Original Article

Long-Term Adverse Events of Rituximab in Multiple Sclerosis Patients, Isfahan, Iran

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Abstract

Background: This study's objective was to assess the adverse events (AEs) of rituximab (RTX) therapy in people with multiple sclerosis (pwMS). **Methods:** This observational study was conducted on clinical data of pwMS who visited an MS center in Iran from January 2015 to January 2018 and underwent RTX therapy. The primary efficacy outcomes assessed were disability progression and the annual relapse rate. Initially the patients received 2 g of RTX (Zytux AryoGen Pharmed Company Iran) delivered in four 500-mg doses via an intravenous line each of which took 6 hours to avoid unwanted reactions. Afterward two 500-mg doses of RTX were administered every 6 months. we administered each dose within 4–6 hours to minimize unwanted reactions. **Results:** A total of 307 RTX-treated patients were included in the study. Around 75.2% of patients were female. The mean (standard deviation (SD)) age was 37.9 (9) years, and the mean (interquartile range (IQR)) disease duration was 7 (7) years. During treatment, the Expanded Disability Status Scale (EDSS) remained unchanged for patients with shorter disease duration (<3 years), and it was significantly improved for patients with longer disease duration (>3 years, *P* value = 0.015). Around 39.4% of the patients had at least one side effect, most of which were minor infections of the urinary and respiratory tract, all mild in nature. **Conclusions:** RTX treatment is well-tolerated and safe, with a minor risk of mild infusion reactions and minor side effects for MS patients.

Keywords: *Adverse drug reactions, MS, multiple sclerosis, rituximab, safety*

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, immune-mediated disease of the central nervous system (CNS) that manifests as a relapsing-remitting MS (RRMS) or a progressive MS (PMS).[1-5] A growing body of studies has pointed out that the B cells and humoral immunity are significant contributors to the pathogenesis of MS.[6] Rituximab (RTX) works as an anti-CD20 chimeric monoclonal antibody, which results in a significant depletion of B-cell circulation. RTX is expected to alter B-cell-mediated antigen presentation and, in turn, subsequent T-cell activation, antibody production, and cytokine secretion.

Various studies have demonstrated that patients with both RRMS and PMS experience significant improvements following using RTX, particularly in lowering relapse rates and reducing disease activity.[7,8] Though RTX is primarily approved for the treatment of other medical conditions and off-label for MS, it is effective, safe, and well-tolerated in many patients.[8-10]

B-cell dysregulation that causes neurological autoimmune disorders can be halted by suppressing the B-cell population as a result of RTX.[11] RTX effectively decreases relapse rate and disability progression in RRMS and PMS patients.[12] Additionally, the superiority of RTX over glatiramer acetate (GA) or interferon-beta (IFN-β) with respect to controlling relapses was pointed out, while its superiority in controlling disability remains a question.[13] However, general side effects, such as fever, chills, bronchitis, headache, nausea, vomiting, hypotension, thrombocytopenia, and neutropenia, are common due to treatments of different diseases with RTX.[14] Adverse event (AE) profile of RTX and dosing schedule are not well studied and determined for MS therapy.[15] This study's primary goal is to evaluate the long-term AEs of RTX in MS patients followed at the MS clinic of Kashani Hospital, affiliated with Isfahan University of Medical Sciences, Isfahan, Iran.

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Methods

Study population

This observational study was conducted using data gathered from MS patients visiting the clinic of Kashani Hospital, affiliated with Isfahan University of Medical Sciences in Isfahan, Iran, from January 2015 to January 2018. Patients who were diagnosed with MS and were about to undergo RTX treatment were included initially. Patients were diagnosed with MS by neurologists based on the 2017 revised McDonald criteria[16] at the clinic. Among MS patients who received RTX treatment, a certain number were selected randomly for the study. As for the exclusion criterion, we removed all patients with prior or concomitant diseases that prompted RTX use from the sample and diagnosis of hypogammaglobulinemia. From all participating patients, written informed consent was obtained upon their selection. The research ethics committee of the Isfahan University of Medical Sciences approved the methods and procedures of the study.

