

# Effect of immunomodulatory drugs on Expanded Disability Status Score in multiple sclerosis-a prospective study

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## ABSTRACT

**Objective:** To evaluate the effectiveness of different immunomodulatory treatments in slowing disability progression in patients with multiple sclerosis (MS), using the Expanded Disability Status Scale (EDSS) over one year.

**Methods:** This prospective observational before-and-after study was conducted at the Neurology Department, Dr. Ruth K. M. Pfau Civil Hospital Karachi, from July 2022 to December 2023. Newly diagnosed, drug-naïve MS patients aged 14-50 years, meeting McDonald criteria, were enrolled and followed for 12 months. EDSS scores were recorded at baseline, 6 months, and 12 months post-treatment initiation. A Pearson correlation analysis was conducted to assess the association between different immunotherapies and EDSS scores at 12 months. Additionally, one-way ANOVA was used to compare EDSS scores across various immunotherapy groups, with post-hoc analyses performed to identify significant pairwise differences.

**Results:** Fifty-six patients (majority aged 20-40 years, predominantly female) completed the study. Immunotherapy significantly reduced mean EDSS scores from baseline (5.49) to 12 months (4.67) (mean difference=0.82;  $p<0.001$ ). However, there was no significant correlation between specific immunotherapies administered and EDSS scores after one year ( $r=-0.022$ ,  $p=0.876$ ). ANOVA revealed no significant differences in EDSS scores among different immunomodulatory agents ( $F(4,50)=0.204$ ,  $p=0.935$ ).

**Conclusion:** Immunomodulatory treatments significantly improved disability outcomes in MS patients over one year. However, no specific agent demonstrated superior efficacy, emphasizing the importance of personalized treatment strategies in managing multiple sclerosis.

**Keywords:** Multiple Sclerosis (MeSH); Expanded Disability Status Scale (Non-MeSH); Immunomodulatory (MeSH); Disability Progression (Non-MeSH); Autoimmune Diseases (MeSH); Immunotherapy (MeSH).

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increments, with higher scores indicating more severe impairment.<sup>3</sup> It evaluates multiple functional domains such as mobility, coordination, vision, and mental status, and is commonly used in both clinical practice and research to monitor disease progression and treatment efficacy.<sup>4</sup>

In recent years, advancements in MS therapies have significantly improved disease management. Treatment strategies include corticosteroids for managing acute relapses, symptomatic therapies targeting spasticity, fatigue, and pain, as well as disease-modifying therapies (DMTs) that aim to reduce relapse frequency and delay disability progression.<sup>5</sup> A relapse is defined as the emergence of new symptoms or worsening of preexisting symptoms lasting over 24 hours and occurring at least 30 days after a previous episode.<sup>6</sup> Current DMTs include injectable agents such as interferon beta-1a and beta-1b, glatiramer acetate; monoclonal antibodies like natalizumab, alemtuzumab, and ocrelizumab; and oral agents such as fingolimod, dimethyl fumarate, and teriflunomide. These medications act by modulating the immune response to prevent further CNS damage. However, patient responses to these therapies vary widely, underscoring the importance of individualized treatment approaches.<sup>7</sup>

Despite substantial evidence supporting the efficacy of immunosuppressive (IMS) and immunomodulatory (IMM) therapies in reducing relapse rates and MRI lesion burden in MS,<sup>8</sup> there is a paucity of data on their long-term effect on disability progression-especially in low-resource settings like Pakistan. Addressing this gap, the present study

## INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disorder characterized by inflammation and progressive demyelination within the central nervous system, primarily affecting the brain and spinal cord. This degeneration leads to significant physical and cognitive disability in affected individuals.<sup>1</sup> The underlying pathology involves lymphocyte activation and clonal expansion of T-cell subpopulations, which play a pivotal role in the immune-mediated attack on myelin sheaths. MS predominantly affects young adults and is more common in females.<sup>2</sup> The

clinical presentation is diverse, with the most frequent initial symptoms including sensory disturbances in the limbs and unilateral vision loss due to optic neuritis, followed by progressive motor deficits and diplopia.

