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Factors affecting response to relapse treatment in multiple sclerosis patients

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ABSTRACT

Aims: Relapses, a hallmark of multiple sclerosis, often lead to functional loss and a decline in quality of life. While the accelerating effect of intravenous methylprednisolone treatment on the recovery from multiple sclerosis relapses is well established, the rates of recovery can vary between relapses. This study aimed to evaluate the responses to intravenous methylprednisolone treatment administered during relapses in multiple sclerosis patients and to investigate the clinical factors and imaging characteristics influencing these responses.

Methods: Patients diagnosed with relapsing-remitting multiple sclerosis who presented within the first 3 weeks of the onset of relapse symptoms were included in the study. Along with the patients' demographic information, disease characteristics, Expanded Disability Status Scale scores during relapses, affected functional systems, and brain and spinal cord magnetic resonance imaging findings were recorded. As relapse treatment, patients were administered 1000 mg/day of intravenous methylprednisolone for 5 days. Expanded Disability Status Scale scores were calculated on the 5th, 15th, and 30th days of treatment. Patients were compared in terms of disease characteristics and imaging findings based on changes in Expanded Disability Status Scale scores before and after treatment on the 30th day.

Results: A total of 50 relapsing-remitting multiple sclerosis patients (13 men and 37 women, mean age 32.5±9.2 years, mean disease duration 4.7±5.3 years) were included in the study. Improvements of varying degrees were observed in half of the patients by the 5th day of treatment and in all patients by the 15th and 30th days. The mean Expanded Disability Status Scale score of the patients before treatment was 3.2±1.0, which decreased to 1.4±0.9 on the 15th day and 0.4±0.6 on the 30th day after intravenous methylprednisolone treatment. In the group with greater improvement (≥3-point reduction in Expanded Disability Status Scale) on the 30th day compared to the group with less improvement (<3-point reduction in Expanded Disability Status Scale), the following were observed: higher pre-treatment Expanded Disability Status Scale scores ($p<0.001$), more frequent involvement of the pyramidal system during relapses ($p<0.001$), a higher number of patients with cerebellar demyelinating lesions on brain magnetic resonance imaging ($p=0.01$), and more frequent infratentorial lesion locations ($p=0.04$).

Conclusion: Our findings demonstrated that symptom improvement on the 30th day of intravenous methylprednisolone treatment was greater than on the 15th day, suggesting that evaluating recovery from relapses before one month may be misleading. Furthermore, it was observed that improvement was more pronounced in relapses accompanied by pyramidal symptoms, which were more severe and disabling.

Keywords: Multiple sclerosis, relapse, methylprednisolone, disability

INTRODUCTION

Multiple sclerosis (MS) is a disease characterized by demyelination, inflammation, and axonal damage in its pathogenesis, exhibiting heterogeneity in various aspects, including histopathology, clinical course, neuroimaging features, and treatment responses. Relapses are a hallmark of MS, and most patients experience a relapsing-remitting course (relapsing-remitting MS, RRMS), which is classified as an active type of disease according to the newly defined classification.[1-3] MS relapses are the clinical manifestation of newly developed demyelinating activity in any segment of the central nervous system or the reactivation of pre-existing demyelinating lesions.[4,5] Relapses often lead to functional impairment and a decrease in the quality of life for patients.

The natural course of most MS relapses include a repair period following the relapse, which achieves clinical remission. The repair phase is slower than the inflammatory phase, with relapses followed by a gradual and variable recovery process lasting weeks to months.[6,7] Especially in the early stages of the disease, the resolution of inflammation and the occurrence of remyelination can result in the complete resolution of relapse-related symptoms. However, in some cases, repeated relapses may lead to limited remyelination and subsequent

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neurodegeneration, resulting in residual deficits and a stepwise progression of disability.[3]

The treatment of MS relapses is important for reducing the recovery time of disability that develops during the relapse and for minimizing the risk of developing permanent disability. Key objectives of relapse treatment include accelerating recovery, alleviating disability, influencing subsequent disease activity, achieving long-term improvement, and minimizing side effects.

In the treatment of MS relapses, the general approach is that mild relapses typically do not require treatment, whereas moderate to severe MS relapses with disabling symptoms are treated with high-dose systemic corticosteroids.[4,5] The efficacy of high-dose intravenous methylprednisolone (IVMP) in treating MS relapses has been well established, and it is recommended as the first-line treatment.[8-10] Corticosteroid therapy has been shown to accelerate the rate of recovery, shorten the duration of relapses, reduce the permeability of the blood-brain barrier, and suppress contrast enhancement in magnetic resonance imaging (MRI).[9,11] While these findings suggest that corticosteroid treatment contributes to a faster resolution of the pathophysiological mechanisms responsible for clinical relapses, data on the degree of recovery remain insufficient. Moreover, information about the characteristics of patients who benefit most from relapse treatment is limited.