Study protocols

RTX treatment may contribute to the increased risk of infection as it suppresses the immune system. Thus, to avoid specific infections, the vaccination status of patients was checked before the treatment. Patients were treated with RTX in sessions in compliance with established standard protocols.[17] Initially, the patients received 2 g of RTX (Zytux, AryoGen Pharmed Company, Iran), delivered in four 500-mg doses via an intravenous line, each of which took 6 hours to avoid unwanted reactions. Afterward, two 500-mg doses of RTX were administered every 6 months; we administered each dose within 4–6 hours to minimize unwanted reactions. To minimize hypersensitivity reactions in the participants, 4 mg of oral chlorpheniramine and 100 mg of intravenous hydrocortisone were delivered to the patients before infusions.

Data collection

For neurological examination and AE evaluation, patients visited the clinic every 4 months as well as before RTX treatment sessions. Additionally, monthly follow-up phone calls were made to monitor patients' AEs and control any unwanted outcomes/events. The information regarding unwanted reactions and side effects was gathered on follow-up sessions via a pre-designed checklist. The checklist was engineered in accordance with the previously reported side effects of RTX.[18,19] The occurrence of infections and malignancies was recorded, along with any other side effects. Infections were labeled as AEs or serious AEs (SAEs) if they required immediate medical intervention or hospitalization. The side effects were categorized into two groups: infusion-related side effects (e.g., chills, fever, nausea, and muscular pain) and non-infusional side effects (e.g. rigors, syncope, severe neutropenia, and upper airway edema). Other demographic and clinical information was also recorded; a neurologist documented the clinical information, such as routine physical examinations, annualized relapse rate, and Expanded Disability Status Scale (EDSS) (primary and current scores).

Statistical analysis

Our analysis was performed in the IBM SPSS software version 23.[20] Descriptive statistical analyses were used to report the captured variables. These analyses consist of reporting frequencies and distribution of the variables for categorical variables and means ± standard deviation (SD) for continuous variables. Cross-tabulations and Chi-square tests were performed to analyze the categorical data. In all our tests, the significance level was set to 0.05 (P value < 0.05 was considered statistically significant). T-test and paired t-test were used to compare the means of different groups. To show the correlation among the numerical variables, the Pearson correlation test was performed.

Results

Among all the MS patients who were initially considered for receiving RTX, a total of 307 patients were selected for this study. Around 71% of the patients were RRMS and the rest were classified as Secondary Progressive Multiple Sclerosis (SPMS). The observation period of patients ranged between 24 and 36 months, with an average of 31.6 ± 7.3 months. Around 75.2% of patients were female, and 24.8% were male. The mean age was 37.93 (SD = 8.97). The average disease duration was 7 years ($Q_3 = 11$; $Q_1 = 4$). Table 1 tabulates the demographic and disease information for participating patients. The table also shows the analysis between two different disease duration groups: 1) less than or equal to 3 years and 2) greater than 3 years. As it shows, primary EDSS was found to be significantly higher in patients with longer disease duration (P value = 0.014). The two groups were found to have no significant differences in terms of gender and current EDSS (P value = 0.749 and 0.052, respectively), although current EDSS is almost significantly higher in patients with longer disease duration.

Concerning the side effects, respiratory distress is the most common infusion-relation side effect among all patients. Around 34.3% (23 cases) and 26.1% (80 cases) of patients with shorter and longer disease duration, respectively, experienced this side effect though the difference between the two groups was not statistically significant (P value = 0.086). Among non-infusional side effects, palpitation was the most common in both groups, with 16.4% (11 cases) and 9.6% (23 cases) prevalence in patients with shorter and longer disease duration, respectively. This difference between the two groups was not statistically significant (P value = 0. 125).

