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Monthly Pulse Methylprednisolone Therapy is Effective in Preventing Permanent Disease Progression in Secondary Progressive Multiple Sclerosis

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ABSTRACT

Introduction: Secondary progressive multiple sclerosis (SPMS) is the phase in which disability continues to worsen with or without accompanying attacks. Monthly methylprednisolone pulse therapy can be used in the secondary progressive phase. The purpose of the present study was to evaluate the effects of methylprednisolone pulse therapy on the basis of clinical and MRI parameters in patients with SPMS.

Methods: This was a multi-center, examiner-blinded, prospective study. Patients with SPMS with EDSS scores of 3 or more, using one or none of azathioprine, interferon or glatiramer acetate, were evaluated. Patients were given IVMP (1 dose of 1 g IV) once a month for 24 months. EDSS scores, MRI findings, quality of life, and adverse events were evaluated.

Results: Ninety-seven SPMS patients were included in the study. Significant decreases in new/enlarging, Gd-enhanced, and spinal lesions were observed from baseline to year 2. EDSS scores remained stable at the end of the second year. Monthly high-dose IVMP resulted in a significant decrease in attacks.

Conclusion: This study is important in terms of emphasizing that this therapeutic option should not be overlooked, since monthly pulse therapy can halt or even reverse progression, regarded as a natural course in SPMS, albeit to a small extent.

Keywords: Secondary progressive multiple sclerosis, monthly methylprednisolone treatment, disease progression

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. While attacks occur in the inflammatory phase, progression involving loss of the trophic effect established by myelin and axonal loss is involved in the neurodegenerative phase. Secondary progressive MS (SPMS) is the phase in which disability continues to worsen with or without accompanying attacks. Approximately 50% of cases evolve into SPMS within 10 years (1). Although significant progress has been made in the treatment of relapsing remitting MS (RRMS) in the last decade, only limited advances have been made in the progressive form.

Methylprednisolone is used in the treatment of progressive MS. Standard treatment for acute relapse of MS consists of pulse therapy with a high dose of methylprednisolone at 1000 mg/daily for 3 to 10 days. Corticosteroids are employed since treatment protocols in SPMS are still limited. However, the efficacy of corticosteroids in SPMS is unproven, and their role in the treatment of progressive MS is still unclear. One previous study reported a significant decrease in EDSS scores in patients with primary progressive MS (PPMS) following intravenous methylprednisolone (IVMP) therapy (2). Another trial failed to meet its primary endpoint, but showed that methylprednisolone therapy had some effect on time to progression in SPMS (3). Monthly methylprednisolone pulse therapy has recently been reported in one study to be safe, but to have no effect on the primary outcome, which was to show the effect of monthly oral methylprednisolone pulse therapy on intrathecal inflammation in progressive MS. However, some improvements in secondary clinical and MRI outcome measures have been observed (4). The purpose of the present study was to evaluate the effects of methylprednisolone pulse therapy on the basis of clinical and MRI parameters in patients with SPMS.

MATERIALS AND METHODS

Methods

This was a multi-center, examiner-blinded, prospective study. Certification was received from the Local Ethics Committee of the Dokuz Eylül University School of Medicine.

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Patients

Patients with SPMS with EDSS scores of 3 or more, using one or none of azathioprine, interferon or glatiramer acetate (GA), with EDSS scores increasing by at least 0.5 over the previous year or undergoing at least one attack in the previous year and with newly detected T2 lesion, and aged over 18 years were included in this study. Patients were excluded if they had been treated with lymphoid irradiation, mitoxantrone, natalizumab, cyclophosphamide, or long-term systemic glucocorticoids for any reason within the previous 6 months. Patients with a history of peptic ulcer or current symptoms of dyspepsia, major depression, cardiac or renal insufficiency or other serious medical disorders, or with any medical illness requiring treatment with systemic corticosteroids were also excluded. Informed consent was obtained from all patients after being briefed about the study protocol.

