ORIGINAL ARTICLE

Efficacy of rituximab in secondary progressive multiple sclerosis: Insights from magnetic resonance imaging and disability assessments

Fereshteh Ashtari[1], Yousef Mokary[2,3], Iman Adibi[1], Vahid Shaygannejad[1], Neda Ramezani[1], Fariba Davanian[1], Maryam Ahmadi[1]

[1]Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Student Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran

Background: Although there are a few options for the treatment of patients with secondary progressive multiple sclerosis (SPMS), rituximab (RTX) is used as an off-label treatment. This study aimed to investigate the efficacy of RTX on disability status and volumetric magnetic resonance imaging (MRI) findings in SPMS. **Materials and Methods:** This study was conducted on 31 patients with SPMS treated with RTX 1000 mg intravenously every 6 months. Expanded Disability Status Scale (EDSS), 25-Foot Walk Test (25-FWT), 9-Hole Peg Test (9-HPT), and brain MRI were performed at the baseline and after 12 months. **Results:** No significant changes were observed in EDSS, timed 25-FWT, and 9-HPT within 12 months of RTX treatment ($P > 0.05$). There was a decrease in 9-HPT time in both the right and left hands, but it was not significant. During the 12-month assessment, white matter (WM) and gray matter volumes decreased by −41.48 ± 2.36 and −31.65 ± 8.84, respectively. However, these differences were not statistically significant ($P > 0.05$). The only significant change was an increase in the volume of deep WM lesions (WMLs) (0.26 ± 0.19 vs. 0.38 ± 0.29, $P = 0.024$). A significant association was found between the EDSS at the 12th month and baseline deep WML volume ($r = 0.383$, $P = 0.044$). **Conclusion:** Our results showed that the level of disability based on EDSS, timed 25-FWT, and 9-HPT did not increase significantly during 12 months of treatment with RTX. These findings suggest that RTX may play a role in disease stabilization and preventing disability progression, especially in the upper limbs. Further studies with larger sample sizes are necessary to confirm this finding.

Key words: Efficacy, magnetic resonance imaging, multiple sclerosis, rituximab

How to cite this article: Ashtari F, Mokary Y, Adibi I, Shaygannejad V, Ramezani N, Davanian F, *et al.* Efficacy of rituximab in secondary progressive multiple sclerosis: Insights from magnetic resonance imaging and disability assessments. J Res Med Sci 2025;30:39.

INTRODUCTION

Multiple sclerosis (MS), which is classified as an autoimmune disorder, is characterized by progressive demyelination in the central nervous system (CNS).[1] Conventionally, CD4+ type 1 helper T cells were considered responsible for the development of MS, and the role of B cells has been neglected in the pathophysiology of MS.[2] In recent years, the role of B cells in MS pathogenesis has been proposed. The B cells contribute to MS development by aiding the T cells in presenting antigens and releasing cytokines.[3] Decreases in B cells have been shown to limit the progression of CNS autoimmune disorders.[4]

Rituximab (RTX) is a monoclonal antibody targeting the fragment antigen-binding (Fab) domains of CD20 B-lymphocytes, reducing the number of B cells in circulation.[5] There has been a growing trend in using RTX as a treatment for MS.[6] It is hypothesized that a B-cell exchange exists through the blood-brain barrier, and RTX may impact the B-cell population in the CNS.[7,8] Given these findings, studies have evaluated RTX in different forms of MS. In relapsing-remitting MS (RRMS), RTX induced reduced white matter lesions (WMLs) and clinical relapses compared to placebo.[2] In another study, RTX failed to slow disease progression in primary progressive MS (PPMS).