After the RTX treatment, we found tolerability to be satisfactory. After following up on all 307 patients, none has reported serious or life-threatening AEs. The AEs of

Table 1: Demographic and clinical features of the study sample by disease duration

Variable	Level	Disease duration			
		Overall (*n*=307)	<=3 (*n*=67)	>3 (*n*=240)	*P*
Sex; *n* (%)	Male	76 (24.8)	15 (22.4)	61 (25.4)	0.749
	Female	231 (75.2)	52 (77.6)	179 (74.6)	
Age; mean (SD)		37.9 (9.0)	34.51 (9.10)	38.88 (8.72)	<0.001
Primary EDSS; median (Q_3-Q_1)		3 (4.5-2)	2.5 (2-3)	3 (2-5)	0.014
Current EDSS; median (Q_3-Q_1)		3 (4-1.5)	2.5 (1.5-3)	3 (1.5-5)	0.052
MS phenotype	RRMS	220 (71.7)	58 (86.6)	162 (67.5)	0.002
	SPMS	87 (28.3)	9 (13.4)	78 (32.5)	
Relapse rate; *n* (%)	0	261 (85)	62 (92.5)	199 (82.9)	0.133
	1	43 (14)	5 (7.5)	38 (15.8)	
	2	3 (1)	0 (0)	3 (1.3)	
Infusion-related side effects; *n* (%)	Chills	20 (6.5)	3 (4.5)	20 (6.5)	0.582
	Fever	13 (4.2)	2 (3)	13 (4.2)	0.741
	Nausea	3 (1)	1 (1.5)	3 (1)	0.524
	Muscular pain	4 (1.3)	0 (0)	4 (1.3)	0.58
	Hypotension	12 (3.9)	2 (3)	12 (3.9)	0.659
	Transitory rash (and itching)	6 (2)	1 (1.5)	6 (2)	0.757
	Respiratory distress	80 (26.1)	23 (34.3)	80 (26.1)	0.086
Non-infusional side effects; *n* (%)	Rigors	0 (0)	0 (0)	0 (0)	-
	Syncope	2 (0.7)	0 (0)	2 (0.8)	0.611
	Severe neutropenia	0 (0)	0 (0)	0 (0)	-
	Upper airway edema	1 (0.3)	1 (1.5)	0 (0)	0.218
	Bronchitis	3 (1)	1 (1.5)	2 (0.8)	0.524
	Severe infection	4 (1.3)	1 (1.5)	3 (1.3)	0.877
	Primary VZV infection	1 (0.3)	0 (0)	1 (0.4)	0.782
	Other infection	16 (5.2)	3 (4.5)	13 (5.4)	0.76
	Palpitation	34 (11.1)	11 (16.4)	23 (9.6)	0.125

RTX treatment were also investigated. Overall, 60.6% of the patients had no side effects or reactions, and in 19.9% of the cases, there was only one account of side effects observed throughout the study, which was minor uncomplicated side effects with no need for hospitalization. On the contrary, four cases experienced severe infection that needed medical intervention. However, no patient experienced SAE, such as severe neutropenia, cardiac involvement, renal involvement, hepatitis, encephalitis, hemolytic anemia, thrombocytopenia, and thyroid disorder, during the follow-up period.

Minor infusion-related side effects were reported by 45.0% of the patients, which were limited by the administration of chlorpheniramine and hydrocortisone. No significant correlation was found between the disease duration and the total number of AEs. Specifically, 35 (52.2%), 19 (28.4%), 10 (14.9%), two (3%), and one (1.5%) patients with shorter disease duration had 0–4 side effects, respectively. In the patients with longer disease duration, 62.9% (151 cases), 17.5% (42 cases), 14.6% (35 cases), 4.2% (10 cases), and 0.8% (two cases) experienced 0–4 side effects, respectively, while no significant difference was found between the two groups in the number of side effects (*P* value = 0.340).