Procedures

One physician was the neurologist responsible for the overall care of the patient, including assessment and management of adverse events. A second physician acted as the "evaluating neurologist," assessing patients at scheduled visits and at unscheduled relapse examinations. Patients were given IVMP (1 dose of 1 g IV) once a month for 24 months. Initially, we collected demographic data and medical histories from the study group. Clinical neurological examinations including EDSS were performed. We also performed laboratory tests (complete blood count, blood chemistry, and standard urinalysis) and measurements of bone density in the lumbar spine. After the baseline visit, patients attended a further study visit every 3 months. Patients were assessed on the basis of EDSS every 3 months and using the MuSIQoL scale every 6 months. Patients were followed up for at least 2 years after commencement (plus a possible 6-month period to confirm sustained disability).

Bone mineral density (BMD) was measured using dual energy X-ray absorptiometry (DEXA) scanning at baseline and week 52. Patients were identified as "osteoporotic" if their T-scores were below -2.5, and these subjects were ineligible for inclusion in the study. Osteopenic patients (T-score between -1.0 and -2.5) were eligible for inclusion if treated with bisphosphonates. MRI scans were performed using a 1.5T scanner. T1-weighted (pre-and post-gadolinium), T2-weighted, and fluid attenuated inversion recovery (FLAIR) were performed. The treating physician examined the patient at every monthly visit and recorded adverse events, concomitant medication use, and the results of laboratory tests. The evaluating neurologist calculated the study group EDSS scores.

The primary outcome was the time to sustained disability progression, defined as an increase sustained for 6 months of at least 1 point at EDSS. Secondary outcome measures of disease activity included the mean number of documented relapses per patient per year (mean yearly relapse rate) and MS Quality of Life scale score. Numbers of Gd-enhanced lesions, new or enlarging T2 lesions and new spinal lesions were also documented. For MRI, the parameters were compared with values determined 2 years before inclusion in the study. Relapses were defined as the appearance of new, or worsening of old, neurological symptoms, without fever, persisting for more than 24 hours, and preceded for more than 30 days by a stable or improving condition. Safety measures were number and type of adverse events (AE) and changes in BMD.

QoL was assessed at baseline and at the end of the study using MusiQoL questionnaires. The MusiQoL questionnaire comprises 31 questions in 9 dimensions (subscales): activities of daily living (8 items), psychological well-being [4], symptoms [4], relationships with friends [3], relationships with family [3], sentimental and sexual life [2], coping [2], rejection [2], and relationships with the healthcare system [3]. The index score is computed as the mean of these subscale scores. We used only the index score, which was linearly transformed and standardized on a 0 to 100 scale, where 0 indicates the worst possible level of QoL, and 100 indicates the best possible level.

For MRI investigations, we obtained 3 mm axial images using a T1-weighted spin-echo sequence before and after gadolinium contrast injection, a proton-density and T2-weighted turbo-spin-echo sequence, and a fluid-attenuated inversion recovery sequence.

Analysis

Statistical Package for Social Sciences (SPSS) version 16.0 for Windows was used for all statistical analyses, and a p value lower than 0.05 was considered statistically significant for all results. The chi-square test was used to compare categorical variables, and the p value was calculated using Fisher's test where necessary. For data with non-normal distribution, comparison of the means of two independent groups was performed using the nonparametric Mann-Whitney U test. Comparison of means among more than two groups was performed using nonparametric Kruskal-Wallis analysis of variance. Comparison of means between two dependent groups was performed using the Wilcoxon test. Pearson's correlation test was used to identify the direction and strength of relationships between variables.