This study aimed to evaluate the responses to IVMP treatment administered during relapses in RRMS patients and to identify the clinical and imaging characteristics that influence these treatment responses.

METHODS

Ethical Considerations

The study was initiated with the approval of the Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.03.2015, Decision No: 21/09). Written consent was obtained from all the patients participating in this study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Fifty consecutive patients who fulfilled diagnosis of RRMS based on the 2010 McDonald criteria, with pre-relapse EDSS scores ≤1, and who presented within the first 3 weeks of the onset of relapse symptoms, were prospectively included in the study. Patients with a diagnosis of secondary or primary progressive MS, those with mild relapses not requiring treatment, those with contraindications to corticosteroid therapy, and those with neurological disorders other than MS were excluded from the study.

Patients were included after confirming that their symptoms met the definition of a relapse, which includes new or worsening symptoms lasting at least 24 hours, arising acutely or subacutely, without fever or infection, and accompanied by typical objective findings of MS.

Data Collection

The demographic information of the patients was recorded, including age at disease onset, disease duration, total number of relapses, annual relapse rate, time from relapse onset to initiation of IVMP treatment, EDSS scores during relapse, and the affected functional systems (pyramidal, cerebellar, brainstem, sensory, bowel-bladder, visual, mental). The relapses were categorized as mono- or polysymptomatic.

Findings from contrast-enhanced brain and spinal cord MRI were documented, including plaque locations and contrast enhancement. Demyelinating lesions detected on T2 and FLAIR images were classified by location as juxtacortical, deep white matter, periventricular, corpus callosum, brainstem, cerebellar, or spinal cord. Locations of contrast-enhancing MRI lesions were identified as deep white matter, periventricular, callosal-pericallosal, brainstem, cerebellar, or spinal cord.

Treatment Protocol and Evaluation

All patients received 1000 mg/day IVMP for 5 days, and the time between relapse onset and initiation of treatment was recorded. Patients were assessed on the 5th day of treatment and during follow-up on the 15th and 30th days, with EDSS scores calculated at each evaluation. Patients were compared in terms of disease characteristics and imaging findings based on the changes in their EDSS scores before treatment and on the 30th day post-treatment.

Statistical Analysis

The statistical analysis was performed using the SPSS 22.0 software (Statistical Package for the Social Sciences, version 22.0 for Windows, SPSS Inc., Chicago, IL). The normality of the distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were presented as mean±SD or median (minimum-maximum), and categorical variables were expressed as numbers (%).

For comparisons between groups, the student's T test or Mann-Whitney U test was used for continuous variables, while the Pearson chi-square test was employed for categorical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Fifty RRMS patients (37 females, 13 males; mean age 32.4±9.2 years) were included in the study. The mean disease duration was 4.7±5.3 years. MRI of the brain and spinal cord during the relapse revealed contrast-enhancing lesions in 46 patients (92%). The mean duration from symptom onset to initiation of IVMP treatment was calculated as 9.7±6.2 days. By the 5th day of IVMP treatment, a reduction in EDSS scores was observed in 25 patients, and by the 15th and 30th days, all patients showed a decrease in EDSS scores. The mean EDSS score was 3.2±1.0 before treatment, which decreased to 1.4±0.9 on the 15th day and 0.4±0.6 on the 30th day (**Table 1**).

Comparison of patients based on EDSS score changes (**Table 2**):

By the 30th day, 21 patients showed <3 points reduction in EDSS, while 29 patients had ≥3 points reduction. The group with greater improvement had higher pre-treatment EDSS

Table 1. Demographic and clinical characteristics, brain and spinal cord imaging findings	
	n=50
Age (years)	32.5±9.2
Gender (female/male)	37 (74%)/13 (26%)
Age at disease onset (years)	27.8±7.15
Disease duration (years)	4.7±5.3
Total number of relapses	3.5±2.6
Annualized relapse rate	2.2±2.35
Pre-IVMP EDSS score	3.2±1.0
EDSS score on day 15 post-IVMP	1.4±0.9
EDSS score on day 30 post-IVMP	0.4±0.6
Time from relapse onset to IVMP (days)	9.7±6.2
MRI T2-FLAIR lesion locations	
Juxtacortical	18 (36%)
Deep white matter	31 (62%)
Periventricular	44 (88%)
Corpus callosum	43 (86%)
Brainstem	25 (50%)
Cerebellar	26 (52%)
Spinal cord	32 (64%)
Patients with contrast-enhancing MRI lesions	46 (92%)
Contrast-enhancing lesion locations	
Deep white matter	20 (40%)
Periventricular	25 (50%)
Callosal-pericallosal	6 (12%)
Brainstem	11 (22%)
Cerebellar	8 (16%)
Spinal cord	14 (28%)

IVMP: Intravenous methylprednisolone, EDSS: Expanded Disability Status Scale, MRI: Magnetic resonance imaging

scores (p<0.001), more frequent involvement of the pyramidal system during the relapse (p<0.001), and a higher prevalence of cerebellar demyelinating lesions on brain MRI (p=0.01) and infratentorial lesion localization (p=0.04). Although cerebellar system involvement and total relapse numbers were more frequent in this group, the differences were not statistically significant. No significant differences were observed in the localization of contrast-enhancing MRI lesions between the groups.