Tables 2–4 show how different demographics and clinical characteristics may contribute to infusion-related and non-infusion-related AEs based on MS type, sex, and EDSS. Also, Table 5 suggests the influence of demographic and clinical characteristics on the odds of having infusion-related and non-infusion-related side effects. With males as the reference group, the table shows that being female significantly increases the likelihood of having infusion-related side effects by a factor of 3.77 (*P* value < 0.001). Additionally, having lower primary EDSS increases the likelihood of having infusion-related side effects by about 20%. The evidence is not statistically enough to confirm other characteristics' contribution to different classes of side effects (*P* values > 0.05).

Clinical disease activity was limited during RTX therapy. A total of 261 (85%) of the patients were relapse-free during the follow-up period. Forty-three patients (14%) experienced one relapse during the therapy, and three patients (1%) experienced two relapses during the follow-up period. The situation is better for patients with shorter disease duration; 62 (92.5%), five (7.5%), and zero (0%) patients experienced zero, one, and two relapses, respectively, during the follow-up period. This difference is not significant, though, between the two groups (*P* value = 0.133). Concerning disability, no

Table 2: Demographic and clinical features of the study sample by MS type

Variable	Level	MS type		
		RRMS (*n*=220)	SPMS (*n*=87)	*P*
Sex; *n* (%)	Male	47 (21.4)	29 (33.3)	0.029
	Female	173 (78.6)	58 (66.7)	
Age; mean (SD)		36.30 (8.68)	42.05 (8.40)	<0.001
Primary EDSS; median (Q_3-Q_1)		2.5 (1)	5.5 (2)	<0.001
Current EDSS; median (Q_3-Q_1)		2 (2)	6 (1)	<0.001
Disease duration; mean (SD)		6.98 (4.74)	12.53 (7.03)	<0.001
Relapse rate; *n* (%)	0	192 (87.3)	69 (79.3)	0.206
	1	26 (11.8)	17 (19.5)	
	2	2 (0.9)	1 (1.1)	
Infusion-related side effects; *n* (%)	Chills	18 (8.2)	2 (2.3)	0.060
	Fever	11 (5)	2 (2.3)	0.290
	Nausea	2 (0.9)	1 (1.1)	0.847
	Muscular pain	3 (1.4)	1 (1.1)	0.881
	Hypotension	11 (5)	1 (1.1)	0.117
	Transitory rash (and itching)	2 (0.9)	4 (4.6)	0.035
	Respiratory distress	67 (30.5)	13 (14.9)	0.005
Non-infusional side effects; *n* (%)	Rigors	0 (0)	0 (0)	-
	Syncope	2 (0.9)	0 (0)	0.372
	Severe neutropenia	0 (0)	0 (0)	-
	Upper airway edema	1 (0.5)	0 (0)	0.529
	Bronchitis	3 (1.4)	0 (0)	0.274
	Severe infection	4 (1.8)	0 (0)	0.206
	Primary VZV infection	1 (0.5)	0 (0)	0.529
	Other infection	8 (3.6)	8 (9.2)	0.048
	Palpitation	26 (11.8)	8 (9.2)	0.509

Table 3: Demographic and clinical features of the study sample by sex

Variable	Level	Sex		
		Male (*n*=76)	Female (*n*=231)	*P*
Infusion-related side effects; *n* (%)	Chills	3 (3.9)	17 (7.4)	0.296
	Fever	2 (2.6)	11 (4.8)	0.424
	Nausea	0 (0)	3 (1.3)	0.318
	Muscular pain	0 (0)	4 (1.7)	0.248
	Hypotension	1 (1.3)	11 (4.8)	0.179
	Transitory rash (and itching)	0 (0)	6 (2.6)	0.156
	Respiratory distress	6 (7.9)	74 (32)	<0.001
Non-infusional side effects; *n* (%)	Rigors	0 (0)	0 (0)	-
	Syncope	0 (0)	2 (0.9)	0.416
	Severe neutropenia	0 (0)	0 (0)	-
	Upper airway edema	0 (0)	1 (0.4)	0.566
	Bronchitis	0 (0)	3 (1.3)	0.318
	Severe infection	3 (3.9)	1 (0.4)	0.019
	Primary VZV infection	0 (0)	1 (0.4)	0.566
	Other infection	2 (2.6)	14 (6.1)	0.243
	Palpitation	2 (2.6)	32 (13.9)	0.007