RESULTS

Ninety-seven SPMS patients were included in the study. One patient did not complete the study due to AEs. Two further patients did not complete the full 2 years for personal reasons. Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics of the study group

Duration of progressive phase years ± SD (min-max)	8.3±6.1 (1–24)
EDSS at baseline mean ± SD (min-max)	5.97±4.16 (3.0–8.0)
Ongoing MS treatment no. (%)	
None	26 (27.7)
Azathioprine	60 (93.8)
Interferon beta (SC)	5 (5.3)
Glatiramer acetate	3 (3.2)

Clinical Outcomes and QoL

Table 2 shows the clinical outcomes. Mean EDSS score improved from baseline to year 2. Seventy-one out of 94 (75.6%) patients had stable EDSS scores, 16 (17%) had improved scores, while only 7 (7.4%) had worse EDSS scores. No gender difference was observed. There was also no difference between the treatment groups in terms of mean EDSS scores. Annual relapse rates were better in the group receiving methylprednisolone in addition to other treatments compared to the group receiving methylprednisolone alone (Table 2). Since this was one of the inclusion criteria, all patients had sustained disability progression. A significant decrease was observed in the second year (94 patients compared to 7). There was no change in mean MUSIQOL scores within the 2-year period.

Table 2. Mean EDSS scores, total number of relapses, relapse rate and mean MuSIQoL score of study group at baseline and end of the study

	Baseline	**Year 2**	**p**
Mean EDSS score ± SD (min-max)	5.97±4.16 (3.0–8.0)	5.3±5.02 (3.0–8.0)	0.004
Total number of relapses (2-year period)	26	17	0.007
Relapse rate over 2 years mean ± SD (min-max)	0.28±1.1 (0–3)	0.18±1.3 (0–2)	0.006
No treatment	0.42±1.3 (1–3)	0.31±1.2 (1–2)	0.026
AZA, IFN, G	0.22±0.8 (0–2)	0.13±0.7 (0–1)	<0.001
P	**0.003**	**0.001**	
Mean MuSIQoL score ± SD	64.5±14.6	69.3±17.3	0.009

EDSS: expanded disease status scale; AZA: azathioprine; IFN: interferon; GA: glatiramer acetate.

MRI Outcomes

Significant decreases in new/enlarging, Gd-enhanced and spinal lesions were observed from baseline to year 2 (Table 3). Numbers of new T1 hypointense lesions (black holes) also decreased, but the difference was not statistically significant.

Table 3. Magnetic resonance imaging findings in the study group

	Previous 2 years	Study period	p
New/enlarging T2 lesions mean ± SD	0.98±1.7	0.6±1.1	0.014
Gd enhanced lesions mean ± SD	0.58±0.9	0.22±1	0.009
New black holes mean ± SD	0.2±0.6	0.1±0.6	0.068
New spinal lesions mean ± SD	0.07±0.2	0.03±0.1	0.02

Gd: gadolinium.

Safety Outcomes

No serious adverse events (SAE) were observed. Forty-eight AEs were recorded. All AEs constituted well-known side effects in close temporal relation to treatment. Insomnia, flushing and acne were the most common side-effects (12–15%). A metallic taste, palpitations and edema were also frequently seen (8–10%). Urinary tract infections were also recorded (3%). One patient suffered avascular necrosis. No change was observed for the T-score in the DEXA exam.

DISCUSSION AND CONCLUSION

MS is the second most common cause of disability in young people after trauma, and since disability may be expected to increase as the disease progresses, considerable research aimed at slowing or preventing progression has been performed in recent years. The second most common form of MS after the relapsing-remitting form is the secondary progressive (SPMS) form, in which attacks occur initially, and insidious progression is observed over the years, either with or without accompanying attacks. Various therapeutic options have emerged in recent years in order to prevent or even reverse increasing physical disability in SPMS (5). Considerable experience has been accumulated, and in addition to mitoxantrone therapy that has been used since 2002 (6), several other new agents have begun being employed in this area in recent years. More effective treatment management is anticipated with results to be obtained in the future. However, appropriate drug selection for the appropriate patient within such a wide spectrum is often confusing and problematic for the physician.