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_690_24

Address for correspondence: Dr. Maryam Ahmadi, Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: sm.ahmadi69@gmail.com
Submitted: 06-Dec-2024; **Revised:** 02-May-2025; **Accepted:** 08-May-2025; **Published:** 24-Jul-2025

However, in a specific group of patients (age <51 years), it showed a reduction in disease progression.[9]

Secondary progressive MS (SPMS) is defined by changes in disability, assessed by the Expanded Disability Status Scale (EDSS), and progression of disease severity.[10] EDSS is a standard tool for evaluating disability in SPMS patients.[11] In addition, brain magnetic resonance imaging (MRI) is a sensitive, objective, and quantifiable modality for assessing MS activity in daily practice or research projects. Reduction of gray matter (GM) and white matter (WM) volumes in the brain and development of cortical lesions in MS led to increased disease severity, disability, and lowered quality of life.[12,13] Thus, measuring volumes of brain lesions, GM, and WM can be used to determine prognosis.[13] The existing disease-modifying therapies for MS primarily focus on minimizing the intensity and occurrence of relapses. However, the effectiveness of these treatments is limited in the case of SPMS.[14] The utilization of RTX as an off-label therapy in patients with SPMS has yielded inconclusive outcomes, prompting us to conduct this investigation. This study aimed to explore the impact of RTX on disability progression and changes in MRI parameters after a 12-month treatment.

METHODS

Patients

This study was conducted from January 2019 to October 2020 on 31 SPMS patients referred to the Kashani MS center in Isfahan, Iran. Inclusion criteria were as follows: (1) patients with a definite diagnosis of SPMS according to Lorscheider *et al*.'s criteria[10] (sustained progression of EDSS at least one point during 12 months follow-up); (2) age between 18 and 55 years; (3) EDSS scores between 2.5 and 5.5; (4) utilizing pregnancy prevention methods for women in reproductive ages. Exclusion criteria included the presence of other neurological disorders causing disability, acute relapse within the past 8 weeks, and hypersensitivity to RTX. All eligible patients received 1000 mg RTX (two vials of Zytux® 500 mg/15 ml, produced by AryoGen, Iran) in 500 cc of normal saline 0.9% by intravenous infusion every 6 months. Before each infusion, 100 mg of methylprednisolone and 10 mg of chlorpheniramine were administered.

All patients were visited by an expert neurologist at baseline and after one year. Disability scores, physical function tests, and MRI findings were assessed at each visit.

Clinical assessment

The primary endpoint was clinical disability progression after 12 months, which was evaluated by EDSS score, timed 25-foot walk test (25-FWT), and time to perform 9-hole peg test (9-HPT).

The secondary endpoint was "Changes in the volume of brain lesions on MRI as a marker of disease progression."[15] Patients who experienced an acute relapse were treated with intravenous high-dose methylprednisolone, and clinical evaluations were performed at least 8 weeks after the relapse.

Magnetic resonance imaging acquisition

In this study, MS patients eligible to enter underwent imaging with a Siemens (AVANTO) 1.5 Tesla device.[16] The obtained data were evaluated for visual quality.

Brain analysis

Different types of MRI scans were acquired during the study, each using specific imaging parameters to highlight various tissue characteristics. Among the sequences obtained from the patients, magnetization-prepared rapid gradient echo, a high-resolution T1 sequence, was analyzed for evaluating anatomical structures. The following image acquisition characteristics were used: repetition time (TR) = 2200 ms; echo time (TE) = 2.75 ms; inversion time (TI) = 900 ms; flip angle = 8°; field of view (FOV) = 256 mm × 256 mm; acquisition matrix: 256 by 240; slice thickness = 1 mm; number of slices = 176; and voxel size = 1 mm^3. Fluid-attenuated inversion recovery (FLAIR) images were used to measure the pathology volume. The FLAIR-3D parameters were as follows: TR = 4500 ms; TE = 331 ms; TI = 1800 ms; flip angle = 120°; FOV = 256 mm × 256 mm; acquisition matrix: 256 by 240; slice thickness = 1 mm; number of slices = 176; and voxel size = 1 mm^3.[16] Among the obtained images, proper-quality images were uploaded to the Volbrain website[17] for initial segmentation. This site performs preprocessing on the images first.[18,19] The segmentation process is then done automatically on the images. We used this site for the initial automated measurement of GM, WM, and total brain volume. In addition, the MS lesions' masks (periventricular, juxtacortical, deep WM lesion (DWML), and infratentorial lesions) generated from the segmentation process were extracted from the site for the next processing steps. All masks obtained from the site underwent manual review and editing by an image processing-trained physician using the slice-by-slice method. Another expert repeated this process. Finally, a neuroradiologist proficient in image processing reviewed and manually edited the revised masks.

