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Rituximab as an off Label, High Efficacy Therapy in the Treatment of Multiple Sclerosis and Related Central Nervous System Demyelinating Diseases: Single Centre Experience and Literature Review

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Abstract

Objective: Rituximab has emerged as a promising off-label drug for multiple sclerosis (MS) and related demyelinating diseases of the central nervous system. Despite its exclusion from further development for MS treatment, it continues to be used clinically due to its cost-effectiveness compared with approved therapies. However, the optimal dosing and treatment intervals remain variable and non-standardised. This study aimed to share our experience of treating demyelinating disorders with rituximab, focusing on our treatment protocol and safety data.

Methods: This retrospective, single-centre observational study evaluated adult patients diagnosed with MS and related demyelinating disorders who received rituximab. The treatment protocol included a loading dose of 1 g rituximab, administered as two 500 mg doses two weeks apart, followed by maintenance dosing of 500 mg every six months. An exception was made for patients with neuromyelitis optica spectrum disorder (NMOSD), who received 1 g two weeks apart, then 1 g every six months. The primary outcomes included changes in disability scores from baseline to the last follow-up and the incidence of adverse events.

Results: A total of 102 patients received rituximab, the majority of whom were female (70%), with a mean age of 32 years. The reduction in disability scores after treatment was statistically significant, with mean scores improved from 2.65 (SD: 1.35) to 1.76 (SD: 2.08) ($P = 0.013$). Most patients (86.27%) experienced no adverse effects. The most common side effect was recurrent urinary tract infections (8.82%), followed by allergic reactions and one case of meningitis. Treatment was discontinued in 9.80% of patients. Also, because of its favorable cost-effectiveness profile, it offers a feasible and affordable treatment option that is especially appropriate for use in environments with limited resources.

Conclusion: Rituximab, administered at a moderate dose (500 mg every six months), proved to be effective and safe. It may represent an excellent treatment option in resource-limited settings. However, further studies are needed to standardise the optimal rituximab dosing strategy that balances efficacy and safety.

Keywords: Rituximab, multiple sclerosis, demyelinating disorders, neuromyelitis optica spectrum disorder

Introduction

Growing evidence indicates that B cell depletion is a safe and effective therapeutic option for managing multiple sclerosis (MS) and other autoimmune diseases. Over a decade ago, an inaugural randomised controlled phase II trial of an anti-CD20 antibody (rituximab) showed significant efficacy in treating multiple sclerosis.[1,2] Rituximab was excluded from further development programmes for relapsing-remitting multiple sclerosis (RRMS); however, other B-cell depleters (e.g., ocrelizumab, ofatumumab, and ublituximab) have been approved for multiple sclerosis treatment.[3–5]

Rituximab continues to be used off-label in many areas around the world due to its cost profile and accessibility. Despite being off-label, it has demonstrated strong clinical efficacy, especially in reducing relapse rates and subsequently stabilising disability progression.[1] Rituximab is regarded as a viable therapeutic option in regions where access to approved, high-efficacy standard medication is limited.[6] Several studies have demonstrated that rituximab has a higher efficacy than approved platform therapies such as dimethyl fumarate.[7,8]

Recently there has been a growing emphasis on initiating high-efficacy treatments early in the disease course. This has been clearly recommended in the Saudi consensus recommendation for the treatment of MS and the Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS) guidelines.[9,10] The rising costs of healthcare services necessitate the provision of effective treatments at cost-effective rates. Given its comparable efficacy to that of approved high-efficacy treatments such as ocrelizumab and natalizumab, rituximab is often favoured for its significantly lower cost.[11,12]

Rituximab is therefore increasingly used in resource-limiting settings as a cost-effective option for treating chronic diseases such as MS and other central nervous system autoimmune diseases, such as neuromyelitis optica spectrum disorder (NMOSD). Consequently, the World Health Organization (WHO) has added rituximab to the essential medications list for MS, alongside glatiramer acetate and cladribine.[13]