The remaining variables, including supratentorial, spinal cord lesions, and contrast-enhanced lesion localizations, showed no significant differences.

DISCUSSION

In our study, all patients demonstrated varying degrees of improvement in relapse symptoms and findings by the 15th and 30th days of IVMP treatment. This could be attributed to most patients being in the early stages of the disease and the natural course of MS, which tends to result in relapse recovery with minimal or no deficits.[6] Additionally, nine patients had disease durations exceeding 10 years but maintained EDSS scores below 3, suggesting they might have a benign form of MS, potentially contributing to better responses to relapse treatment.

The effectiveness of corticosteroid treatment for MS relapses has shown variability across studies. Factors such as individual differences, the definition of recovery, methods and scales used to quantify recovery, and the timing of evaluations significantly influence these results. A meta-analysis reported that patients treated with high-dose steroids had a 0.76-point reduction in EDSS scores after 5-7 days and a 0.85-point reduction after 2-4 weeks compared to placebo.[8] Another meta-analysis noted that high-dose steroids reduced the non-recovery rate by 0.2 at five weeks post-treatment compared to placebo.[9] The NARCOMS study, which retrospectively evaluated 4,238 patients through self-reporting, found that one month after corticosteroid treatment, 40% of patients reported improvement, 25% noted no change, and 35% experienced worsening of symptoms. Among those treated with IVMP, 51% reported improvement compared to 47% in the oral corticosteroid group.[12]

In our study, EDSS score reductions were greater on the 30th day of IVMP treatment compared to the 15th day. While improvements were observed in half of the patients by the 5th day, these changes were less pronounced compared to the subsequent evaluations. These findings suggest that evaluating relapse recovery at one month may provide a more accurate assessment than earlier evaluations at 15 days. However, the extent to which spontaneous remission influenced our results remains uncertain. Most MS relapses, regardless of treatment, exhibit varying degrees of spontaneous recovery. This natural course, combined with the heterogeneity of relapse phenotypes, makes it challenging to distinguish the specific contributions of any given treatment.[6]

The duration of maximum improvement and recovery processes after relapses have been investigated in various studies. It has been reported that at least a one-point reduction in EDSS scores occurred in 44% of patients by the 1st month, 56% by the 3rd month, and 52% by the 6th month following corticosteroid treatment.[13] Another study found recovery rates of 78% at three months and 86% at six months post-relapse.[14]

In our study, no correlation was found between the duration from relapse onset to the initiation of IVMP treatment and treatment response. Although earlier treatment (within one week of symptom onset) is generally considered more effective, there is no direct evidence supporting this. Some studies suggest that treatment initiated within 1-2 months of relapse onset can still be effective.[4,13]

Patients with higher EDSS scores during relapses demonstrated greater improvement by the 30th day of IVMP treatment. This aligns with previous findings indicating that moderate to severe relapses are more likely to show significant recovery after corticosteroid treatment.[13] Our study also found that patients with pyramidal system involvement during relapses experienced greater improvement, suggesting that this could be a predictor of better treatment response.

Interestingly, while pyramidal, brainstem, cerebellar, and sphincter involvement are associated with poor prognosis,

