Current Journal of Neurology

Original Paper

Curr J Neurol 2020; 19(3): 103-6

Evaluation of safety of rituximab in patients with multiple sclerosis: A retrograde study

Received: 18 Mar. 2020
Accepted: 20 Apr. 2020

Nastaran Majdinasab[1,2], Mitra Sadrian[1], Davood Kashipazha[1], Maryam Moradi[3]

[1] Department of Neurology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2] Musculoskeletal Rehabilitation Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3] Department of Biostatistics and Epidemiology, School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Keywords
Multiple Sclerosis; Rituximab; Side Effects; Safety

Abstract

Background: The study aimed to judge the safety and possible side effects of rituximab (RTX) drug in patients with multiple sclerosis (MS).

Methods: This retrospective observational study was performed on 91 patients with MS who had been treated with RTX between 2016 and 2019. Each patient was visited and examined a minimum of once. The side effects of the drug and therefore the drug-related reactions to the injection were asked via phone calls, which were recorded separately as mild, moderate, and severe modes with the necessity for hospitalization.

Results: A total of 91 patients were enrolled within the study: 80 patients with relapsing-remitting MS (RRMS), 6 patients with secondary progressive MS (SPMS), and 5 patients with primary progressive MS (PPMS). The mean age of the patients was 32.18 ± 8.71 years (18 to 60 years). The injection-related side effects occurred in 30.8% of the injections, most of which were mild and one of the mild complications was urinary tract infection (UTI). Two cases of complications with moderate severity were recorded.

Conclusion: The observations from this study demonstrated that RTX did not cause serious complications in patients with MS.

Introduction

Multiple sclerosis (MS) is an immune-mediated inflammatory disease causing demyelination and progressive neuronal degeneration within the central nervous system (CNS).[1] Clinically, there are various types of MS. The most usual is the relapsing-remitting (RR) form identified by the occurrence of acute symptoms or relapses of neurological deficits followed by complete or incomplete healing or remission. After a different number of years, most patients evolve a secondary progressive (SP) course identified by a progression of the neurological disability associated or not with overlying relapses. Another less common types include the primary

How to cite this article: Majdinasab N, Sadrian M, Kashipazha D, Moradi M. Evaluation of safety of rituximab in patients with multiple sclerosis: A retrograde study. Curr J Neurol 2020; 19(3): 103-6.

Corresponding Author: Nastaran Majdinasab
Email: n.madjdinasab@gmail.com

progressive (PP) form, in which there is slow progression of neurological disability and symptoms without relapses.[2] The disease includes a prevalence of less than 1 per 100000 in equatorial areas, 6 to 14 per 100000 within the southern United States (US) and southern Europe, and 30 to 80 per 100000 in Canada, northern Europe, and the northern US.[3] MS has a serious influence on the quality of life for most patients. MS symptoms can limit an individual's physical activity and income-earning ability. The main target of treatment in MS is to prevent the long-term gathering of irreversible disability. Nowadays, all first-line therapy agents aim to reduce disease.[4] The traditional view of MS pathophysiology has held that inflammation is mainly mediated by CD4+ type 1 helper T cells.[5] B cells were ignored in MS pathogenesis for decades, and the disease was always considered as a T cell-mediated disorder. Recent evidence reveals that there is an antigen-driven B cell response in the CNS of patients with MS, and memory B cell/plasma cells are detectable in MS lesions.[6] Rituximab (RTX) is commonly used off-label in neuro-inflammatory diseases like MS.[7] RTX, a chimeric mouse-human immunoglobulin G1 (IgG1) antibody, was developed in 1994 as a new therapeutic agent in human lymphoma therapy.[8] The Fab domain of RTX binds to the CD20 antigen on B lymphocytes and the Fc domain enrolls immune effector cells that result in B cell death. RTX reduces B cell by antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and inducing apoptosis through cross-linking of membrane CD20.[9] RTX may be used either in progressive MS, where treatment options are restricted, or in RRMS, when patients do not respond to the frequently available and approved treatment options.[7] Over recent years, a good number of studies have been published in order to address the effect of RTX on patients with MS.[7,10-14] Numerous studies have been conducted on new treatments for MS targeting B cells and CD20 that have shown the efficacy of B cell depletion treatments compared to placebo.[5,6,8,9,15] RTX performs better than other commonly-used disease-modifying drugs (DMDs) in patients with newly-diagnosed RRMS.[16] Furthermore, RTX is a very good choice for cases where natalizumab administration cannot be continued for any reason.[17] In addition, this medication may be effective in patients with PPMS aged under 51 and with enhancing lesions on magnetic resonance imaging (MRI).[18] Given the high prevalence of MS in Iran,[19,20] especially central regions (around 15.94 per 100000 populations in Tehran), more efficient treatments are highly needed.[21]