Rituximab has been used extensively in MS treatment; however, treatment protocols vary widely. The standard regimen consists of 1000 mg for induction and 500–1000 mg for maintenance; however, some studies have investigated alternative dosing strategies.[14–17] One study had examined the administration of 100 mg weekly for three consecutive weeks as an induction dose, followed by 100 mg every 6–12 months for maintenance purposes.[18] The low-dose regimen demonstrated cost-effectiveness and good tolerability, particularly in patients with limited access to higher doses.[7,19] Several studies have used weight-based dosing, specifically 375 mg/m² weekly for

four weeks, which is equivalent to the dosing regimen used for rituximab in other approved indications, including non-Hodgkin's lymphoma.[17,19,20] Recent studies have investigated the possibility of extending the maintenance interval beyond six months, with evidence indicating that rituximab may remain effective despite considerable B cell repopulation.[21,22] Despite the well-documented therapeutic benefits of rituximab, its real-world dosing practices remain heterogenous, and guidance on optimised low-cost regimens is limited.[23,24]

This study aimed to present our centre's experience using rituximab for MS and related demyelinating disorders, with a focus on the treatment protocol and safety profile in a real-world clinical setting.

Materials and Methods

Study Design and Setting

This retrospective, single-centre, observational study was conducted at King Abdulaziz University Hospital, a tertiary care facility in Jeddah, Saudi Arabia. This study assessed adult patients diagnosed with MS and related demyelinating disorders, who received rituximab therapy between January 2016 and January 2025.

Study Population

Patients were included if they met the following criteria: (1) aged ≥18 years; (2) had a confirmed diagnosis of all types of MS: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and other demyelinating disease such as NMOSD, myelin oligodendrocyte glycoprotein-associated disease (MOGAD), or autoimmune encephalitis (AE); and (3) received at least one cycle of rituximab therapy during the study period. Patients with incomplete medical records or unclear diagnostic classifications were excluded.

The rituximab treatment protocol involved a loading dose of 1 g (administered as two 500 mg infusions spaced two weeks apart), followed by 500 mg maintenance every six months. For patients with NMOSD, due to the nature of severe relapses, the loading dose was 2 g (two 1-gram infusions two weeks apart), followed by 1 g every six months for maintenance.

Data Collection

Data were extracted from electronic medical records and pharmacy databases using standardised data collection sheets. Demographic information (age and sex), disease characteristics (type and duration), previous exposure to disease-modifying therapy (DMT), rituximab treatment duration, and clinical outcomes, including Expanded Disability Status Scale (EDSS) scores before and after therapy, were recorded. Adverse events, discontinuation rates, and pretreatment infection screening results (hepatitis B core antibody and tuberculosis testing) were also documented.

Outcomes

The primary outcomes were changes in the EDSS from baseline to the last recorded follow-up and the proportion of patients experiencing adverse events. Secondary outcomes included the proportion of treatment-naïve versus previously treated patients, types of prior DMTs, and treatment duration.

Statistical Analyses

Descriptive statistics were used to summarize demographic and clinical characteristics, including means, standard deviations (SD), ranges, and proportions. To assess the change in disability status before and after rituximab treatment, the Expanded Disability Status Scale (EDSS) scores were compared using a **paired Student's *t*-test**. A ***P*-value less than 0.05** was considered statistically significant. All statistical analyses were performed using **IBM SPSS Statistics for Windows, version 28.0** (IBM Corp., Armonk, NY, USA).

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of King Abdulaziz University Hospital (Approval No. HA-02-J-008). Given the retrospective design of the study, which involved the analysis of de-identified data collected during routine clinical care, the IRB waived the need for informed consent.

Results

To provide a global perspective on rituximab dosing practices, we first reviewed major studies using standardised outcome metrics (e.g., ARR, EDSS changes, and follow-up duration), as summarised in Table 1. Rituximab treatment protocols varied across nine international studies. For example, induction regimens ranged from low-dose weekly infusions (e.g., 100 mg weekly in China) to high-dose biweekly infusions (e.g., 1 g on Days 1 and 15 in Mexico, Lebanon, and others), with maintenance dosing every 6 to 12 months. Most studies reported a significant reduction in annualised relapse rate (ARR), with some decreasing to zero. EDSS scores generally improved or remained stable, though occasional worsening was observed in progressive MS cases. Adverse events were mostly mild, with infusion-related reactions being the most common; serious side effects were rare.

In our cohort of 102 patients receiving rituximab therapy had a mean age of 32.41 years (SD: 10.53), ranging from 18 to 65 years. The majority of patients were female (70.59%, $n = 72$), while males accounted for 29.41% ($n = 30$). The mean disease duration was 5.86 years (SD: 4.58), ranging from 1 to 21 years. Figure 1 shows the diagnostic composition of the diagnosis of the cohort. The most common diagnosis was RRMS (70.59%, $n = 72$), followed by NMOSD (15.69%, $n = 16$). Additional diagnoses included SPMS (5.88%, $n = 6$), AE (3.92%, $n = 4$), MOGAD (1.96%, $n = 2$), and PPMS (1.96%, $n = 2$).

