Research Article

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Journal of Hospital and Medical Management
ISSN 2471-9781

2022
Vol.8 No. 8:1000328

Efficacy and Safety of Rituximab in Treatment of the Patients with Neuromyelitis Optica: A Prospective Case Study

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Received: 14 August, 2020, Manuscript No. M- IPJHMM -20-5802; **Editor assigned:** 19 August, 2020, PreQC No. P- IPJHMM -20-5802; **Reviewed:** 2 Septmber, 2020, QC No. Q-IPJHMM -20-5802; **Revised:** 22 August, 2022, QI No. Q- IPJHMM-20-5802; Manuscript No.R-IPJHMM-20-5802; **Published:** 19 September, 2022, DOI: 10.36648/2471-9781.8.8.328.

Citation: Farhadi P, Jaberi AR, Rostami A, Gourabjiri YA (2022) Efficacy and Safety of Rituximab in Treatment of the Patients with Neuromyelitis Optica: A Prospective Case Study. J Hosp Med Manage Vol: 8 No: 8: 328.

Abstract

Object ve: To report the results of rituximab treatment in Iranian patients with Neuro Myelitis Optica (NMO) during 12 months follow-up.

Methods: This was a prospective case study of the use of rituximab in NMO. The study was performed on 15 NMO patients older than 18 years who were referred to 2 referral neurology centers during 6 months period. Treatment protocol of rituximab consisted of 1000 mg infusion twice at a 2 weeks interval. Disability (expressed as expanded disability status scale score), MRI evaluation, and safety of rituximab treatment were considered as outcomes.

Results: The average age for starting rituximab therapy was 42.9 years ± 13.5 years (range, 21 years-65 years). Two patients died during the 12 months follow-up due to a severe relapse (patients no 8 and 15). The mean EDSS score before starting treatment (n=15) was 6.9 ± 2.4 (range, 2-9.5), whereas it was 5.2 ± 2.6 (range, 1-10) at the end of follow-up (P=0.03). In 13 patients (86.6%), the disability was either improved or stabilized after rituximab treatment. MRI assessment revealed no significant change in the CNS MRI of 9 alive patients. On the other hand, T_2-hyperintense lesion segments of the spinal cord decreased in three patients, while it was increased in one patient.

Conclusion: In conclusion, our study provides promising initial results that rituximab may also prevent further neurological deterioration and especially considering the strong suppression of disease activity in NMO patients.

Keywords: Neuromyelitis optica; Monoclonal antibody; Rituximab; Disability

Introduction

Neuro Myelitis Optica (NMO) or Devic's disease is a rare heterogeneous condition consisting of the inflammation and demyelination of the central nervous system. For a long time, it was classified as the optico spinal variant of Multiple Sclerosis (MS) because of its characteristic attacks of transverse myelitis and optic neuritis [1]. Recurrent, severe relapses that unpredictably involve the optic nerves and the spinal cord causing irreversible damage and permanent disability are the most common manifestations of the disease [2]. According to previous data, more than 50% of patients are blind in one or both eyes, or need ambulatory help within 5 years from onset. In addition, the mortality rate was 3%-25%. Although more recent investigations report a less severe disease course with permanent bilateral blindness (18%) and a permanent motor disability (34%), after a mean disease duration of 75 months [3,4].

Indeed, untreated NMO may lead to blindness, tetraplegia and death. However brain lesions have been detected in confirmed NMO patients, but they aren't similar to the typical MS lesions [5]. Therefore, NMO needs early diagnosis and long-term disease modification. Since the autoantibody that targets Aquaporin 4 (AQP4) was discovered in NMO patients, many studies have surveyed anti-AQP4 Antibody (AQP4-Ab) mediated autoimmunity in the pathogenesis of NMO and provided strong evidence for the use of therapies targeting B cells in NMO [6].

Intravenous high-dose methylprednisolone with slow tapering is the best treatment choice in acute NMO attacks followed by plasma exchange or intravenous immunoglobulin should be considered for steroid-resistant patients. In recent years, controlling the relapses of NMO has become difficult, because these patients respond poorly to traditional treatments. Prophylactic medications for preventing relapses include oral prednisone, mycophenolate mofetil, azathioprine and rituximab. Other medications for refractory patients include cyclophosphamide, methotrexate, and tocilizumab [7]. Among

the medications which have been used in cases with NMO, rituximab therapy has achieved the highest response rate (more than 70%) by depleting B cells [8-11].