Materials and Methods

This study was a retrospective observational study, which was conducted on 91 patients with MS who had been treated with RTX in the neurology ward of Golestan Hospital, Ahvaz, Iran, between 2016 and 2019. The patients whose disease had been confirmed by the MS Society of Khuzestan Province were included in the study. The treatment regimen of patients, depending on the type of disease, was delivered to them in the form of injecting two 500-mg doses with a two-week interval, which was then repeated every 6 months or injecting two 1000-mg doses with a two-week interval repeated every 6 months. In the hospital neurology ward, to prevent known drug reactions, a combination of 1 g oral acetaminophen, 150 mg oral ranitidine, 10 mg chlorpheniramine by intravenous (IV) injection, and 100 to 250 mg methylprednisolone succinate by IV infusion were administrated usually for all patients before injecting the main drug. All patients underwent cardiac monitoring during the drug administration. Prior to drug administration, the complete blood count (CBC), electrolyte tests, liver and kidney function tests, and viral tests, as well as the evaluation of latent tuberculosis (TB) [purified protein derivative (PPD)] were requested for all patients. The basic demographic information of patients was extracted by phone calls and from patients' records. In this study, the underlying variables were age, gender, ethnicity, duration of disease before starting the treatment with RTX, duration of treatment with RTX, type of disease, and previous treatment. Each patient was visited and examined at least once. Questions about the side effects of the drug and the drug reactions associated with the injection were asked several times over phone calls. The side effects extracted were divided as mild, moderate, and severe degrees with the need for hospital admission and recorded by type. The patients who went to another center other than Golestan Hospital to receive subsequent doses of RTX were excluded from the study.

The sample size was determined by the census method. By this method, all patients with a diagnosis of one of the MS types, RRMS, SPMS,

and PPMS who had the indication of being treated with RTX and had referred to Golestan Hospital of Ahvaz for the injection of the drug between 2016 and 2019 were included in the study.

To determine the prevalence of the research variables, the descriptive statistics methods, including frequency and percentage of frequency were used for qualitative variables and the mean and standard deviation (SD) were employed for quantitative variables. To evaluate the correlation between the research variables, after normalizing the data using the Kolmogorov-Smirnov test (K-S test), the parametric or nonparametric tests (independent t-test, chi-square test, Mann-Whitney U test, etc.) were applied. All analyses were performed using the SPSS software (version 22, IBM Corporation, Armonk, NY).

Results

A total of 91 patients were included in the study with a mean age of 32.18 ± 8.71 years (18 to 60 years). Of this, 72 patients (79.1%) were women and 19 patients (20.9%) were men. Of all, 80 patients (87.9%) had RRMS, 6 (6.6%) had SPMS, and 5 (5.5%) had PPMS. The patients were treated with 500 or 1000 mg RTX every 6 months that the annual total dose was considered as a variable for the patients. In total, 64 patients (70.3%) were treated with an annual 1000 mg of RTX, 16 patients (17.6%) were treated with 2000 mg of RTX annually, 8 patients (8.8%) received 1500 mg of RTX annually, and 3 patients (3.3%) were treated with 500 mg of RTX annually.

The duration from the time of diagnosing MS until the start of treatment with RTX was recorded as a variable. In total, for 34 patients (37.4%), more than five years had passed since their diagnosis; this time was less than one year for 31 patients (34.1%) and between one to five years in the case of 26 patients (28.6%) when they started the treatment with RTX.

Out of the 91 patients enrolled, the duration of being treated with RTX was as follows: 39 patients (42.9%): Between one and two years, 31 patients (34.1%): Less than one year, and 21 patients (23.1%): More than two years.