Regarding treatment history, 60.78% ($n = 62$) were treatment-naïve, whereas 39.22% ($n = 40$) had previously received DMTs. Among the previously treated (non-naïve) group, prior treatments included interferon (40%, $n = 16$), fingolimod (15%, $n = 6$), ocrelizumab (10%, $n = 4$), dimethyl fumarate (5%, $n = 2$), glatiramer acetate (5%, $n = 2$), and azathioprine (5%, $n = 2$).

The average pre-treatment EDSS score was 2.65 (SD: 1.35), ranging from 0 to 6. As illustrated in Figure 2, the mean EDSS score improved after treatment to 1.76 (SD, 2.08), with a range from 0 to 10. The reduction in EDSS scores after rituximab treatment was statistically significant ($P = 0.013$, paired t-test). No clinical relapses were documented in any

Table 1. **Rituximab treatment protocol from different studies across the world**

Country	Mexico[1]	China[2]	Thailand[3]	Italy[4]	Lebanon[5]	Iran[6]	India[7]	USA[8]	Morco[9]
Year	2022	2023	2023	2020	2018	2020	2020	2016	2024
Number of cases	85	9	10	69	89	99	80	285	50
Rituximab dose	**Induction**: 1 g on Day 1 and Day 15 **Maintenance**: 500 mg to 1 g every 6 months	**Induction**: 100 mg weekly for 3 consecutive weeks **Maintenance**: 100 mg every 6 months	**Induction**: 1 g followed by another 1 g after 2 weeks **Maintenance**: 1 g every 6 months	**Induction**: 1 g twice with 8-week interval **Maintenance**: 1 g every 6 months	**Induction**: 1 g repeated after 2 weeks **Maintenance**: 1 g every 6 months	**Induction**: 500 mg repeated after 2 weeks **Maintenance**: 500 mg every 6 months	**For RRMS**: 500 mg every 6–12 months **For progressive MS**: 1–2 g every 6 months.	**Induction**: 1 g initially **Maintenance**: 500 mg every 6 months	**For RMS**: 500 mg on Day 1 and Day 15 **Maintenance**: 500 mg every 6–9 months **For progressive MS**: 1 g on Day 1 and Day 15, then 2 g every 6 months
ARR reduction	Reduced from 0.82 to 0.36	Reduced from 1.1 to 0	Reduced from 2.14 to 0	Reduced from 0.75 to 0.36	Reduced from 1.07 to 0.11.	19 relapse during treatment (no mention of ARR)	Reduced from 0.44 to 0.05.	Two patients had 3 clinical relapses (no mention of ARR).	Mean ARR reduced by 0.72.
EDSS change	Mean reduction of 0.25	Mean reduction 2 to 0	Mean reduction 3.25 to 1	1 patient had increased EDSS at 12 months.	remained stable	Mean reduction in RRMS 0.32. EDSS increased in SPMS 0.19.	Improved by a score of 0.5–2.0 in (85%) patients, remained same in (12.5%) and worsened in (2.5%) patients.	Not available.	NO confirmed disability worsening in 86% of the patients.
Side effect	(2.4%) experienced infusion-related mild adverse events.	35 episodes of mild allergic reactions	Not mentioned.	43.5% had infusion-related reactions. 26.3% leukopenia.	25.8% had infusion-related all of which were mild and self-limited.	2 cases have severe allergic reactions. 1 case transient thrombocytopenia.	91% had no side effect. No opportunistic infection or neoplasm	3 patients had febrile neutropenia...	98% had no side effect.

ARR: Annualised relapse rate.

