ORIGINAL ARTICLE

The preventive Effectiveness of Rituximab in Pediatric Autoimmune and Inflammatory CNS Diseases Relapse an Iranian Experience

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Abstract

Objectives

To determine the effectiveness of Rituximab (RTX) therapy as the first therapeutic choice for the long-term prevention of secondary relapse in children with Autoimmue Neurological Disease (AIND) that had relapse after primary treatment with immunosuppressive agents other than RTX.

Materials & Methods

We conducted a single-center retrospective study of 9 consecutive pediatric patients (≤ 18 years old) registered on Autoimmune and Demyelinating Disorders Database (ADDD) of Mofid Children Hospital, from 2012 to 2016 and experienced relapse following therapeutic interventions with immunosuppressive agents other than RTX.

Result

A remarkable reduction of 94.13% (p=0.015) occurred in annualized relapse rate (ARR) as a clinical indicator of therapeutic efficacy comparing before and after initiating RTX therapy.

Conclusion

Rituximab is an effective drug in relapse prevention of AIND when administrated to patients for whom initial treatment with other immunosuppressive agents fail.

POWER OF EVIDENCE: This study represents Class IV evidence that RTX therapy significantly reduces ARR in pediatric AIND including DDCNS.

Keywords: Rituximab; CNS demyelinating diseases; Immunological disease; efficacy

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Introduction

Autoimmunity is the pathological state in which immune system acts against self. Similarly to systemic autoimmune diseases, autoimmune neurological diseases (AIND) may be mediated by all elements of the immune system, including B cells (1). Demyelinating disease of the central nervous system (DDCNS) such as optic neuritis (ON), multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) has long been considered as mediated primarily by T-cells; however, new evidence showed that the B cells seem to play an essential role in the pathogenesis of either DDCNS or other autoimmune central nervous system (CNS) and peripheral nervous system (PNS) diseases like opsoclonus- myoclonus syndrome (OMS), encephalopathies, peripheral neuropathies, neuromuscular junction disorders, and muscle diseases (1,2). One of an important achievement in the management of immune-based neurological disorders has been the availability of new biological agents targeting B cells or B-cell pathways, emphasizing the role of B-cell in the pathophysiology of neuroimmunological disorders (3).

Rituximab (RTX), a monoclonal antibody directed against B cells, binds to the CD20 antigen on the surface of mature B cells, which it targets for apoptosis and immune system-mediated destruction (3-4). RTX was firstly approved by the US Food and Drug Administration (FDA) in 1997 to treat B-cell non-Hodgkin's lymphomas(5) but has been used as an off-label agent for the treatment of several types of autoimmune disorders among children and adults, such as autoimmune hemolytic anemia, OMS, lupus erythematosus, idiopathic autoimmune thrombocytopenia, rheumatoid arthritis, autoimmune neuropathy, and Wegener's granulomatosis (6-9).

We decided to describe our experience with RTX therapy in 9 children with AIND including DDCNS that had relapse after primary treatment with immunosuppressive agents other than RTX.

Materials & Methods

1) Research objective and study power: The main objective of the present study was to determine the effectiveness of an anti-B-cell therapy with rituximab (RTX) as the first therapeutic choice for the long-term prevention of secondary relapse after the first relapse in the pediatric autoimmune and inflammatory CNS diseases. Given the retrospective nature of our study and the lack of a control group, the evidence represents Class IV (10).

2) Patient and study design: This single-center retrospective study was conducted on consecutive pediatric patients aged ≤18 years who had been registered on the Autoimmune and Demyelinating Disorders Database (ADDD) of Mofid Children Hospital, Tehran, Iran, during 2012-2016 and experienced relapse following therapeutic interventions with immunosuppressive agents other than RTX. The parents of subjects signed informed consent for this board-approved study.

3) Diagnosis criteria: We defined NMO/NMOSD and ON according to the revised Wingerchuk criteria (11, 12) and International Pediatric Multiple Sclerosis Study Group criteria (13), respectively. Although there are no definitive diagnostic tests for OMS, we considered expert diagnostic criteria for diagnosing OMS (14).

4) Planning a first-treatment course: Before the initiation of treatment, we performed pre-treatment workup for blood tests, including whole blood count, liver function tests, and serology for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). Moreover, varicella-zoster virus (VZV) serology was performed if there was no history of primary infection. For latent tuberculosis (TB) in high-risk patients, QuantiFERON-TB Gold(made by QIAGEN Company,USA) or tuberculin skin testing was performed, followed by a chest radiograph if indicated. Therefore, we excluded contraindications of RTX therapy, including:

1) Active and/or severe infection (e.g., TB, sepsis, and opportunistic infections)

2) History and/or clinical findings of immunodeficiency state

5) Administration and dosing

There is no validated dosing strategy for RTX in neuroinflammatory diseases, and there is considerable diversity in the articles. However, two dosing regimens are suggested more commonly by experts:

1) A dosage of 375 mg/body surface area given once weekly for 4 weeks (adopted from hemato-oncology)

2) Two infusions of 500-1000 mg given a fortnight apart (adopted from clinical trials in rheumatoid arthritis). Following two 1000 mg infusions, the mean half-life of RTX is 20.8 days with a range of 8.58-35.9 days.