significant changes were observed in the mean of EDSS before and after the treatment (Eta = 0.04; *P* value = 0.603) in patients with shorter disease duration, although the first and third quartile values dropped by 0.5. The stability of EDSS indicates that the therapy was efficient in controlling the disability progression. The treatment was also satisfactory for the patients with longer disease duration as it dropped EDSS significantly (Eta = 0.025; *P* value = 0.015).

Discussion

RTX is a chimeric monoclonal antibody (mAb) targeting

Table 4: Demographic and clinical features of the study sample by severity of EDSS

Variable	Level	Current EDSS		
		<=3 (*n*=204)	> 3 (*n*=103)	*P*
Infusion-related side effects; *n* (%)	Chills	16 (7.8)	4 (3.9)	0.184
	Fever	10 (4.9)	3 (2.9)	0.414
	Nausea	1 (0.5)	2 (1.9)	0.222
	Muscular pain	3 (1.5)	1 (1)	0.715
	Hypotension	11 (5.4)	1 (1)	0.059
	Transitory rash (and itching)	2 (1)	4 (3.9)	0.083
	Respiratory distress	63 (30.9)	17 (16.5)	0.007
Non-infusional side effects; *n* (%)	Rigors	0 (0)	0 (0)	-
	Syncope	2 (1)	0 (0)	0.313
	Severe neutropenia	0 (0)	0 (0)	-
	Upper airway edema	0 (0)	1 (1)	0.159
	Bronchitis	2 (1)	1 (1)	0.994
	Severe infection	4 (2)	0 (0)	0.153
	Primary VZV infection	1 (0.5)	0 (0)	0.477
	Other infection	7 (3.4)	9 (8.7)	0.048
	Palpitation	25 (12.3)	9 (8.7)	0.354

Table 5: Influence of demographic and clinical characteristics on the odds of having infusion-related and non-infusion-related side effects (Multivariate logistic regression)

	Infusion				Non-infusion			
	RRMS		SPMS		RRMS		SPMS	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.023 (0.988-1.058)	0.200	1.001 (0.932-1.073)	0.998	1.027 (0.986-1.069)	0.199	1.006 (0.939-1.078)	0.866
Sex (Ref.=Female)	0.387 (0.178-0.843)	0.017	0.081 (0.009-0.698)	0.022	0.370 (0.124-1.105)	0.075	0.376 (0.092-1.541)	0.174
Primary EDSS	0.791 (0.569-1.102)	0.166	0.631 (0.337-1.182)	0.150	1.019 (0.697-1.491)	0.921	0.761 (0.414-1.399)	0.379
Current EDSS	1.435 (1.045-1.970)	0.026	1.044 (0.503-2.165)	0.909	1.008 (0.699-1.455)	0.964	1.264 (0.585-2.727)	0.551
Disease duration (Ref.=>3)	1.601 (0.827-3.103)	0.163	0.799 (0.077-8.287)	0.851	1.336 (0.602-2.965)	0.476	1.497 (0.249-9.011)	0.659
Relapse (Ref.=Yes)	0.565 (0.242-1.321)	0.188	0.449 (0.126-1.604)	0.218	0.627 (0.238-1.649)	0.344	5.174 (0.621-43.08)	0.129

the CD20 antigen, which is predominantly expressed on the surface of B lymphocytes.[7] As a result of binding to CD20, it targets the B cells and destroys them through a variety of mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of apoptosis.[7] There is extensive evidence to support the efficacy of RTX for the treatment of B-cell malignancies, such as diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia.[7] There is, however, an active research effort underway to identify the causes of variability in patient response as well as the exact mechanisms that contribute to its therapeutic effectiveness.[7,21]