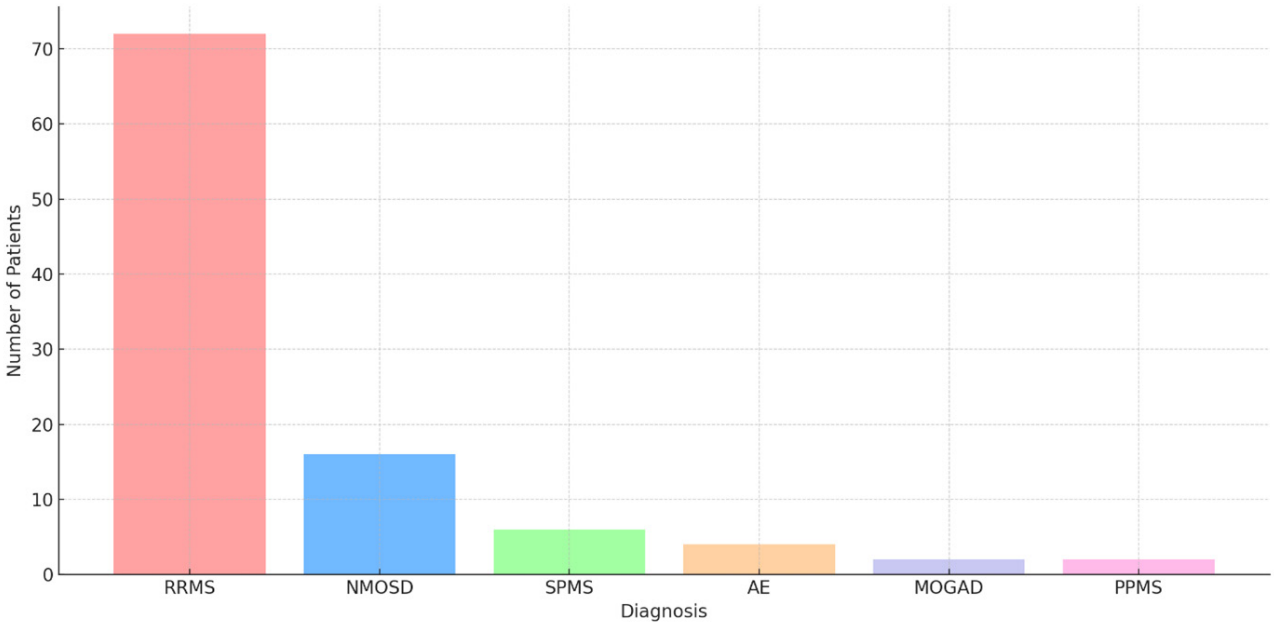

Fig. 1 **Diagnosis Distribution Among Rituximab-Treated Cohort (*n* = 102). RRMS = Relapsing-Remitting Multiple Sclerosis, NMOSD = Neuromyelitis Optica Spectrum Disorder, SPMS = Secondary Progressive Multiple Sclerosis, AE = Autoimmune Encephalitis, MOGAD = Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease, PPMS = Primary Progressive Multiple Sclerosis.**