We identified nine patients with NMO/NMOSD and ON who received RTX courses (<14 years at first dose). We employed the dosage of 375 mg/body surface area weekly for 4 weeks. It is infused over 3-6 h intravenously. Premedication with corticosteroids and antihistamines was administered. Immunization with influenza vaccine was performed in all patients except one because the parent expressed their disagreement. Furthermore, pneumococcal vaccination was recommended for all patients if possible. We repeated treatment courses at regular 6-month intervals even if there were no clinical or laboratory relapses (CD19>0.5%) (15).

6) Data collection: Demographic, clinical, and paraclinical data of patients were extracted from ADDD. Data collection focused on the relationship between RTX administration (timing, dose, the number of courses, and adverse reactions) and relapses. The data included age, gender, birth and development history, and preceding events. Clinical profile details, including the age of onset, duration, symptoms and signs, investigations, follow-up duration, relapses, and response to treatment, were noted. In addition, the results of MRI sequences and other paraclinical modalities, such as Visual Evoked Potential (VEP) and antibody levels, were reviewed and assessed for the presence of worsening or improvements over time. Disease duration before RTX therapy was defined as the time between the onset (first event) and initiation of RTX therapy. RTX treatment duration was defined as the time between RTX initiation and last follow-up (for patients with ongoing RTX therapy). We used annualized relapse rate (ARR) as a clinical indicator of therapeutic efficacy by comparing the ARR pre- and post-RTX therapy. ARR is defined as

the number of relapses with onset occurring during a specific period of time, adjusted to a one-year period. Patient-level ARR was calculated by the number of relapses experienced by that patient divided by the number of days the patient participated in the study, and the ratio multiplied by 365.25;it only included patients who were followed up after treatment for at least 6 months. Relapses were analyzed 15 months before the initiation of therapy and the duration of therapy.

7) Statistical analysis: Data were analyzed by the SPSS statistical software version 22. In this study, descriptive statistics included range, mean, median, standard deviation, number, and percentage. The number of pre-and post-RTX clinical events was compared using the Wilcoxon test. Moreover, Spearman's rank correlation coefficient (non-parametric) was used to assess the relationship between the number of relapses and treatment duration. $P<0.05$ was considered statistically significant.

Results

1) Demographics: We identified a total of nine children with autoimmune neurological diseases (AIND) hospitalized at our center during 2012-2016. There were five female (56%) and four male (44 %) patients. All patients met the published clinical criteria for individual AINDs (11-14). The mean and median age of disease onset was 7.6±3.4 and 9.5 years (range: 3-12 years), respectively.

2) Clinical presentation: There were seven patients (78%) with NMO/NMOSD, one (11%) with chronic relapsing idiopathic ON (CRION), and one (11%) with OMS. Several clinical presentations occurred in every relapse episode before and during RTX therapy, with hemiparesis being the most common sign detected in five patients (55.6%). Other presentations are shown in Table 1.

3) Paraclinical findings: Brain and/or spinal MRI as well as a VEP were performed in eight cases (89%) with suspected NMO/NMOSD and CRION;these subjects represented abnormal MRI and VEP findings consistent with the suspected conditions. All nine patients had normal immunoglobulins before treatment. The NMO-IgG levels (i.e., an autoantibody against AQP4) were measured in seven patients with suspected NMO/NMOSD (Table 1).

4) Immune therapies before RTX therapy: The administrated medications and/or therapeutic interventions before RTX therapy included first-line (intravenous methylprednisolone, oral prednisolone, plasmapheresis, and IVIG) and second-line (azathioprine) immune treatments (Table 1). Before RTX, all patients received IV methylprednisolone (mean of 2.9±1 courses per patient, range: 2-4), followed by oral prednisolone. Plasmapheresis was administered in six patients (mean of 7.2±2.2 cycles per patient, range: 5-10). IVIG was administered in all patients (mean of 4.6±1 cycles per patient, range: 3-6). Moreover, eight patients (89%) received azathioprine, and eight cases (89%) were vaccinated against varicella before receiving RTX.