Ethics statement

All patients independently provided their written informed consent after receiving an explanation of the study protocol. Furthermore, the patients were unable to provide consent; a legal representative provided one on their behalf. The Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran, approved the study (IR.MUI.MED.REC.1400.351).

Statistical analysis

The IBM SPSS Statistics software package (version 19; IBM Corp., Armonk, NY, USA) facilitated data analysis. Continuous variables are described using means and standard deviations; qualitative variables are described using frequencies and percentages. A paired *t*-test was conducted to assess the difference in continuous variables between two-time points. The Chi-square test was also utilized to compare qualitative variables. Spearman's correlation analysis was also used to evaluate the associations between disability measurements and volumetric MRI parameters. A $P < 0.05$ was used to determine statistical significance.

RESULTS

Baseline demographic and clinical characteristics

A total of 31 SPMS patients with a mean age of 39.90 ± 6.91 years were evaluated in our study. Twenty (64.5%) patients were females. The disease duration was 10.58 ± 6.31 years.

The mean weight of patients was 65.87 ± 15.18 kg. None of the patients had significant comorbidity. The family history of MS was positive in four (12.9%) patients. Two (6.5%) patients were smokers, and one (3.2%) was a drug abuser. Before starting RTX, 20 (64.5%) patients were treated with first-line drugs (interferon or glatiramer acetate), and 11 (35.5%) patients with fingolimod.

Disability and motor function assessments

EDSS changed from 3.59 ± 0.83 at baseline to 3.50 ± 0.85 at month 12. The time of 25-FWT increased from 40.41 ± 41.12 at baseline to 41.41 ± 42.28 at the end of the study. The time of 9-HPT at the right and left sides decreased from 43.69±19.67 to 41.38±13.66 and 44.86±17.57 to 43.24±12.83, respectively, without significant difference (p-values > 0.05), as shown in Table 1.

Magnetic resonance imaging measurements

WM and GM volumes decreased by −2.36 ± 41.48 and −8.84 ± 31.65 mm^3, respectively. Total lesion load and periventricular lesion volume increased by 0.64 ± 4.17 and 0.67 ± 3.93 mm^3, respectively. The volume of DWML increased significantly (0.26 ± 0.19 vs. 0.38 ± 0.29 mm^3, $P = 0.024$).

It is worth noting that GM volume changes were more than WM volume alterations (−8.84 vs − 2.36); however, it was not statistically significant [Table 2].

Table 1: Expanded Disability Status Scale, 25- foot walk test, and 9- hole peg test tests at baseline and one-year periods

Parameters	Baseline	After one-year	Change over 12 months	*P*
EDSS	3.59±0.83	3.50±0.85	−0.093±0.636	0.456
25-FWT	40.41±41.12	41.41±42.28	1.00±18.32	0.771
9-HPT (right)	43.69±19.67	41.38±13.66	−2.31±12.23	0.318
9-HPT (left)	44.86±17.57	43.24±12.83	−1.62±11.57	0.457

EDSS: Expanded Disability Status Scale, 25-FWT: 25-Foot Walk Test, 9-HPT: 9-Hole Peg Test; SD=Standard deviation

Correlations between brain magnetic resonance imaging volumetry and motor function or disability assessments

According to Spearman's correlation analysis, baseline DWML volume was directly correlated with EDSS at 12 months ($r = 0.383$, $P = 0.044$). At the end of the study, the right 9-HPT performance time was correlated with WM ($r = −0.489$, $P = 0.007$) and GM ($r = −0.583$, $P = 0.001$) volumes. This correlation was also observed for left 9-HPT performance time with WM ($r = −0.44$, $P = 0.017$) and GM volumes ($r = −0.496$, $P = 0.006$). However, other correlations between MRI parameters and disability assessments were not significant ($P > 0.05$) [Table 3].