The last drug used to treat the studied patients before starting using RTX was as follows: 37 patients (40.7%): Interferon, 5 patients (5.5%): Fingolimod, 2 patients (2.2%): Dimethyl fumarate, 2 patients (2.2%): Glatiramer acetate, 2 patients (2.2%): Natalizumab, and 2 patients (2.2%): Teriflunomide. In 41 patients (45.1%), the first drug used in treating patients was RTX (Table 1).

Table 1. Patient's baseline characteristics

Clinical variables		n (%)
Disease duration at RTX start	Less than one year	31 (34.1)
	One to five years	26 (28.6)
	More than five years	34 (37.4)
Follow-up time since RTX start	Less than one year	31 (34.1)
	One to two years	39 (42.9)
	More than two years	21 (23.1)
MS type	RRMS	80 (87.9)
	SPMS	6 (6.6)
	PPMS	5 (5.5)
Last DMD before RTX	Interferon	37 (40.7)
	Dimethyl fumarate	2 (2.2)
	Glatiramer acetate	2 (2.2)
	Natalizumab	2 (2.2)
	Teriflunomide	2 (2.2)
	Fingolimod	5 (5.5)
	Treatment-naive	41 (45.1)
RTX dose infusion (mg)	500	3 (3.3)
	1000	64 (70.3)
	1500	8 (8.8)
	2000	16 (17.6)

RTX: Rituximab; MS: Multiple sclerosis; DMD: Disease-modifying drug; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; PPMS: Primary progressive multiple sclerosis

Adverse effects: The adverse reactions associated with drug injection were seen in 28 (30.8%) patients, most of which were mild. Two cases of moderate reaction were recorded, including one case of chills during the first injection and one case of generalized urticaria during the second injection.

The other side effects were as follows: 6 cases (6.6%) of dyspnea, 6 cases (6.6%) of palpitations, 6 cases (6.6%) of itchy ear and throat, 4 cases (4.4%) of itchy skin and urticaria (one case of which was moderate), 3 cases (3.3%) of mild headache, one case (1.1%) of fever during infusion, and one case (1.1%) of urinary tract infection (UTI) (Table 2).

Table 2. Drug-related adverse reactions

Adverse reactions	n (%)
Headache	3 (3.3)
Chills	1 (1.1)
Dyspnea	6 (6.6)
Skin disorders	4 (4.4)
Fever	1 (1.1)
Palpitation	6 (6.6)
Itchy ear and throat	6 (6.6)
UTI	1 (1.1)
Total	28 (30.8)

UTI: Urinary tract infection

Discussion

In general, the utilization of RTX in MS treatment has no long history. Although the drug is not approved, its use within the treatment of MS is increasing.[22] This study was performed to evaluate the complications and safety of RTX on patients with MS.

To this end, 91 patients with MS, including 72 women and 19 men with a mean age of 32.18 years treated with RTX, were studied. These individuals had different treatment regimens and different treatment indications. Most of our patients (80 patients) were patients with the RRMS type.

The injection-related adverse effects were seen in 30.8% of our patients, which were often mild and included shortness of breath, palpitations, ear and throat itching, itching and redness of the skin, and fever. One case of severe skin reaction was recorded as generalized urticaria in the second injection which was in a patient with RRMS. Apart from one case of mild UTI, no infections were seen within the patients. In similar studies, most patients reported adverse effects, including headache, chills, hypertension (HTN), shortness of breath, itching, rash, headache, and sore throat, especially in the first injection, most of which were mild to moderate. The infections included nasopharyngitis, bronchitis, upper respiratory tract infection (URTI), and UTI that none of them were severe.[1,10-14] All these studies were similar to our study.

Conclusion

This observational study showed that treatment with RTX was not related to serious complications in patients with MS.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

This study is a component of Mitra Sadrian thesis project and the financial support was provided by Ahvaz Jundishapur University of Medical Sciences. We would like to thank Golestan Hospital Clinical Research Development Unit, Ahvaz Jundishapur University of Medical Sciences, and the staff and participants of the study.