RTX was shown to be well-tolerated in most cases, with manageable AEs. It also showed satisfactory effects on controlling disease progression in certain disease groups by reducing disability. Our results showed that the treatment was also satisfactory for patients with longer disease duration as it dropped EDSS significantly. It was matched with previous studies.[22] Patients with prolonged disease duration, who typically exhibit higher baseline EDSS scores, are more likely to demonstrate noticeable reductions in these scores than patients with lower disease duration.

The AEs of RTX in MS patients have been investigated in few studies of studies with limited sample sizes or limited follow-up periods. In this study, 39.4% of the patients had at least one side effect, most of which were minor infections of the urinary and respiratory tract, all mild in nature. A higher value, 71.9%, is reported in another study.[12] The rate of infection was 17.9%, while the majority of the patients with infection had experienced mild episodes. The infection rate in our study was relatively low; 15.7% is reported in Ref.[12] In a study on RRMS patients, 60 of 253 patients were reported to develop a form of infection.[23] Additionally, 1.3% (four patients) experienced severe infection, which is similarly reported in previous studies.[12] A higher value of 2.2% for severe infections was reported in one study, resulting in discontinuation of the patient's treatment experiencing severe infections.[12] Moreover, in another study, a higher incidence of severe infections is reported (4.5%) in patients treated with RTX, reported to be significantly higher than the placebo

patients.[24] In a clinical trial study comparing the safety and efficacy of RTX and dimethyl fumarate (DMF), the RTX group showed 40.9 per 100 patient-years of infusion-related events, and the DMF group presented flush (47.4 per 100 patient-years) and gastrointestinal reactions (47.4 per 100 patient-years) as the most prevalent AEs.[25]

In our study, infusion-related AEs were among the most common AEs with a prevalence of 45%. A recent observational study reported the prevalence of 8.7% among MS patients followed at a single center in the Middle East.[12] In that study, a sample of 59 RRMS and 30 PMS were selected. In another study, 18.8% of patients were reported to have infusion-related AEs.[26] When symptoms arise, it is advisable to take the appropriate treatment, such as acetaminophen for fever. Although these studies reported lower occurrence of infusion-related AEs, some studies reported values similar to our observation; evaluating RTX therapy on a group of 30 patients; Kim *et al*.[27] reported 40% for the incidence of non-serious infusion-related AEs during 2 years of treatment.

Regarding the non-infusion-related AEs, Leonidou *et al*.[28] reported two cases of respiratory tract infection, two cases (of 30 patients) of neutropenia, two cases of hypogammaglobulinemia, and one case of drug-induced psoriasis. Zecca *et al*.[29] also reported that 25% of their patients manifested non-infusion-related AEs when treated with RTX. In our study, other than infection and palpitation, two patients (0.7%) had syncope, one patient (0.3%) had upper airway edema, and three patients (1%) had bronchitis. Higher values are reported in some studies; Bar-Or A *et al*.[30] reported 15.4% and 19.2% for incidences of bronchitis and upper respiratory tract infection, respectively. In a cumulative of 13 studies included in the 2020 meta-analysis, it was shown that infusion-related events in patients undergoing RTX were 31%, and infection was reported in 33% of these patients.[31] Hauser *et al*.[32] reported that 4.3% of MS patients treated with RTX had AEs, and one death was also reported in the group being treated with RTX. We did not observe other non-infusion-related AEs. Additionally, a total of 60.6%, however, reported experiencing no AEs, which is a relatively high value (28.1% in (12) and 31.8% in[33]). Moreover, Mazdeh *et al*.[34]'s study demonstrated that 60% of patients experienced grade 1 or 2 of AEs associated with their first infusion.

