

# Side Effects of Rituximab in Patients with Multiple Sclerosis

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## Abstract

**Background:** Multiple Sclerosis (MS) is the most common demyelinating inflammatory disease of the central nervous system. Rituximab is an anti-CD20 monoclonal antibody used as a primary drug for MS; however, it can cause injection and post-consumption side effects.

**Objectives:** This study aimed to determine the side effects of rituximab in patients with Multiple Sclerosis.

**Methods:** This descriptive-analytical study focused on MS patients who had received Rituximab and regularly visited Isfahan Multiple Sclerosis clinics in 2021. These patients had received at least two doses of Rituximab (1000 mg), and their symptoms and examinations were documented during face-to-face visits using checklists. The data were analyzed using SPSS version 22.

**Results:** In this study, 150 patients with MS participated. The number of attacks (more than one) before and after using Rituximab was 22% and 4.7%, respectively. The mean EDSS score among them before and after Rituximab was  $3.53 \pm 1.30$  and  $3.66 \pm 1.51$ . 68.7% of the patients showed infusion side effects, such as a sore throat and dyspnea. Moreover, post-consumption side effects included muscle spasm, weight gain, arthralgia, and edema of the extremities.

**Conclusion:** The mean EDSS score before and after using Rituximab showed a slight increase, indicating no significant effects on improving dysfunctions, but the attack rate was reduced.

**Keywords:** Multiple Sclerosis, Rituximab, Side Effects

## 1. Background

Multiple sclerosis (MS), the most prevalent neurological disability, is an autoimmune-mediated disorder that affects the central nervous system (CNS) and often leads to severe physical or cognitive incapacitation as well as neurological problems in young adults.<sup>1</sup> The treatment of MS has changed over the last twenty years.<sup>1</sup> Anti-CD20 monoclonal antibodies, including Ocrelizumab, Rituximab, Ublituximab, and Ofatumumab, are used to treat MS.<sup>2</sup>

In the United States, Rituximab was approved for use in chronic lymphocytic leukemia and lymphoma (non-Hodgkin) in 1997 and was subsequently used in severe autoimmune conditions, such as refractory rheumatoid arthritis, Wegener's granulomatosis (granulomatosis with polyangiitis), and autoimmune diseases.<sup>3</sup>

As Rituximab is clinically well tolerated with serious and rare side effects, it is an attractive treatment option for patients with resistant autoimmune conditions.<sup>4</sup> Based on immunological bases, some treatments and drugs with different levels of efficiency and symptoms have been discovered for MS, which mainly suppress the immune system to maintain the myelin sheath; in this case, the patient may experience a recovery period.<sup>5</sup> Some side effects of these drugs range from mild to severe. The

most common and general side effects of Rituximab include anaphylactic or allergic reactions in 80% to 90% of patients, usually within 30 minutes to 2 hours after the first injection of Rituximab, and they range from mild to life-threatening. Injectable reactions may include fever, hypotension, chills, skin rash, urticaria, acute respiratory distress syndrome (ARDS), ventricular fibrillation, angioedema, shock, anaphylaxis, and death. Infections (bacterial, viral, and fungal) such as JC virus, Varicella-zoster virus, herpes simplex virus, Cytomegalovirus (CMV), hepatitis C, and B infections are also possible.<sup>6</sup>

## 2. Objectives

Several studies have confirmed the high efficacy, safety, low cost, and convenient administration of Rituximab and have regarded it as an interesting option to treat MS in recent years.<sup>7</sup> Since this drug has recently been widely used off-label in Iran and some other countries, the present study aimed to determine the side effects of Rituximab in undertreated patients with MS.

## 3. Methods

This descriptive-analytical study was conducted at the Isfahan MS clinic in 2021 with the ethical code

(IR.MUI.MED.REC.1400.146) from Isfahan University of Medical Sciences.

In this study, 257 patients with MS disease who were treated with Rituximab and had regular visits were included. Patients with MS who provided their consent to participate in the study and had a medical record at the Isfahan MS clinic met the inclusion criteria. Additionally, their MS diagnosis had to be validated by McDonald's diagnostic criteria and approved by a neurologist. It has been one year since their MS was definitively diagnosed, and they have received at least two 1000 mg Rituximab infusions. The exclusion criteria included patients who did not consent to participate in the study.

Out of 257 patients, 150 were eligible to enter the study. The Rituximab treatment protocol at the time involved receiving one gram of Rituximab at the beginning of treatment, followed by another gram after two weeks, and then one gram every 6 months. Before starting the injection, premedication such as Hydrocortisone (250 mg) and Chlorpheniramine (10 mg) was administered. Due to the high incidence of the COVID-19 virus, some patients received only 500 mg of Rituximab instead of the full one-gram dose, or the period between two Rituximab treatments was extended to 7-9 months instead of the usual 6 months.