MS manifests in several clinical subtypes, including relapsing-remitting MS, primary progressive MS, secondary progressive MS, clinically isolated syndrome, and progressive-relapsing MS. The most widely validated tool for assessing disability in MS patients is the Expanded Disability Status Scale (EDSS). Developed by John Kurtzke in 1983, the EDSS quantifies disability on a scale from 0 to 10 in half-point

aimed to evaluate the clinical effectiveness of various immunomodulatory treatments by monitoring changes in (EDSS) scores over a 12-month period. Specifically, the study sought to determine whether any particular treatment demonstrated superior outcomes in slowing disease progression. Understanding these effects is essential for assessing functional improvement, informing clinical decision-making, and developing individualized treatment strategies tailored to the local healthcare context.<sup>9</sup>

## METHODS

This prospective, cross-sectional before-and-after study was conducted in the Neurology Department of Dr. Ruth K. M. Pfau Civil Hospital, Karachi, over a period of 18 months, from July 2022 to December 2023. Participant enrollment occurred during the first six months of the study. Each patient was followed for 12 months from the time of enrollment, allowing the final participant enrolled in month six to complete their follow-up at the 18-month mark. Ethical approval was obtained from the Institutional Review Board of Dow University of Health Sciences (IRB - 2414/DUHS/Approval/2022/855).

EDSS was used to assess disability at three time points: baseline (at enrollment), 6 months, and 12 months post-treatment. Patients' therapeutic responses were monitored over the one-year follow-up period.

Eligible participants were drug-naïve, newly diagnosed MS patients aged 14 to 50 years, classified according to the McDonald criteria. All clinical subtypes, including relapsing-remitting, primary progressive, secondary progressive, and clinically isolated syndrome, were included in the study. Patients who were pregnant, immunocompromised, had coexisting neurological or psychiatric conditions, or were already receiving immunomodulatory therapy were excluded.

Treatment efficacy was evaluated by comparing EDSS scores before and after immunotherapy using a paired t-test. A Pearson correlation analysis assessed the association between specific immunotherapies and EDSS

scores at 12 months. Additionally, one-way ANOVA was used to compare outcomes across different immunomodulatory treatments, with post-hoc tests applied to identify any statistically significant pairwise differences.

## RESULTS

Among the 56 participants most of the patients were in the 20 to 40 years of age and female were in higher number than the males as shown in Figure 1. The statistical analysis conducted on the dataset revealed several key findings. The paired t-test indicated a statistically significant reduction in EDSS scores from onset (mean=5.49) to 12 months' post-immunotherapy (mean=4.67), with a significant correlation ( $r=0.620$ ,  $p<0.001$ ) and a significant mean difference (mean difference=0.82,  $t(54)=4.051$ ,  $p<0.001$ ) (Table I & Figure 2). However, the relationship between

the administered immunotherapy and EDSS scores after 12 months was statistically insignificant ( $r=-0.022$ ,  $p=0.876$ ). The ANOVA comparing EDSS scores across different immunotherapies shows no significant difference ( $F(4, 50)=0.204$ ,  $p=0.935$ ), and post-hoc tests confirm no significant pairwise differences (Table II & Figure).

## DISCUSSION

The findings from this study highlight the effectiveness of various immunomodulatory drugs in reducing disability progression in MS patients, as assessed by the EDSS. Previous studies have consistently demonstrated the benefits of immunomodulatory therapies in managing MS. For instance, interferon beta has been shown to decrease relapse rates and delay disability progression in patients with relapsing-remitting MS.<sup>10</sup> Similar advantages have been noted for