DISCUSSION

RTX is commonly employed beyond its intended purpose in treating MS, even though its effectiveness, safety profile, and dosing regimen remain unclear.[20] The efficacy of RTX in RRMS has been investigated in previous studies.[21,22] The effectiveness of RTX in people with a progressive course is uncertain, so more studies are needed. We found that in patients with SPMS treated by RTX, volumes of different brain parts remained stable and did not undergo significant atrophic changes after 12 months. In addition, disability status and motor tests showed no significant difference at 12 months compared to the baseline, indicating functional stability of SPMS patients with the administration of RTX.

Rituximab versus disability assessments

In our patients, all of whom had increased EDSS in the year before the study, no significant disability progression was observed during the one-year study. Consistent with our findings, Airas *et al*. have also reported that mean EDSS has shown no change after RTX administration compared to baseline, and 35% of patients showed no difference in disability score.[23] Naegelin *et al*. have reported that the reduction in EDSS score after RTX treatment has been significant compared to controls. They reported that RTX could significantly delay the time of progression compared to the control group.[24] A study by Boremalm *et al*. found that RTX contributes to long-term control of inflammation and that reactivation of the disease is rare in patients who have discontinued treatment.[25] A systematic review of pre-planned subgroup analyses of the PPMS study found that RTX delayed the time to confirm disease progression.[26] Bribiesca-Contreras *et al*. found that RTX

Table 2: The volumes of brain structures and spinal cross-sectional area of C1–C3 segments in baseline and one-year magnetic resonance imaging scans

MRI parameters	Baseline	After 12 months	Change over 12 months	*P*
Brain white matter volume (mm^3)	399.69±75.22	397.33±65.53	−2.36±41.48	0.753
Brain gray matter volume (mm^3)	634.31±82.15	625.47±73.58	−8.84±31.65	0.130
Total brain lesion load (mm^3)	12.79±9.61	13.44±11.34	0.64±4.17	0.394
Periventricular lesion volume (mm^3)	10.94±8.97	11.61±10.58	0.67±3.93	0.347
Brain deep white matter lesion volume (mm^3)	0.26±0.19	0.38±0.29	0.11±0.27	0.024*

*Significance based on a paired *t*-test. Data were presented as mean±SD. MRI=Magnetic resonance imaging; SD=Standard deviation

Table 3: Correlation of magnetic resonance imaging parameters with disability scale and functional motor tests

MRI parameters	EDSS		25-FWT		9-HPT (right)		9-HPT (left)	
	Baseline	one-year	Baseline	one-year	Baseline	one-year	Baseline	one-year
12 months white matter volume								
r	0.009	0.030	0.129	0.088	−0.423	−0.489	−0.445	−0.440
P	0.964	0.878	0.488	0.650	0.018*	0.007*	0.012*	0.017*
12 months gray matter volume								
r	−0.236	−0.288	−0.193	−0.236	−0.376	−0.583	−0.366	−0.496
P	0.209	0.137	0.298	0.219	0.037*	0.001*	0.043*	0.006*
Baseline total lesion load								
r	0.161	−0.070	0.013	0.037	0.258	0.142	0.359	0.223
P	0.394	0.723	0.945	0.848	0.161	0.462	0.057	0.246
Baseline periventricular lesion								
r	0.183	−0.067	0.035	0.053	0.291	0.155	0.388	0.239
P	0.332	0.734	0.850	0.785	0.113	0.422	0.051	0.212
Baseline deep white matter lesion								
r	0.047	0.383	0.152	0.267	−0.106	0.013	−0.164	−0.067
P	0.805	0.044*	0.414	0.162	0.571	0.947	0.377	0.731