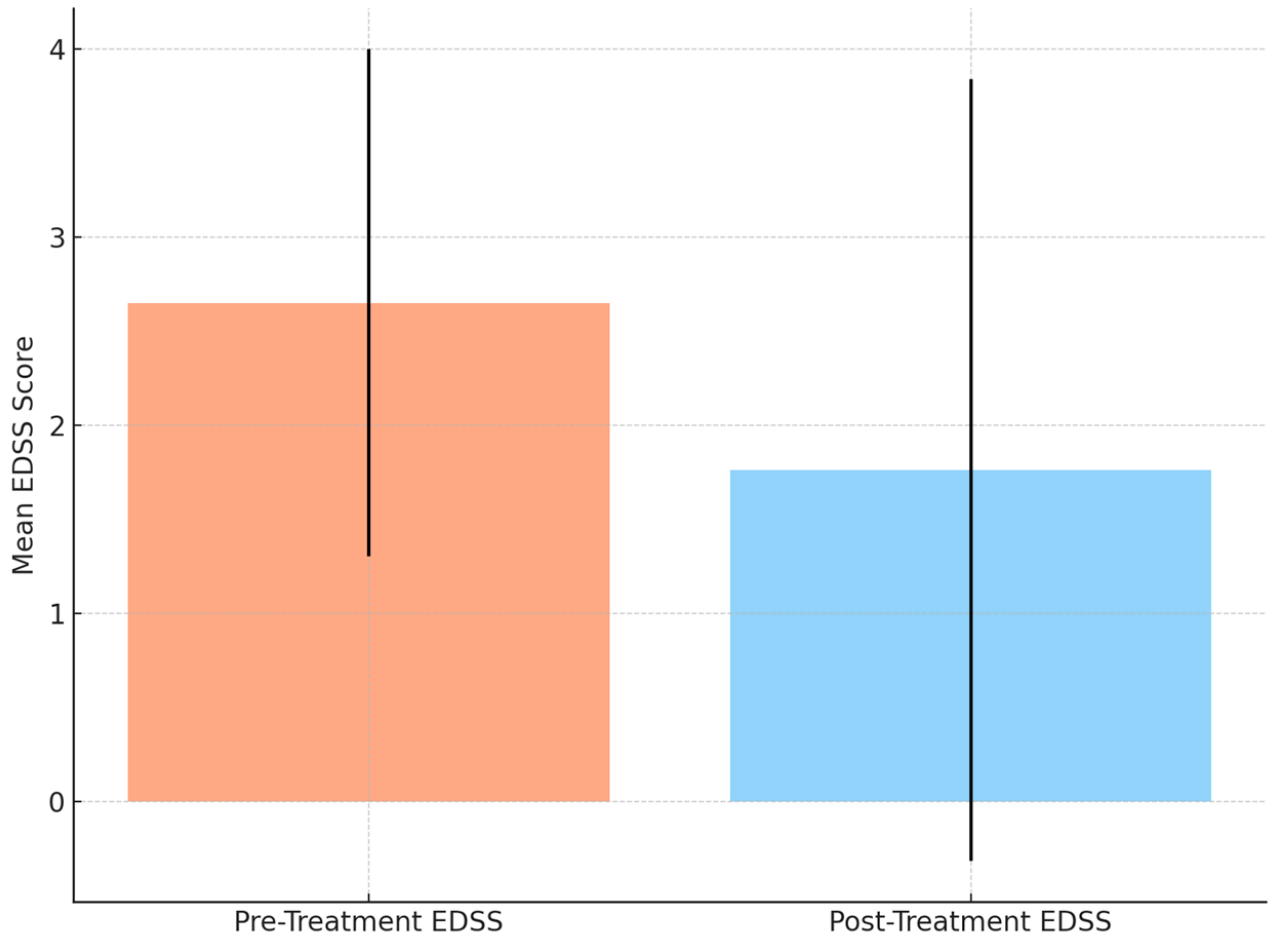

Fig. 2 **EDSS Scores Before and After Rituximab. EDSS = expanded disability status score.**

patients except for one case of MOGAD, who experienced recurrent attacks of optic neuritis, necessitating a treatment switch to other agents. The average treatment duration with rituximab up to 2025 is 4.2 years (SD: 1.81), ranging from 1 to 9 years.

Adverse events were infrequent, with 86.27% (n = 88) of the patients reporting no side effects. Among the remaining patients, recurrent urinary tract infections were most frequently reported (8.82%, n = 9), followed by a single case of fatal meningitis (0.98%, n = 1). Three patients (2.9%; n = 3) had severe allergic reactions to infusions, and one patient had delayed hypersensitivity reactions to rituximab. Treatment discontinuation occurred in 9.80% (n = 10) of the patients due to two cases of severe allergic reactions, one case of MOGAD with recurrent relapses while on treatment, one case of meningitis, and six patients lost to follow-up. Pretreatment infection screening revealed that 7.84% (n = 8) of the patients tested positive for hepatitis B core antibodies (anti-HBc), while 5.88% (n = 6) were positive for tuberculosis.

Discussion

Real-World Efficacy and Tolerability of Rituximab

The safety profile of rituximab in the treatment of MS has been extensively studied. Rituximab, an anti-CD20 monoclonal antibody, is primarily known for its efficacy in depleting B cells, which play a crucial role in the pathogenesis of MS and related demyelinating diseases.[25,26] While its therapeutic benefits are well-documented, especially in off-label use in MS, evaluating its safety and local clinical application remains essential. This cohort study provides additional valuable insights into the real-world use of rituximab for central nervous system demyelinating diseases, particularly MS.

We implemented a moderate-dose rituximab regimen at our centre. Most patients received a 1-gram loading dose administered as two separate 500 mg infusions two weeks apart, followed by 500 mg maintenance doses every six months. An exception was made for patients with NMOSD, who received a higher dose comprising a 1-gram loading dose given two weeks apart, followed by 1 g every six months. This protocol was generally well tolerated, with minimal adverse effects. Treatment efficacy was reflected in the significant reduction in EDSS scores, suggesting disease stabilisation in most patients.