Methylprednisolone therapy, used in the treatment of attacks in MS for many years (7), and also in the suppression of inflammation and repairing the blood brain barrier (8), is also frequently employed when the disease proceeds to progression. However, the number of studies on this subject and the data obtained are very limited. Pulse steroid therapy is also used to reduce the frequency of attacks in relapsing remitting MS and in reducing the progression of the disease (9–11). This study investigated the effectiveness, reliability and tolerability in disease progression of the high-dose IVMP employed for many years as the gold standard in attack treatment when administered as monthly pulse therapy.

In our study, EDSS score, a marker of disability, remained stable at the end of the second year following administration of pulse steroid therapy once every 4 weeks for 2 years, while an improvement in EDSS scores was observed in 17% of patients, while progression persisted in only 7%. This study is important in terms of emphasizing that this therapeutic option should not be overlooked, since monthly pulse therapy can halt or even reverse progression, regarded as a natural course in SPMS, albeit to a small extent. Additionally, in our study monthly high-dose IVMP resulted in a significant decrease in attacks. Since attacks in SPMS sometimes do not resolve completely, and given the contribution to progression of attack frequency and severity, this finding once again shows the efficacy of monthly pulse therapy against progression. In addition, no significant side-effects being observed with monthly pulse therapy at the end of the study, and the determination of a significant improvement in quality of life assessed using MuSIQoL compared to pre-treatment levels, are also important in terms of emphasizing the need for monthly pulse therapy to be maintained as a therapeutic option in SPMS.

While neuroinflammation, neurodegeneration and permanent axon injury are seen in the pathogenesis of MS, the dominant process may vary depending on subtypes of the disease, and from patient to patient within the same subtype. Preventing an increase in lesion numbers and atrophy at MRI of the brain, one of the main parameters of progression in MS, has been one of the aims of several studies. One study reported that monthly oral methylprednisolone therapy was effective in progression of the disease on the basis of both clinical and MRI findings, and that this effect made it quite reliable (4). Another study from 1988 reported that 500 mg prednisolone therapy administered once every 2 months was effective against SMPS progression (3). Studies in which pulse steroid therapy has been combined with mitoxantrone therapy have also reported that pulse therapy is effective against disease progression and produces a reduction in MS plaques (12, 13). In our study, we observed a significant decrease in new lesion numbers at brain and spinal MRI and in numbers of contrast involving lesions. While the study designs differ, when the detailed demonstration of the positive effect of pulse steroid therapy at MRI in our study is combined with the findings of previous studies, this once again highlights the effect of the use of pulse therapy in SPMS.

Various factors can complicate treatment management in both oral and high-dose intravenous methylprednisolone therapy. These include dermatological problems such as facial rash, moon face, fat deposition in the body, acne and telangiectasia, delayed wound healing, weight gain associated with sodium and water retention, hypertension, amenorrhea, hirsutism, hyperglycemia, changes in lipid profile, muscular weakness, gastric and duodenal ulcer, increased risk of infection, thrombocytosis, bone fractures and aseptic necrosis at the head of the femur and humerus. Despite this wide spectrum, the majority of these side-effects are associated with long-term, continual or oral use. No serious side-effect was observed in our patient group receiving a month single dose of IVMP therapy. Additionally, the majority of side-effects can be prevented by close monitoring, or when side-effects do appear, they can be easily managed.

In conclusion, this is the first time that the effectiveness and reliability of monthly pulse therapy, which clinicians employ on an occasional basis in clinical practice with SPMS patients, has been studied in such detail using both clinical and MRI parameters. Our study shows that monthly pulse therapy can be added to treatment in SPMS or safely used alone as a therapeutic option when other alternatives are unsuccessful.

Ethics Committee Approval: Certification was received from the Local Ethics Committee of the Dokuz Eylül University School of Medicine

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Author Contributions: Concept - SO; Design - SO; Supervision - SO; Resource - BPC, GK, BBK; Materials - BPC, DO, TK; Data Collection and/ or Processing - BBK, GK, DO, TK; Analysis and/or Interpretation - SO, BPC, GK; Literature Search - TK, BBK, DO; Writing - SO, BPC, GK; Critical Reviews - SO, BPC, TK.

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