*Significance based on a Spearman correlation analysis. EDSS=Expanded Disability Status Scale; 25-FWT=25-foot walk test; 9-HPT=9-hole peg test; MRI=Magnetic resonance imaging

treatment improved the clinical and radiological symptoms of naive and non-naive MS patients.[27]

Our study showed that motor function tests, including the timed 25-FWT and 9-HPT, remained stable for 12 months after RTX administration. Although there was no significant difference in the timed 9-HPT at baseline and 12-month follow-up, the time of performance of 9-HPT decreased in both arms over the study period. We hypothesize that the small differences could be due to the small sample size and lack of statistical power. Thus, it seems promising that continuing RTX for extended periods may lead to significant improvement of hand function, as measured by 9-HPT.[28] A study of 108 patients with a progressive course receiving RTX indicated that the rate of progression in the 9-HPT at 2 years was similar to that in the EDSS (37.5%) and less than that in 25-FWT (74.1%).[29]

This study supports our findings that RTX could be effective in reducing the progression of upper limb dysfunction and may show greater effects with long-term use.

Rituximab versus magnetic resonance imaging parameters

Volumetric MRI findings showed no significant alterations or atrophic changes developed in SPMS patients 12 months after beginning RTX administration. An exception was the DWML volume, which increased in that period. Still, this finding is not clinically important compared to the beneficial effects of RTX in progression prevention. Unlike our findings, Hawker *et al*. found that RTX-treated patients had a significant increase in T2 lesion volume ($P < 0.001$) compared to controls, while brain volume changes were similar ($P = 0.620$).[9] von Büdingen *et al*. reported nearly complete stabilization of brain WMLs for a decade with anti-CD20 therapy.[7] Hauser *et al*. also reported significantly lower counts of gadolinium-enhancing lesions up to 24 weeks after administration of RTX. Moreover, a significant reduction in the development of new lesions on MRI was noted within that time.[2] A systematic review indicated that, comparing the RTX and placebo groups, the T2 lesion volume increased less after 96 weeks in RRMS.[26] It was observed that the annualized relapse rate and MRI disease activity levels were low during treatment with RTX.[30] Yamout *et al*. found that RTX therapy increased the proportion of patients without new MRI lesions from 18.6% to 92.6% in RRMS and 43.3% to 82% in PMS by the final follow-up.[20] RTX effectively reduces relapse rates and MRI activity in MS patients without causing discontinuation or death.[31]

Magnetic resonance imaging parameters versus disability assessments

The WML load (WMLL) is commonly used as an outcome measurement in MS to assess the inflammatory burden and quantify the neurodegenerative aspects of the disease.[32,33] The cerebral WM regions that exhibit hyperintensity on T2-weighted MRI and hypointensity on computed tomography are commonly recognized as WMLs. WML volumes (WMLV) are classified into two categories: periventricular WMLs and DWML.[34] Previous research has primarily focused on exploring the link between total WML burdens and disability. However, it is deemed necessary to conduct further investigations that exclusively focus on the effects of DWML. According to our findings, EDSS at 12-month follow-up was associated directly with baseline DWML volume in SPMS patients. The inverse correlation between WM volume and lesion load suggests that higher lesion loads may contribute to greater WM atrophy, potentially leading to cognitive decline and disability.[35] Fisniku *et al*. have suggested that WM T2 lesion volumes might rise in parallel with distinct anatomical and mechanistic alterations that occur independently of the factors primarily responsible for long-term disability.[36] In addition, a study conducted with 5-year follow-ups discovered that WM and GM pathology are independent predictors of disability progression as measured by the EDSS.[13] Furthermore, Chung *et al*.'s study with a 30-year follow-up revealed that DWML volume at one-year is strongly predictive of the development of SPMS at 30 years.[37] The study by Treaba *et al*. revealed that WMLL plays a vital role in cortical atrophy development, emphasizing the significance of WM pathology in giving rise to disability.[33] However, another longitudinal study by Treaba *et al*. found no significant associations between WMLV and changes in EDSS scores.[38] This insignificant association could be due to the small sample size and lack of statistical analysis.