Table 2. Comparison of demographic and clinical characteristics, MRI findings based on EDSS score changes			
	EDSS reduction <3 points (n=21)	**EDSS reduction ≥3 points (n=29)**	**p**
Age	33.2±10.2	32.0±8.6	0.67
Gender (female/male)	16 (76.2)/5 (23.8)	21 (72.4)/8 (27.6)	0.86
Age at disease onset (years)	28.9±8.7	27.1±5.8	0.40
Disease duration (years)	2 (1-16)	3 (1-23)	0.47
Total number of relapses	2 (1-14)	3 (1-10)	0.06
Annualized relapse rate (n/disease duration)	2 (0.5-8)	1.3 (0.25-12)	0.42
Pre-IVMP EDSS score	2 (2-3.5)	3.5 (3-6)	<0.001
Post-IVMP day 30 EDSS score	0 (0-2)	0.5 (0-2)	0.16
Duration from relapse onset to IVMP initiation (days)	10 (2-20)	7 (2-20)	0.72
Functional systems affected during relapse			
Pyramidal	10 (47.6)	25 (86.2)	<0.001
Cerebellar	4 (19)	13 (44.8)	0.06
Brainstem	7 (33.3)	8 (27.6)	0.66
Sensory	14 (66.7)	21 (72.4)	0.66
Bowel-bladder	7 (33.3)	11 (37.9)	0.74
Visual	5 (23.8)	9 (31)	0.57
Mental	4 (19)	7 (24.1)	0.67
Relapse symptoms			
Monosymptomatic	6 (28.6)	3 (10.3)	0.10
Polysymptomatic	15 (71.4)	26 (89.7)	
MRI T2-FLAIR demyelinating lesion locations (number of patients)			
Juxtacortical	8 (38.1)	10 (34.5)	0.79
Deep white matter	13 (61.9)	18 (62.1)	0.39
Periventricular	18 (85.7)	26 (89.7)	0.5
Corpus callosum	18 (85.7)	25 (86.2)	0.64
Brainstem	8 (38.1)	17 (58.6)	0.15
Cerebellar	6 (28.6)	20 (69)	0.01
Spinal cord	12 (57.1)	20 (69)	0.39
Supratentorial MRI lesions	21 (100)	29 (100)	-
Infratentorial MRI lesions	11 (52.4)	23 (79.3)	0.04
Spinal cord MRI lesions	12 (57.1)	20 (69)	0.39
Number of patients with contrast-enhancing MRI lesions	19 (90.5)	27 (93.1)	0.74
Contrast-enhancing MRI lesion locations (number of patients)			
Deep white matter	8 (42.1)	12 (44.4)	0.88
Periventricular	8 (42.1)	17 (63)	0.16
Callosal-pericallosal	2 (10.5)	4 (14.8)	0.67
Brainstem	7 (36.8)	4 (14.8)	0.09
Cerebellar	2 (10.5)	6 (22.2)	0.3
Spinal cord	6 (31.6)	8 (29.6)	0.89
Supratentorial contrast-enhancing lesion	14 (73.7)	23 (85.2)	0.33
Infratentorial contrast-enhancing lesion	8 (42.1)	10 (37)	0.73
Spinal cord contrast-enhancing lesion	6 (31.6)	8 (29.6)	0.89

MRI: Magnetic resonance imaging, IVMP: Intravenous methylprednisolone, EDSS: Expanded Disability Status Scale

sensory and visual system involvement is linked to better prognosis.[17] This highlights that the effects of IVMP on relapse remission may differ from these prognostic factors. Prognostic factors such as age, gender, disease duration, annualized relapse rate, and mono- or polysymptomatic findings did not correlate with treatment responses in our study.

MRI findings were also evaluated in relation to relapse recovery. Patients with greater improvement on the 30th day of IVMP treatment had more frequent cerebellar demyelinating lesions and infratentorial lesion localization. This suggests that patients with higher infratentorial lesion loads may respond better to relapse treatment. However, no significant relationship was found between contrast-enhancing lesions or their locations and recovery.

Our findings highlight that evaluating relapse recovery before one month may be misleading, as greater improvements were observed on the 30th day compared to the 15th day. Additionally, more severe and disabling relapses, particularly those with pyramidal symptoms, demonstrated greater recovery. Prognostic factors such as age, gender, disease duration, and annualized relapse rate were not associated with treatment responses.

Limitations

Our study has several limitations. First, the patient group evaluated in this study had relatively low pre-attack EDSS scores and mild disability levels, which may have contributed to the generally favorable treatment responses observed during attacks. Another limitation is that treatment responses were assessed only within the first 30 days following an attack; therefore, we could not evaluate long-term treatment outcomes. Additionally, we were unable to assess the impact of spontaneous recovery following an attack on treatment responses. Future studies with larger patient populations may provide more detailed insights into factors influencing treatment response during attacks.

CONCLUSION

This study revealed three key findings on high-dose IVMP for relapses in RRMS. First, although EDSS scores began to improve by day 5, the largest improvements occurred by day 30, showing that assessing recovery before one month may be inaccurate. Second, patients with more severe relapses, indicated by higher pre-treatment EDSS scores and pyramidal involvement, showed greater improvements by day 30, despite having more disabling symptoms at onset. Third, individuals with cerebellar and infratentorial lesions on MRI had better treatment responses. In contrast, age, disease duration, annual relapse rate, and mono-versus polysymptomatic presentations did not significantly affect outcomes. Clinically, these findings underscore the value of evaluating relapse recovery at or beyond one month and highlight that severe relapses and specific MRI features (pyramidal involvement, infratentorial lesions) may predict stronger responses to steroid treatment. Further research could refine our understanding of these patterns and optimize relapse management.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.03.2015, Decision No: 21/09).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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