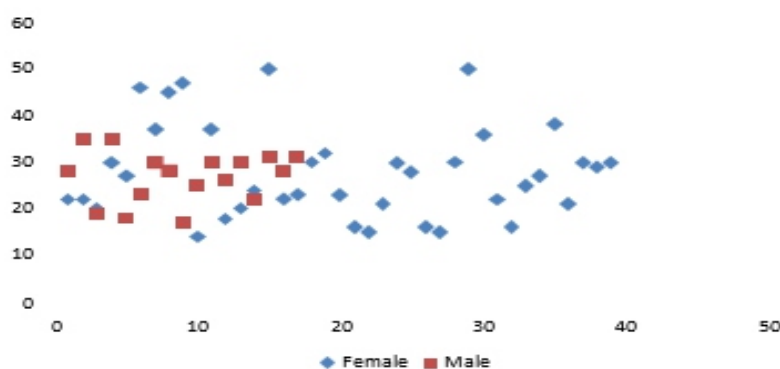


Figure 1: Age and Gender distribution of the participants

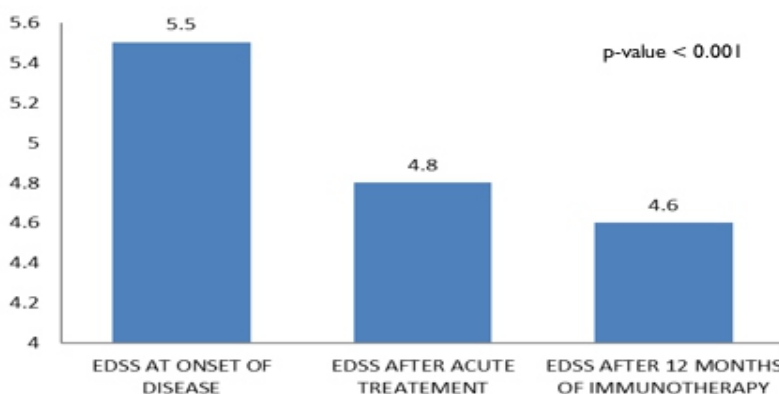


Figure 2: Change in Mean Expanded Disability Status Scale scores (EDSS) over 12 months post-immunotherapy

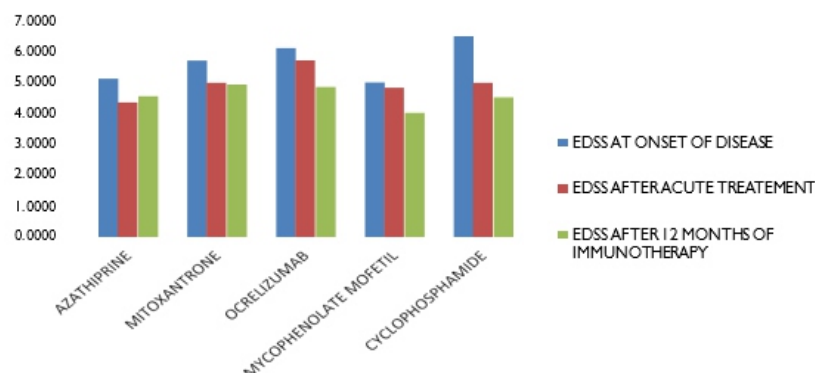


Figure 3: Comparison of EDSS score changes over time for different immunomodulatory treatments in multiple sclerosis patients

**Table I: Comparison of Expanded Disability Status Scale scores at baseline, post-acute treatment, and after 12 months of immunotherapy across different drugs in multiple sclerosis patients**

| Drug name             | EDSS                             | Mean  | SD    | p-value |
|-----------------------|----------------------------------|-------|-------|---------|
| Azathioprine          | At onset of disease              | 5.120 | 1.386 | <0.000  |
|                       | After acute treatment            | 4.360 | 1.923 |         |
|                       | After 12 months of immunotherapy | 4.542 | 2.349 |         |
| Mitoxantrone          | At onset of disease              | 5.706 | 1.480 | <0.000  |
|                       | After acute treatment            | 5.000 | 1.311 |         |
|                       | After 12 months of immunotherapy | 4.911 | 1.563 |         |
| Ocrelizumab           | At onset of disease              | 6.111 | 1.024 | <0.000  |
|                       | After acute treatment            | 5.722 | 0.905 |         |
|                       | After 12 months of immunotherapy | 4.833 | 1.299 |         |
| Mycophenolate mofetil | At onset of disease              | 5.000 | 2.646 | <0.000  |
|                       | After acute treatment            | 4.833 | 2.646 |         |
|                       | After 12 months of immunotherapy | 4.000 | 1.732 |         |
| Cyclophosphamide      | At onset of disease              | 6.500 | 1.443 | <0.000  |
|                       | After acute treatment            | 5.000 | 1.642 |         |
|                       | After 12 months of immunotherapy | 4.500 | 1.871 |         |