Early MS disability may stem mainly from subcortical WMLs, while later stages are driven by cortical pathology and brain atrophy.[39,40] Throughout MS, both WM and GM abnormalities are observed, with the relative dominance of each varying over time. In the early relapsing phases of the disease, the predominance of WMLs is noticeable, while during secondary progression, there is a shift toward a higher GM volume abnormality.[39,41,42] Further research is required to determine any association between GM volume and disability, as no significant correlation was observed in the present study.

Although there was an insignificant correlation between periventricular WML and disability, and we did not assess the entire WMLV, this research emphasized the valuable role of DWML volume in the progression of disability.

Regarding upper limb function, our results indicated that WM and GM volumes at 12 months were negatively associated with timed 9-HPT at baseline and 12 months. Therefore, 9-HPT could be considered a more reliable indicator for evaluating upper limb function and MRI abnormalities. The use of 9-HPT has been recommended with caution in MS settings, particularly for patients with low or high disability levels.[43] Fisniku *et al*. demonstrated that SPMS patients exhibited more GM atrophy compared to RRMS. GM atrophy is more clinically significant over time in MS than lesion load or WM atrophy, as it more closely correlates with long-term disability and disease progression.[44]

Another study by Daams *et al*. revealed that motor dysfunction has a multifaceted composition and cannot be adequately characterized by a solitary neuroimaging marker. Rather, it results from combined pathology in the cerebellum, spinal cord, and corticospinal tract.[45]

The link between physical disability, motor function tests, MRI abnormalities, and the higher risk of brain issues in progressive MS has led to the recommendation that SPMS patients undergo these tests to manage their condition better and prevent further disability progression.

Limitations

Our study had several limitations, which should be resolved in further studies. The first limitation was the relatively short follow-up interval, and the second limitation was the absence of a control group. The small sample size was another limitation of our study that highlighted the need for future studies with larger sample sizes. A key limitation of our study is the reliance on conventional MRI metrics to assess the effects of RTX in MS. While these measures are widely used and provide valuable insights into disease progression, they may not fully capture subtle neuroprotective effects within 12 months. Advanced imaging techniques, such as diffusion MRI or functional connectivity studies, could offer a more comprehensive evaluation of microstructural and network-level changes associated with RTX treatment.

CONCLUSIONS

Based on our findings, RTX may be effective in stabilizing and preventing the progression of disability, brain atrophy, and lesion burden. Furthermore, RTX may improve the performance time of 9-HPT, which highlights the effective role of RTX in maintaining upper limb function. Further studies with greater sample sizes and longer duration are suggested to confirm this finding.

Implication

RTX appears to be a valuable choice for treating SPMS patients, as evidenced by its ability to stabilize disability

progression and MRI markers of disease activity. The observed stability in disability assessments and imaging parameters suggests that RTX may help mitigate further neurological deterioration, offering a potential therapeutic strategy for SPMS management.

Future research

Further investigations are necessary to comprehend the role of RTX fully in the comprehensive care of SPMS.

Acknowledgments

Thanks to the participants of the study and the research deputy of Isfahan University of Medical Sciences for funding the study.

Financial support and sponsorship

This work was supported by the research deputy of Isfahan University of Medical Sciences (code number: 3400222). The funding body has no role in the design of the study, the collection, analysis, and interpretation of data, or in the writing of manuscripts.

Conflicts of interest

There are no conflicts of interest.

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