Rituximab is a monoclonal antibody that targets the human CD20 molecule expressed on the surface of B cells. Rituximab therapy produces a rapid depletion of $CD20^+$ B cells from the circulation but does not directly target pro-B cells and their precursors or plasma cells [12,13]. In 2005 evaluated rituximab therapy in 8 patients with NMO. Thereafter several open mostly retrospective studies assessed the effectiveness of rituximab in patients with NMO [14-17]. These studies showed favourable outcomes with a significant reduction in relapse rate and a stabilization of disability in most cases. Recently, a systematic review performed a meta-analysis of the efficacy of rituximab in NMO [18]. Twenty-six studies were included in this review. The results provide evidence that rituximab therapy reduces the frequency of NMO relapses and improves disability in most patients.

To the best our knowledge, there is not any study focusing on the safety and efficacy of rituximab for NMO in Iran. Therefore, our study is designed with the aim of investigating the effectiveness and adverse effects of rituximab in the treatment of the patients with relapsing NMO.

Materials and Methods

Study design and patient population

The present study was designed as a prospective case study which was performed on all relapsing NMO patients older than 18 years referred to neurology wards of Nemazee and Shahid Faghihi hospitals during a 6 months period, from May to October 2017. The inclusion criteria was that all patients older than 18 years who have relapsing NMO according to the 2015 diagnostic criteria [19]. The exclusion criteria were pregnant women, severe comorbidity (liver or renal failure, evolving cardiac disease), immunodeficiency, and history of hypersensitivity to monoclonal antibodies, history of cancer and chronic infection, or abnormal complete blood cell count and missed follow-up or uncompleted document. The study protocol was approved by the Institutional Review Board (IRB) of sums and we obtained ethics approval from the local ethics committee before the study was commenced. All the participants gave their informed written consent.

Interventions and outcomes

The patients received 1000 mg of rituximab (two vials of RediTux 500 mg/50 ml, produced by Cinna Gen, Iran) in 500 cc of 0.9% sodium chloride through intravenous infusion twice at 2 weeks interval. This regimen was based on the previously reported studies of patients with NMO. Before each infusion, patients received premedication with acetaminophen (1 g oral), chlorphenamine (10 mg IV), and hydrocortisone (100 mg IV) to minimize hypersensitivity reactions. During infusion, patients were closely observed for side effects including hemodynamic compromise and anaphylactoid reactions. Maintenance infusion every 6 months was recommended based on clinical status and patient's preference. All patients were followed up at the neurology unit regularly.

The primary outcome was the neurological status of each patient. In addition, MRI evaluation and adverse events of the drug were considered as secondary outcomes. In order to obtain the values for neurological status, all of the participants were evaluated using Expanded Disability Status Scale (EDSS) score in 2 episodes (before starting the intervention and 12 months after the intervention). Baseline characteristics of the participants including age, gender and disease duration at first rituximab treatment were obtained by a data gathering form.

Statistical analysis

All statistical analyses were performed with the statistical Package for Social Sciences version 19.0 (SPSS) and differences were considered statistically significant at $P<0.05$. All data were expressed as mean ± SD or number and percentage as needed. The 95% confidence intervals for the means of data were calculated and the significance of differences between episodes were assessed using the Wilcoxon signed-rank test.

Results

Baseline characteristics

Fifteen patients were enrolled and treated (11 women, 4 men). The average age for starting rituximab therapy was 42.9 years ± 13.5 years (range, 21 years-65 years) and the median interval from the onset of NMO to treatment with rituximab was 7 years (range, 1 year-13.5 years). The table represents the baseline characteristics of the study patients **(Table 1).**

Table 1: Baseline characteristics of the study patients.

Baseline characteristics	NMO patients (n=15)
Age (year)	42.9 ± 13.5
Median disease duration at first Rituximab treatment (year)	7 (range 1-13.5)
Gender (%)	
Female	11 (73.3%)
Male	4 (26.7%)

Characteristics of dead patients

Two patients died during the 12 months follow-up due to a stage of the disease at the onset of rituximab course (EDSS=8.5). Patient number 8 had multiple T_2-hyperintense lesions through the white matter and a long hyper intense lesion at the level of C3-T5 cervical cord without enhancement. Patient number 15 had a T2-hyper intense lesion across the level of cervico medullary junction extended into the level of C1-C3 cervical level **(Table 2)**.