Our results are aligned with previous studies supporting the efficacy of rituximab in reducing relapse rates and slowing disability progression in MS. Recent studies evaluating the efficacy of rituximab in SPMS also observed significant stabilisation of clinical condition and a decrease in the progression of disability, likely due to sustained B cell depletion.[27,28,29] Furthermore, several studies reported that patients receiving rituximab had a lower incidence of new MRI lesions and demonstrated sustained improvements in EDSS scores.[30,31] Together these findings reinforce the role of rituximab as an effective off-label treatment across multiple MS phenotypes. Our data, along with previous research, supports the potential of rituximab to stabilise the disease course across various MS types.[1,8,14]

Rituximab was generally well tolerated in our cohort, as the incidence of adverse events was low. The most commonly reported issues were recurrent simple urinary tract infections, followed by infusion-related hypersensitivity reactions and one rare case of meningitis. These findings align with existing literature reporting high tolerability and low rates of serious complications. Further supporting the safety of rituximab, a systematic review emphasised that, although treatment can lead to adverse effects, serious complications are rare.[20] Moreover, the study pointed out that the benefits of B cell depletion often outweigh the risks associated with treatment.[32] In addition, multiple studies have indicated that infusion-related reactions remain the most common side effects.[8,16,33]

Safety Considerations and Infection Risk Mitigation

Effective pre-treatment screening is essential to minimise latent infections during rituximab therapy. All patients in our cohort were screened for latent hepatitis, tuberculosis, and varicella immunity. Patients who tested positive for hepatitis B were referred to the hepatology clinic for evaluation and management. Those who received rituximab therapy and had no active hepatitis infection but had evidence of prior exposure received appropriate antiviral prophylaxis to minimise the risk of hepatitis B reactivation during treatment. As tuberculosis infection is common in Saudi Arabia, all patients were screened for tuberculosis prior to initiating treatment, and patients who tested positive were referred to infectious disease speciality clinics to assess the risk of starting immunosuppressive therapy and the need for prophylactic treatment. All patients who tested negative for varicella IgG antibodies were offered vaccination before commencing rituximab therapy to prevent varicella-zoster virus reactivation. The varicella vaccine, which contains live attenuated VZV, is recommended for patients who are serologically negative for varicella before starting immunosuppressive therapies such as rituximab. This is crucial because rituximab can lead to B-cell depletion, diminishing the immune response to infections such as VZV, which can result in severe complications like herpes zoster (shingles) or disseminated varicella. Fulminant hepatitis B reactivation has been reported in patients treated with rituximab. Therefore, screening for hepatitis and other latent infections is essential to prevent such fatal complications.[34–39]

Several studies have emphasised the importance of verifying varicella immunity before initiating rituximab therapy, with vaccination at least four weeks in advance to allow sufficient immune priming.[40–42] All immunisations should be up-to-date in newly diagnosed MS patients.[43,44] Live attenuated vaccines should be administered before commencing immunosuppressive therapy, whereas inactivated vaccines such as the influenza vaccine may be given during treatment, although the immune response may be blunted. Therefore, these vaccines should be timed before therapy initiation or at the end of the dosing cycle.[45,46]

Dosing Strategies, Resource Implications, and Study Limitations

The long-term sustainability of rituximab efficacy in managing MS raises important questions regarding the optimal duration of B cell suppression. Recent studies have suggested that extending the maintenance phase to 12 months may not compromise clinical outcomes, even as B cells gradually recover.[22]

This finding has particular relevance in resource-limited settings where treatment affordability and accessibility are critical considerations. In our study, we followed a regimen of 500 mg every six months. Further investigations are needed to determine the minimal effective dose that maintains disease control while avoiding prolonged immunosuppression. Long-term immunologic monitoring (e.g., CD19 counts) could help refine dosing strategies.

In conclusion, the findings of this study contribute to the growing body of evidence supporting rituximab as a safe and effective off-label treatment for MS and related central nervous system demyelinating diseases. Its low adverse event rates and therapeutic benefits make it a viable therapeutic option, particularly in resource-limited settings where access to other high-efficacy treatments may be limited. Future research should explore long-term safety and cost-effectiveness to ensure that patients receive the best possible care tailored to their unique circumstances.

The limitations of this study include its retrospective design, variability in follow-up duration, and the absence of certain data, such as the monitoring of B cell repopulation through CD19 cell counts and the assessment of immunoglobulin levels. These parameters were not included primarily because they were not part of the routine clinical screening protocol at our center during the study period. Additionally, the retrospective nature of the study limited the availability of such data. Including these markers could have enhanced the assessment of immune suppression and infection risk.

Conflicts of Interest

There are no conflicts of interest.

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