EDSS: Expanded Disability Status Scale

glatiramer acetate, which has also been associated with a favorable safety profile.<sup>11</sup> Although monoclonal antibodies such as natalizumab and ocrelizumab carry a higher risk of side effects, they have demonstrated considerable efficacy in reducing disease activity and progression.<sup>12,13</sup> Our study corroborates the conclusion that ocrelizumab significantly reduced EDSS scores over a 12-month period.

Targeting CD20-positive B cells, ocrelizumab has proven especially beneficial in slowing the progression of both relapsing-remitting and primary progressive MS.<sup>14</sup> The observed decline in EDSS scores from 6.11 at baseline to 4.83 after one year reinforces the strong effectiveness reported in earlier research. Notably, our cohort also exhibited a positive response to mitoxantrone. Although typically

reserved for aggressive forms of MS due to its potential cardiotoxicity and risk of secondary malignancies, our findings suggest that Mitoxantrone can be effective in managing severe disease manifestations, as evidenced by significant reductions in EDSS scores from 5.71 at onset to 4.91 after 12 months. This aligns with previous reports of significant improvements in patients with worsening relapsing-remitting and secondary progressive MS.<sup>15,16</sup>

Azathioprine, another drug evaluated in our study, demonstrated moderate effectiveness, with EDSS scores decreasing from 5.12 to 4.54. Although classified as an older immunosuppressant with a slower onset of action, our findings suggest it may still have a role in certain patient populations, particularly where newer therapies are cost-prohibitive or unsuitable due to comorbidities.<sup>17</sup> The use of mycophenolate mofetil, although less common in the treatment of MS, exhibited promise in recent years. Our observations indicated a reduction in EDSS scores from 5.00 to 4.00, suggesting significant improvement. Primarily used in organ transplantation, mycophenolate mofetil immunomodulatory properties may also benefit MS patients, as supported by a small-scale study reporting similar findings.<sup>18</sup> Cyclophosphamide's effectiveness in our study, reducing EDSS scores from 6.50 to 4.50, reflects its application in severe, refractory MS cases. As an alkylating agent, cyclophosphamide is utilized when other therapies fail, with prior studies emphasizing its benefits in highly active MS.<sup>19</sup>

Despite the promising results, our study emphasizes the importance of individualized treatment strategies in MS management. Given the variability in patient responses to immunomodulatory therapies, it is vital for clinicians to consider individual patient characteristics, such as disease phenotype, severity, comorbidities, and treatment history when making therapeutic decisions. This aligns with the personalized medication strategies endorsed by the latest MS management guidelines.<sup>1</sup> Our research adds to the extending assemblage of proof

**Table II: Post-Hoc comparison of mean Expanded Disability Status Scale scores score differences between immunotherapies at 12 months of follow-up in multiple sclerosis patients**