Table 2: Baseline demographics and clinical and MRI alterations in patients with NMO treated with rituximab.

Patients No	Gender	Age (year)	EDSS score before RTX	EDSS score after RTX	Brain MRI before RTX	Brain MRI after RTX	Spine MRIa before RTX	Spine MRIa after RTX
1	Female	56	2	1	Abnb	Abnb	T1-T4	T1-T3
2	Female	45	2.5	1	N	N	T1-T3	T1-T3
3	Male	22	9.5	8.5	N	N	N	N
4	Female	46	9	8.5	Abnb	Abnb	Abnc with enhancement lesions	Abnc
5	Female	21	7.5	2	N	N	N	N
6	Female	47	6.5	3.5	Abnb	Abnb	C7-T3	C7-T3
7	Male	55	8.5	8.5	Abnb	Abnb	C1-C5	C1-C5
8	Female	50	8.5	10	Abnb	N/A	C3-T5	N/A
9	Female	47	6	2	N	N	C3-C5 T1-T5	C3-C5 T1-T5
10	Female	25	6	3.5	N	N	C5-C7 Cervico medullary junction	C5-C7 Cervico medullay junction
11	Male	55	3.5	3	Abnb	Abnb	C1-C3 Cervico medullary junction	C1-C3 Cervico medullay junction
12	Male	41	8.5	7	N	N	N	Abnc
13	Female	26	8.5	1	Abnb	Abnb	C1-C6 Cervico medullary junction	C3-C4
14	Female	43	8.5	8.5	Abnb	Abnb	C1-C5	C1-C5
15	Female	65	8.5	10	N	N/A	C1-C3 Cervico medullary junction	N/A

Note: N/A: Not changes; available; Abn: Abnormal; N: Normal; RTX: Rituximab; EDSS: Expanded Disability Status Scale (a) T2-hyper intense signal (b) Several T2-hyper intense lesions with non-specific appearance different part of white matter; Diffuse T2-hyper intense lesions at different parts of spinal lesions cord; Enhancement

Disability

The mean EDSS score before starting treatment (n=15) was 6.9 ± 2.4 (range, 2-9.5), whereas it was 5.2 ± 2.6 (range, 1-10) at the end of follow-up (P=0.03). Among all patients, the EDSS score improved in 11 (73.3%) patients and stabilized in 2 (13.3%) of them.

Further deterioration of functional status was observed in 2 (13.3%) patients who died during the follow-up. Moreover, the most reduction in EDSS score was observed in patient number 13 (-7.5).

MRI Findings

Brain and spinal cord MRI of the two dead patients weren't available during follow-up and at the time of death. MRI assessment revealed no significant change in the CNS MRI of 9 alive patients treated with the rituximab during the 12 months follow-up period [20]. On the other hand, T2 - hyper intense lesion segments of spinal cord decreased in patients no 1,4,13 afterrituximab treatment, while it was increased patient no of 12.

Adverse events observed during treatment and follow-up

Transient infusion-related adverse effects (such as hypotension, rash and nausea) occurred in 4 of 15 patients (26.6%). At 12-month follow-up, new infections developed in 2 of 15 patients (13.3%), that didn't require treatment with intravenous anti-infective agents. One patient presented with herpes zoster, and a respiratory tract infection occurred in another patients.

Discussion

In this prospective case study, we evaluated the use of rituximab in patients with NMO with a 12 months follow-up. We observed a favorable reduction in EDSS score after treatment with rituximab in our case study of Iranian patients with NMO. During a 12 month follow-up, disability improved or stabilized in 13 of 15 patients (80%) and the mean EDSS score was significantly decreased. However, deterioration in disability was observed in the two patients, but all of them had an advanced stage of the disease at the onset of rituximab course. This was