References

1. Alldredge B, Jordan A, Imitola J, Racke M. Safety and efficacy of rituximab: Experience of a single multiple sclerosis center. Clin Neuropharmacol 2018; 41(2): 56-9.
2. Castillo-Trivino T, Braithwaite D, Bacchetti P, Waubant E. Rituximab in relapsing and progressive forms of multiple sclerosis: A systematic review. PLoS One 2013; 8(7): e66308.
3. Samuels MA, Ropper AH, Klein J. Adams and Victor's principles of neurology. 10th ed. New York, NY: McGraw-Hill Education; 2014. p. 917.
4. He D, Guo R, Zhang F, Zhang C, Dong S, Zhou H. Rituximab for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev 2013; (12): CD009130.
5. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008; 358(7): 676-88.
6. Rahmanzadeh R, Weber MS, Bruck W, Navardi S, Sahraian MA. B cells in multiple sclerosis therapy-A comprehensive review. Acta Neurol Scand 2018; 137(6): 544-56.
7. Rommer PS, Dorner T, Freivogel K, Haas J, Kieseier BC, Kumpfel T, et al. Safety and clinical outcomes of rituximab treatment in patients with multiple sclerosis and neuromyelitis optica: Experience from a National Online Registry (GRAID). J Neuroimmune Pharmacol 2016; 11(1): 1-8.
8. Gasperi C, Stuve O, Hemmer B. B cell-directed therapies in multiple sclerosis. Neurodegener Dis Manag 2016; 6(1): 37-47.
9. Lulu S, Waubant E. Humoral-targeted immunotherapies in multiple sclerosis. Neurotherapeutics 2013; 10(1): 34-43.
10. Bar-Or A, Calabresi PA, Arnold D, Markowitz C, Shafer S, Kasper LH, et al. Rituximab in relapsing-remitting multiple sclerosis: A 72-week, open-label, phase I trial. Ann Neurol 2008; 63(3): 395-400.
11. Salzer J, Svenningsson R, Alping P, Novakova L, Bjorck A, Fink K, et al. Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy. Neurology 2016; 87(20): 2074-81.
12. Berenguer-Ruiz L, Sempere AP, Gimenez-Martinez J, Gabaldon-Torres L, Tahoces L, Sanchez-Perez R, et al. Rescue therapy using rituximab for multiple sclerosis. Clin Neuropharmacol 2016; 39(4): 178-81.
13. Barra ME, Soni D, Vo KH, Chitnis T, Stankiewicz JM. Experience with long-term rituximab use in a multiple sclerosis clinic. Mult Scler J Exp Transl Clin 2016; 2: 2055217316672100.
14. Naser MA, Darki A, Masoumi P, Hashemi SN, Ghadiri F. Evaluating the efficacy and safety of Zytux(TM) (Rituximab, AryoGen pharmed) in Iranian multiple sclerosis patients: An observational study. Mult Scler Relat Disord 2019; 36: 101419.
15. Bartok B, Silverman GJ. Development of anti-CD20 therapy for multiple sclerosis. Exp Cell Res 2011; 317(9): 1312-8.
16. Granqvist M, Boremalm M, Poorghobad A, Svenningsson A, Salzer J, Frisell T, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. JAMA Neurol 2018; 75(3): 320-7.
17. Alping P, Frisell T, Novakova L, Islam-Jakobsson P, Salzer J, Bjorck A, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann Neurol 2016; 79(6): 950-8.
18. Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, et al. Rituximab in patients with primary progressive multiple sclerosis: Results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol 2009; 66(4): 460-71.
19. Rezaali S, Khalilnezhad A, Naser MA, Chaibakhsh S, Sahraian MA. Epidemiology of multiple sclerosis in Qom: Demographic study in Iran. Iran J Neurol 2013; 12(4): 136-43.
20. Eskandarieh S, Molazadeh N, Moghadasi AN, Azimi AR, Sahraian MA. The prevalence, incidence and familial recurrence of multiple sclerosis in Tehran, Iran. Mult Scler Relat Disord 2018; 25: 143.
21. Eskandarieh S, Heydarpour P, Elhami SR, Sahraian MA. Prevalence and Incidence of Multiple Sclerosis in Tehran, Iran. Iran J Public Health 2017; 46(5): 699-704.
22. Berntsson SG, Kristoffersson A, Bostrom I, Feresiadou A, Burman J, Landtblom AM. Rapidly increasing off-label use of rituximab in multiple sclerosis in Sweden - Outlier or predecessor? Acta Neurol Scand 2018; 138(4): 327-31.