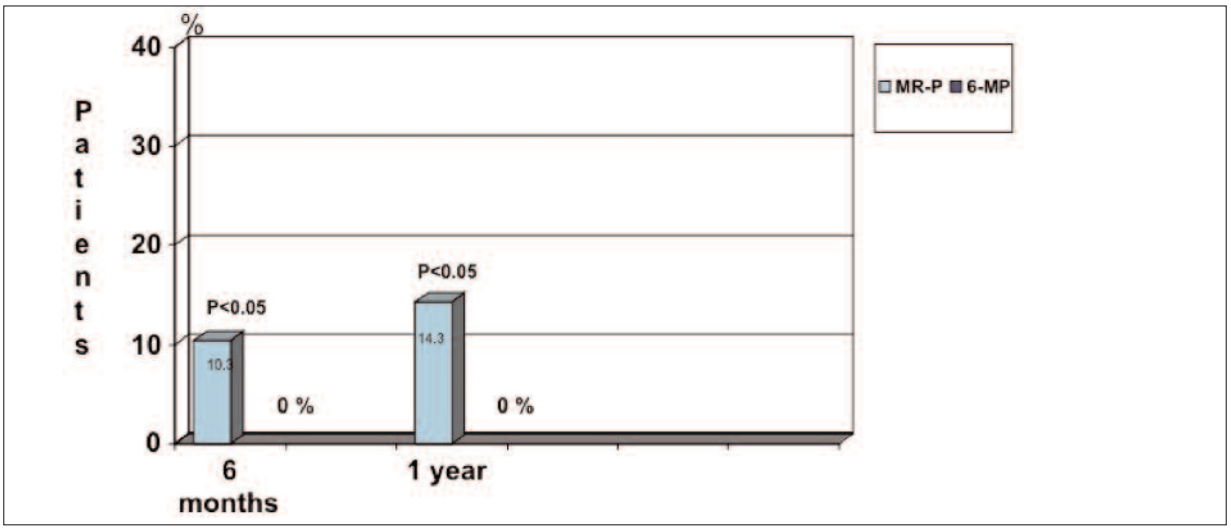

Figure 6. Percentage of the patients discontinning GC.

6 levels whereas there was no change in the comparator group ($p = 0.0322$)[4]. After a further nine months of open-label MR-P therapy[7], IL-6 levels significantly decreased by 50% in comparison with the baseline level of the double-blind phase ($p < 0.05$). Furthermore, another study of RA patients has shown that evening MR-P 5 mg once daily for two weeks affected the circadian variation in IL-6 levels, with peak levels reduced by 50% and a change in the time of peak levels from 8:05 a.m. to 1:21 a.m.[11].

The role of IL-6 has been investigated in various studies: one found an association between the IL-6 -174 allele C and PMR manifestations in patients with GCA[12], whereas an Italian study found the IL-6 promoter polymorphism at position -174 in both PMR patients and controls[13]. These findings suggest that many genes are involved in susceptibility to, and the severity of PMR, and that associations with polymorphisms may be different in different populations. The IL-6 receptor antagonist, monoclonal antibody tocilizumab (TCZ), has been used to treat PMR and correlated with the levels of circulating IL-6 in patients with active disease[14]. Four papers[15-18] have described its use in a total of nine PMR patients (one with newly diagnosed PMR, one with relapsed PMR, and seven who developed PMR during the tapering of GCs prescribed for GCA), three of whom (one with PMR and two with PMR/GCA) were GC-naïve: eight received a dose of 8 mg/kg/month and one a dose of 4 mg/kg/month, and all experienced clinical and serological remission.

GCs represent the gold standard for PMR treatment. Initial daily prednisone doses of > 10 mg are associated with fewer relapses and shorter GC therapy than lower doses, but starting at doses of > 15 mg/day have been related to greater GC accumulation and frequent GC-related adverse events[19]. There is no universally accepted regimen, but the British Society for Rheumatology (BSR) suggests that prednisolone (or its equivalent) should be used at 15 mg/day for three weeks, at 12.5 mg for a further three weeks, and then at 10 mg for 4-6 weeks before being tapered by 1 mg every 4-8 weeks provided no flares occur[20]. Many patients discontinue GCs between six months and two years after the onset of clinical symptoms, but others may require long-standing therapy. In our study, tapering was more rapid with MR-P than with 6-MP, and more MR-P patients could discontinue GC treatment altogether.

Conclusions

In this non-randomized, prospective observational study of low-dose GC treatment, the changes in inflammatory markers were similar in PMR patients treated with 6-MP or MR-P, whereas morning cortisol levels remained unchanged only in the MR-P group. During the first month of treatment, MR-P chronotherapy given at bedtime significantly decreased IL-6 levels, and the percentage of patients stopping GC treatment was higher in the MR-P group than in the 6-MP group.

Funding Statement

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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