concordant with the results from the majority of previous studies. A decreased mean EDSS score from 9 to 6.5, which was at that point, the patient had improved and was able to walk short distances with crutches. A retrospective review of 100 patients to evaluate the treatment outcomes of rituximab in NMO patients. In their study, the median EDSS score was four before rituximab treatment and three after treatment. The EDSS score improved in 58 patients and stabilized in 38 patients. A decrease from 4.5 to 4 in mean EDSS score before rituximab therapy in comparison to the score after therapy is reported in the study. Three of their patients presented with a tendency of EDSS scores reduction, whereas two experienced no changes. They mentioned that although some of EDSS score reductions did not achieve statistical significance, patients experienced significant improvements overall in pyramidal, sensory and bowel functions after therapy. In another cohort study a mean EDSS score of 5.8 ± 2.4 before therapy and a significant decrease in mean EDSS after therapy of 3.9 ± 2.6. They also mentioned that the variations of EDSS scores were not significantly reduced in both groups and the EDSS scores were significantly reduced after rituximab therapy. In contrast, one study reported an increase in the mean EDSS score after rituximab therapy. Five worsened mean EDSS scores, one stable and four improved EDSS scores in a total of 10 patients in their study, demonstrating an increase from 3.65 before rituximab therapy to 5.2 after rituximab therapy. The role of MRI in diagnosis, prognosis, and choosing the distinct treatments of NMO and NMOSD from CNS inflammatory diseases is very important. Results of MRI evaluation in our study demonstrated that no new MRI lesions or activity had been detected in 12 of 13 alive patients, however T_2-hyper intense lesion segments of spinal cord increased in one patient. Imaging findings before and after rituximab therapy has been reported in some studies. Overall, it gives the impression that MRI findings suggest no new, active or extended lesions after rituximab therapy [21]. Long-term safety and efficacy of rituximab therapy on 21 NMO patients are investigated. MRI was done every 6 months or in the presence of new clinical symptoms. Finally, new or enlarged lesions or pathological gadolinium enhancement weren't observed in serial brain and spinal cord MRIs, except for those observed concomitantly with clinical relapses. 5 patients with deteriorating NMO and NMOSD treated with rituximab are surveyed. Respectively, there were 8, 7.5, 4, 1, and 6 lesion segments of the spinal cord before treatment with rituximab in these five cases, which decreased to 3.5, 1, 1, 0.5, and 5 after treatment. According to MRI assessment, no new T_2 lesions and no enhancement in the CNS was detected in all five cases treated with rituximab during the 1-year follow-up period. The median of total T_2 lesions in the brain and spinal cord slightly decreased from 3 before rituximab therapy to 2.5 after treatment. On the other hand, the median length of spinal cord lesions significantly reduced from 5 to 2.5 over the 1-year period [22].

The safety profile of rituximab in this study was consistent with previous experience. Transient infusion-related adverse effects (such as hypotension, rash and nausea) or limited infections developed in 6 of 15 patients. The majority of the studies mentioned some adverse effects in rituximab therapy for NMO patients [23]. Some of these adverse effects were related to rituximab infusion and most of them were almost transient. Two patients developed some types of infusion-related adverse effect after the first dose of rituximab, whereas it was transient and was resolved with administration of 80 mg methylprednisolone and an antihistamine [24]. In another study, serious infectious status due to rituximab therapy led to death. In addition, this study reported mild hematological adverse events [25]. Some studies reported death of patients after rituximab therapy; However, some of them were due to background disorders. For example, several severe adverse effects in six of ten cases with NMO. However, the death of one patient was related to past cardiovascular disorder [26]. In a Chinese study, just two patients could not tolerate infusion and developed transient hypotension. Indeed, no patient developed an opportunistic infection during the follow-up period. Moreover, progressive multifocal leukoencephalopathy after rituximab therapy has been seen in a few cases with autoimmune diseases. At the end, it should be mentioned that we followed up the patients for 12 months and long-term consequences of repeated rituximab therapy in patients with NMO are unknown.

Conclusion

To the best of our knowledge, this is the first study which especially investigates efficacy and safety of rituximab in Iranian NMO patients. In conclusion, our study provides promising initial results that rituximab may also prevent further neurological deterioration, and especially when considering the strong suppression of disease activity in NMO patients. To further confirm the efficacy and safety of rituximab in NMO patients, multicenter, double-blind, randomized, placebo controlled trials should be performed.

Limitation

Our study was limited by short-term follow-up, the small number of patients, and the absence of a control group. Moreover, we didn't consider the post-treatment relapse rate as the main outcome to confirm the efficacy of rituximab. Despite these limitations, considering the rarity of the disease, the limited evidence of rituximab therapy in NMO and the ethical issues in conducting randomized clinical trials, our results are encouraging and should reassure physicians about the efficacy and safety of rituximab therapy in NMO.

Conflict of Interest

No authors report a conflict of interest.

Acknowledgment

This article was extracted from the thesis written by Abolfazl Rostami for the degree of specialty in neurology and was financed and supported by Research Vice-chancellor of Shiraz University of Medical Sciences (grant No. 9215).

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