5) Rituximab administration: A total of 59 RTX courses were administered to nine patients. The mean and median age at the initiation of RTX therapy was 8.6±3.4 and 10 years (range: 4-13.1 years), respectively. The mean interval between disease onset and RTX therapy was 12.1±3 months, with a range of 6-18 months. The mean duration of RTX therapy was 16.6±9.7 months, with a range of 4-30 months. (Table 2)

6) Infusion reactions and adverse events: Infusion reactions to treatment and/or adverse events occurred in five patients (55.6%). One individual who did not have a history of varicella-zoster immunization and had not received a related vaccine before treatment was affected by chickenpox (Table 2).

7) Rituximab efficacy and relapse episodes: Five (55.6 %) patients (patients 5-9) were relapse-free during RTX therapy in the follow-up of 6-12 months. In the four relapsing patients (44.4 %), five relapse episodes occurred during RTX therapy, while 21 relapse episodes occurred in these cases before RTX therapy with a long disease course (15-22 months). The mean number of relapse episodes before and during RTX therapy was 4.6±1.01 (range: 3-6 episodes) and 0.56±0.73 (range: 0-2 episodes), respectively. There was a statistically significant reduction in ARR after initiating RTX therapy when the first events were included ($P<0.008$) (Table 2).

The mean of ARR during 15 months before initiating RTX therapy was 4.6. After the median therapy duration of 29 months (range: 13-48 months), the mean ARR declined to 0.56, with a remarkable reduction of 88.7%. The mean of relapse episodes was 4.3 months, with a range of 2-8 months after the last RTX therapy course.

As presented in Figure 1, the results revealed a significant relationship between the duration of RTX therapy and a reduced number of episodes ($P=0.005$, $r=0.837$). However, the relationship of RTX therapy with gender was not significant ($P>0.05$). Figure 2 shows the distribution of relapse episodes before and during treatment with RTX, along with the median number of RTX therapy courses in this period. In our study, RTX therapy was generally initiated after ≥3 relapse episodes.

Table 1. Clinical and paraclinical features and first-line and second-line immune treatments administered before Rituximab therapy

Patient	Gender	Diagnosis	Age at disease onset (yr)	VEP	MRI findings	NMO antibody	MOG antibody	Type of clinical event	Prior immunosuppressive medications
1	M	NMOSD	10	Abnormal	Abnormal	-	-	Hemiparesis, vision disorder	IVMP, OP, PE, IVIG, AZA
2	F	NMOSD	3.5	Abnormal	Abnormal	+	-	Hemiparesis	IVMP, OP, PE, IVIG, AZA
3	F	NMOSD	9.5	Abnormal	Abnormal	+	-	Hemiparesis, blurred vision	IVMP, OP, PE, IVIG, AZA
4	F	NMOSD	10	Abnormal	Abnormal	+	-	Hemiparesis, fever, speech problem, vision disorder, convulsion, dLOC	IVMP, OP, PE, IVIG, AZA
5	F	NMOSD	9.5	Abnormal	Abnormal	-	-	Paraplegia, Neck pain, Urine retention	IVMP, OP, IVIG
6	M	NMOSD	7.5	Abnormal	Abnormal	-	-	Speech problem, Dysphagia, Hemiparesis, Urine retention	IVMP, PE, OP, IVIG, AZA
7	F	CRION	12	Abnormal	Abnormal	Not performed	Not performed	Blurred vision	IVMP, PE, OP, IVIG, AZA
8	M	OMS	3.5	Not done	Normal	Not performed	Not performed	OMS	IVMP, OP, IVIG, AZA
9	M	NMOSD	3	Abnormal	Abnormal	-	-	Paraplegia	IVMP, OP, IVIG, AZA

Abbreviations: *VEP=Visual Evoked Potential; MRI=Magnetic Resonance Imaging; NMO=Neuromyelitis Optica;* MOG=Myelin Oligodendrocyte Glycoprotein; M=Male; F=Female; OMS=Opsoclonus-Myoclonus Syndrome; N*MOSD=Neuromyelitis Optica Spectrum Disorders; CRION*=Chronic Relapsing Idiopathic Optic Neuritis; -=Negative; +=Positive; IVMP=IV Methylprednisolone; OP=Oral Prednisolone; AZA=Azathioprine; PE=Plasmapheresis; dLOC=Decreased Level of Conscious

Table 2. Duration of disease, frequency of clinical events, and side effects of Rituximab

Patient	Disease duration pre-RTXT (m)	Age at RTXT (yr)	RTXT duration (m)	RTXT courses (no.)	CEF before RTXT (no.)	CEF during RTXT (no.)	ARR before RTXT	ARR during RTXT	Side effects of RTX therapy
1	12	11	22	8	6	2	6	1.09	Tachycardia, vomiting
2	12	4.5	18	7	5	1	5	0.67	None
3	12	10.5	15	6	5	1	5	0.80	Dyspnea, abdominal pain, skin allergy
4	12	11	17	7	5	1	5	0.71	None
5	6	10	7	5	3	0	6	0	Dyspnea, hypoxemia
6	18	9	30	9	5	0	6	0	None
7	13	13.1	30	8	5	0	4.6	0	Fever and chills
8	12	4.5	6	5	4	0	4	0	Chickenpox
9	12	4	4	4	3	0	3	0	None
Mean±SD	12.1±3.02	8.6±3.4	16.6±9.7	6.6±1.7	4.6±1.01	0.56±0.73	4.96±1.01	0.36±0.45	
Median	12	10	17	7	5	0	5	0	
Range	6-18	4-13.1	4-30	4-9	3-6	0-2	3-6	0-1.09	