The eligible patients were contacted via the phone number listed in their documents, and the study's purpose was explained to them. They were requested to visit the clinic on a specified date, with an emphasis that the visit did not require any financial payment. One hundred and fifty of them gave consent to participate. During the face-to-face visit, the patients were examined by a neurologist, and all necessary information about their symptoms and side effects was collected.

A checklist used for data collection had two parts: first, the demographic characteristics such as age, sex,

occupation, and past medical history; and second, the MS disease characteristics including the type of MS disease, the duration of the disease, the first symptom of MS, the drug taken before starting Rituximab therapy, the time the patient was in our care, the number of attacks before and after taking Rituximab, their Expanded Disability Status Scale (EDSS) score one year before and one year after starting Rituximab, Rituximab injection, and post-consumption side effects.

The Expanded Disability Status Scale (EDSS) is a way of measuring how much someone is affected by their MS. Neurologists use it to monitor changes in the level of someone's disability over time. The EDSS has a range from 0 to 10. Scores are in half-unit steps – 3, 3.5, 4, and so on. The greater the level of disability, the higher the score out of ten.

### 3.1. Statistical Analysis

The obtained data were analyzed using SPSS version 22. The quantitative data were described using standard deviation and mean, while the qualitative data were described using distribution and frequency percentages. Statistical analysis was performed using t-tests and chi-square tests.

## 4. Results

A total of 150 MS patients were included in the study, comprising 104 females (69.3%) and 46 males (30.7%). The average age of the participants was  $40.04 \pm 9.18$  years. 48% of the patients were housewives.

The first signs of MS disease in the patients were weakness (31.3%), blurred vision (22%), paresthesia of extremities (20%), imbalance (10.7%), diplopia (10.7%), vertigo (4.7%) and seizure (0.7%). The comorbidities among the MS patients were hypertension (4.7%), diabetes (3.4%), hyperlipidemia (2%) and cancer (0.7%).

**Table 1.** Demographic Characteristics

Variable		N (%)
Sex	Female	104 (69.3)
	Male	46 (30.7)
Age, years, (mean $\pm$ SD)		40.04 $\pm$ 9.18
Work	Housewives	72 (48)
First Signs of MS Disease	Weakness	47 (31.33)
	Blurred Vision	33 (22)
	Paresthesia of Extremities	30 (20)
	Imbalance	16 (10.7)
	Diplopia	16 (10.7)
	Vertigo	7 (4.7)
	Seizure	1 (0.7)
Comorbidities Among the MS Patients	Hypertension	7 (4.7)
	Diabetes	5 (3.4)
	Hyperlipidemia	3 (2)
	Cancer	1 (0.7)
Duration of MS Disease, years, (mean $\pm$ SD)		10.83 $\pm$ 6.53
Duration of MS Disease and Using Rituximab, years, (mean $\pm$ SD)		2.80 $\pm$ 1.59
MS Type	Relapsing-Remitting	82 (54.7)
	Secondary Progressive	53 (35.3)
	Primary Progressive	15 (10)

SD: Standard Deviation; N: Number.

The mean duration of MS disease and use of Rituximab were  $10.83 \pm 6.53$  and  $2.80 \pm 1.59$  years, respectively.

Interferon was the previous medication in 58.7% of the MS patients. The prevalence of MS types was 54.7% Relapsing-

Remitting, 35.3% secondary progressive, and 10% primary progressive (Table 1). 22% of the patients had more than one attack before using Rituximab, and 4.7% of the patients had more than one attack after using Rituximab, with a statistically significant difference in the number of attacks before and after taking Rituximab ( $P = 0.0001 < 0.05$ ).

The mean EDSS scores before and after using Rituximab were  $3.53 \pm 1.30$  and  $3.66 \pm 1.51$ , respectively, with a statistically significant difference between them ( $P = 0.0001 < 0.05$ ). The injection side effects of Rituximab are shown in Table 2. Table 3 shows the side effects of Rituximab that occurred after 48 hours.

**Table 2.** The injection Side Effects of Rituximab

Variable	N (%)
Injection Side Effects of Rituximab	
Sore throat	43 (28.7)
Dyspnea	27 (18)
Headache	14 (9.3)
Nausea	7 (4.7)
Hypotension	5 (3.3)
Chest pain	4 (2.7)
Tachycardia	3 (2)

**Table 3.** Side Effects of Rituximab that Occurred after 48 Hours

Variable	N (%)
Side Effects of Rituximab that Occurred after 48 Hours	
Muscle Spasm	25 (16.7)
Weight Gain	22 (14.7)
Insomnia	21 (14)
Dyspepsia	19 (12.7)
Arthralgia	19 (12.7)
Edema of Extremities	9 (6)
Capillary Leak Syndrome	2 (1.3)
Anemia	10 (6.7)
Hypothyroid	6 (4)
Pneumonia	4 (2.7)
Hypertension	4 (2.7)
Hyperglycemia	3 (2)
Candidiasis	1 (0.7)
Sinusitis	1 (0.7)

## 5. Discussion

In recent years, Rituximab and other anti-CD20 drugs have become the main treatment options, and sometimes the first choice, for MS diseases, not only in relapsing but also in the active progressive types of MS disease. A study was conducted on 150 MS patients (104 female, 46 male) at the Isfahan MS clinic who were treated with Rituximab to evaluate the side effects of Rituximab therapy.