Although most of the studies mentioned above focused on RTX efficacy and did not deploy a systematic approach to assess RTX's AEs, their results are comparable to our findings as they also promote the tolerability of RTX. The existing discrepancies could originate from several sources, such as patients' demographics, medical history, and previous immunomodulatory therapies. To elaborate, based on statistics presented in Table 1, patients participating in our study were relatively young and not severely disabled, which are regarded as important factors in AE studies. Lower age and primary EDSS can be major contributors to prevent a minor post-treatment insult from developing into AEs or SAEs.[35] This can justify our high number of patients with no AEs. Our analysis also showed a significant association between sex and infusion-related side effects and between primary EDSS and infusion-related side effects. However, they were not conclusive to show the association of infusion (or non-infusion)-related side effects with age. Moreover, no correlation was found between disease duration and the occurrence of AEs.

A rate of 85% was reported for patients who had no relapses for at least 12 years after the start of the treatment. In a study, 60% of patients were reported to be relapse-free due to RTX treatment.[36] During a clinical trial study by Svenningsson *et al*.,[25] in the RTX group, 3% of patients and, in the DMF group, 16% of patients had a relapse. Regarding disability, we found that outcomes of RTX treatment in our study group are favorable for patients with longer disease duration in reducing EDSS. A similar observation is reported in the literature. Alcalá *et al*.[26] reported that EDSS dropped from 4.9 to 4.6 after 1 year of treatment. In another study on RRMS, SPMS, and PPMS patients, a decrease in EDSS score from 6 to 4.75 is observed.[28] Scotti *et al*.[37] observed that, in a group of patients with an average age of about 48 years, EDSS worsened in 16.3% of RRMS and 20.5% of PMS patients and remained the same for the rest of the patients. We observed the stability of EDSS through the treatment period in patients with shorter disease duration. Zecca *et al*.[29] reported similar values; EDSS progression was observed in 14.6% of RRMS. Naismith *et al*.[38] reported the stability of EDSS for a patient group with an average age of about 43 years after being treated with RTX. Yamout *et al*.[12] also observed stable EDSS for both RRMS and PMS patients, with a trend to reduce EDSS in RRMS patients. In addition, Mazdeh *et al*.[34] in 2020 showed relapse rate was reduced from mean ± SD of 0.95 ± 0.64 to 0.25 ± 0.36 following treatment with RTX.

Patient adherence to treatment is also crucial to the efficacy of the treatment. According to Bawand *et al*.'s[39] cohort study, the treatment adherence rate was 82.5%, and it was associated with a higher level of education, marriage, and type of disease modifying therapies (DMTs) (RTX, GA, and fingolimod had the highest rates of adherence).

Conclusions

To conclude, the main side effects of RTX treatment comprise infusion reactions and infections. Injection side effects were encountered frequently and were mostly controlled by antihistamines, IV steroids, or slow up-titration of RTX. Our results indicated that RTX therapy is well-tolerated and safe in the majority of cases. RTX also favorably stabilizes the disability, which nominates RTX as a safe treatment option for MS patients. It is, however, necessary to conduct more clinical trials to clarify this issue.

Ethical approval

The research ethics committee of the Isfahan University of Medical Sciences approved the methods and procedures of the study.

Consent to participate

All participants provided written informed consent before enrolment in the study.

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Code of ethics

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Authors' contributions

Ali Rahimisadegh: Conceptualization, methodology, data curation, formal analysis, writing—original draft, and project administration. Omid Mirmosayyeb: Conceptualization, supervision, methodology, formal analysis, and writing—review and editing. Shakiba Houshi: Data collection, data curation, statistical analysis, and writing—original draft.Alireza Afshari-Safavi: Methodology, statistical analysis, and writing—review and editing. Elham Moases Ghaffary: Literature review, writing—original draft, and writing—review and editing. Fereshteh Ashtari: Supervision, conceptualization, and critical revision of the manuscript. Vahid Shaygannejad: Supervision, conceptualization, and final approval of the manuscript.

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Conflicts of interest

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