| Primary Drug Name     | Other drugs for comparison | Mean Difference | Std. Error | p-value | 95% Confidence Interval |             |
|-----------------------|----------------------------|-----------------|------------|---------|-------------------------|-------------|
|                       |                            |                 |            |         | Lower Bound             | Upper Bound |
| Azathioprine          | Mitoxantrone               | -0.370          | 0.612      | 0.974   | 2.1006                  | 1.3604      |
|                       | Ocrelizumab                | -0.292          | 0.754      | 0.995   | -2.4254                 | 1.8421      |
|                       | Mycophenolate mofetil      | 0.542           | 1.182      | 0.991   | -2.8013                 | 3.8846      |
|                       | Cyclophosphamide           | 0.042           | 1.419      | 1.000   | -3.9761                 | 4.0594      |
| Mitoxantrone          | Azathioprine               | 0.370           | 0.612      | 0.974   | -1.3604                 | 2.1006      |
|                       | Ocrelizumab                | 0.078           | 0.796      | 1.000   | -2.1720                 | 2.3288      |
|                       | Mycophenolate mofetil      | 0.912           | 1.208      | 0.942   | -2.5068                 | 4.3304      |
|                       | Cyclophosphamide           | 0.412           | 1.442      | 0.998   | -3.6691                 | 4.4926      |
| Ocrelizumab           | Azathioprine               | 0.292           | 0.754      | 0.995   | -1.8421                 | 2.4254      |
|                       | Mitoxantrone               | -0.078          | 0.795      | 1.000   | -2.3288                 | 2.1720      |
|                       | Mycophenolate mofetil      | 0.833           | 1.286      | 0.966   | -2.8060                 | 4.4727      |
|                       | Cyclophosphamide           | 0.333           | 1.508      | 0.999   | -3.9342                 | 4.6009      |
| Mycophenolate mofetil | Azathioprine               | -0.542          | 1.181      | 0.991   | -3.8846                 | 2.8013      |
|                       | Mitoxantrone               | -0.912          | 1.208      | 0.942   | -4.3304                 | 2.5068      |
|                       | Ocrelizumab                | -0.833          | 1.286      | 0.966   | -4.4727                 | 2.8060      |
|                       | Cyclophosphamide           | -0.500          | 1.761      | 0.999   | -5.4834                 | 4.4834      |
| Cyclophosphamide      | Azathioprine               | -0.042          | 1.419      | 1.000   | -4.0594                 | 3.9761      |
|                       | Mitoxantrone               | -0.412          | 1.442      | 0.998   | -4.4926                 | 3.6691      |
|                       | Ocrelizumab                | -0.333          | 1.508      | 0.999   | -4.6009                 | 3.9342      |
|                       | Mycophenolate mofetil      | 0.500           | 1.761      | 0.999   | -4.4834                 | 5.4834      |

EDSS: Expanded Disability Status Scale

supporting the adequacy of different immunomodulatory prescriptions in the treatment of MS. The way that all treatment bunches showed significant reductions in EDSS scores confirms the significance of these mediations in treating this disease. As the relationship of MS with different disorders is being established, future research ought to investigate a variety of factors, such as the efficacy of combination therapies, the optimization of treatment protocols, and the identification of biomarkers that correlate with favorable treatment outcomes.<sup>20</sup>

### Limitations of the study

This study has several li-mitations that should be acknowledged when interpreting the findings. Firstly, it was an observational study with a relatively

small sample size, which may have limited the statistical power to detect differences between treatment groups. Secondly, there was no randomization in treatment allocation; patients with more severe disease were more likely to receive biologics, while those with milder disease often received conventional therapies such as azathioprine. This treatment bias may have influenced outcome comparisons. Thirdly, the use of the Expanded Disability Status Scale (EDSS) as the sole outcome measure may have limited sensitivity in detecting subtle or early treatment effects, particularly in relapsing forms of MS. Lastly, as this study reflects real-world clinical practice over a relatively short time period of one year, the findings may not mirror outcomes from controlled

clinical trials, and should therefore be interpreted with caution. Further large-scale, prospective studies are needed to validate these observations.

### CONCLUSION

This study demonstrated that immunomodulatory therapies are effective in reducing disability progression in MS patients, as evidenced by a statistically significant improvement in EDSS scores over a 12-month period. While all treatments contributed to clinical improvement, no individual immunotherapy showed statistically superior efficacy over others. These findings highlight the importance of early initiation of immunotherapy and highlight the need for a personalized approach in MS



management. In resource-limited settings like Pakistan, where access to advanced therapies may be constrained, the observed benefit across various treatment options is encouraging and supports the continued use of available immunomodulatory agents in slowing disease progression. Further longitudinal studies with larger sample sizes are warranted to confirm these findings and guide treatment optimization strategies.

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### AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

**SRU:** Conception and study design, drafting the manuscript, approval of the final version to be published

**SMS:** Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

**WJ, QUN & NNS:** Conception and study design, acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

**WF:** Analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

*Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

### CONFLICT OF INTEREST

The authors declared no conflicts of interest, financial or otherwise, that could compromise the integrity, objectivity, or validity of their opinions.

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### DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request



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