Our evaluation showed that Rituximab therapy significantly reduced the attack rate. Before treatment, the number of attacks was 33 (22%), while after treatment, it decreased to 7 (4.7%). This reduction in attack frequency aligns with findings from a study by Almatrafi et al., which also reported a decrease in yearly recurrence rates for MS patients treated with Rituximab.<sup>8</sup> A study by Patil et al. enrolled 102 patients who were given rituximab, and the mean relapse rate was reduced from 0.8 to 0 for the SPMS group, 2.17 to 0 for the RRMS group, 2.5 to 0.14 for Neuromyelitis Optica Spectrum Disorder (NMOSD), and 3.43 to 1.04 for Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) patients. Furthermore, the mean EDSS score improved in the RRMS group, and there was a non-significant worsening of the EDSS score in the PPMS and PRMS groups. Moreover, 54.8% of SPMS patients showed either unchanged or improved EDSS scores.<sup>9</sup> However, in our study, the mean EDSS scores before and after using Rituximab were  $3.53 \pm 1.30$  and  $3.66 \pm 1.51$ , showing a

slight increase in the EDSS score. This confirms that Rituximab had no significant effect on MS progression and improving disability.

The most common side effects of Rituximab in MS clinical trials are infusion-related reactions, which occur within 30 minutes to two hours of starting the infusion with Rituximab. In our study, 68.7% of patients experienced injection side effects of Rituximab, such as sore throat (28.7%), dyspnea (18%), and headache (9.3%), with no life-threatening events. Roach et al. conducted a study that showed infusion reactions were the most common adverse events in ocrelizumab and Rituximab trials.<sup>10</sup> In another study by Vollmer et al., 6.5% of patients who took Rituximab were hospitalized for infection.<sup>11</sup> Rituximab was shown to have an elevated risk of common infections in MS patients in the randomized controlled trials by Filippini et al., although the absolute risk was minimal, and the data were unclear on the impact of rituximab on major adverse events.<sup>12</sup> Kasi et al., in the review study, showed that the most common reactions (at least 25%) were neutropenia and infusion reactions in patients receiving rituximab monotherapy.<sup>13</sup> Dianhe et al. studied that more patients who received Rituximab had adverse events after the first infusion, such as chills, headache, nausea, pyrexia, and throat irritation.<sup>14</sup>

This study evaluated the most common post-consumption side effects of Rituximab, including muscle

spasms (16.7%), weight gain (14.7%), insomnia (14%), dyspepsia (12.7%), and edema of the extremities (6%). In a study by Cross et al., a patient undergoing Rituximab therapy developed uncomfortable muscle spasms.<sup>15</sup> A case report by Eatemadifar et al. described a 44-year-old man with RRMS who exhibited signs of Cytokine release syndrome (CRS) and bilateral edema of the lower limbs after the last rituximab infusion, along with complaints of generalized arthralgia.<sup>16</sup> Another case report by Fernandez et al. involved a 61-year-old woman with Neuromyelitis Optica (NMO) who was treated with Rituximab and experienced multiple organ failure and capillary leak syndrome (CLS). Episodic capillary hyperpermeability is the cause of CLS.<sup>17</sup> In addition to the two typical CLS patients who were hospitalized and received therapeutic treatment, arthralgia (12.7%) and extremity edema (6%) were adverse events in our study.

In a review study by Hansrivijit et al., the side effects of using Rituximab in minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) include infusion reactions, pneumonia, cutaneous and fixed drug eruptions, type 1 hypersensitivity, and leukopenia.<sup>18</sup> Another review study of renal disease by Nixon et al. discussed infectious complications of Rituximab therapy, such as pneumonia and late-onset neutropenia.<sup>19</sup> In our study, patients also experienced adverse infection events like pneumonia (2.7%) and sinusitis (0.7%) during their Rituximab therapy.

## 6. Conclusion

Rituximab and anti-CD20 drugs are effective in treating MS. However, it is important to be aware of the acute side effects of the injection and the post-consumption side effects of Rituximab. Shortening the injection time and providing premedication can help reduce acute side effects and complications during the infusion.

### Research Highlights

#### What Is Already Known?

Rituximab is an anti-CD20 monoclonal antibody used as a primary drug in MS treatment. However, it can cause injection and post-consumption side effects.

#### What Does This Study Add?

The mean EDSS score before and after using Rituximab shows a slight increase, indicating no significant improvement in dysfunctions. However, the attack rate decreased.

### Author Contributions

Authors contributed equally to this work.

### Conflict of Interest Disclosures

All authors declared that they have no conflict of interest.

### Ethical Approval

This study was approved by the Ethics Committee of Isfahan

University of Medical Sciences under the code IR.MUI.MED.REC.1400.146. Written informed consent was obtained from all participants.

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