Abbreviations: RTXT=Rituximab therapy; CEF=Clinical Events Frequency; ARR=Annualized Relapse Rate

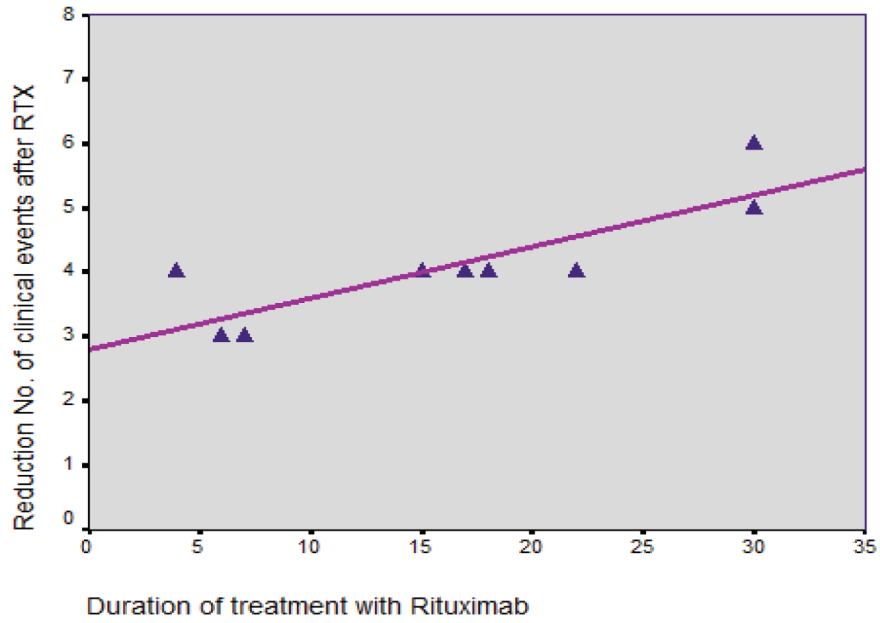

Figure 1. *Relationship between the mean duration of RTX therapy and reduced number of episodes*

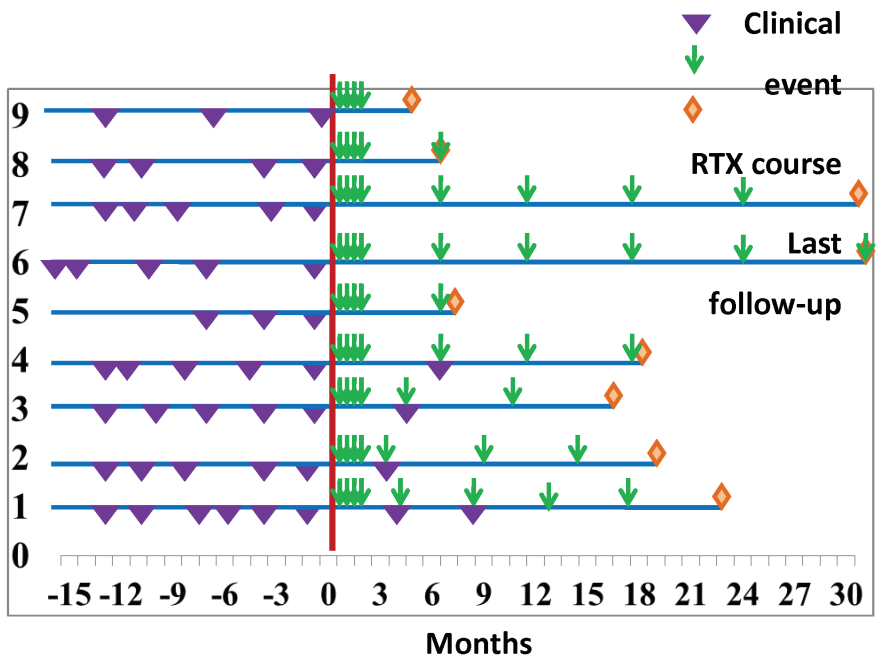

Figure 2. *Distribution of relapse episodes before and during treatment with RTX along with the median number of RTX therapy courses in this period*

Discussion

A) Autoimmune neurological diseases with and without CNS demyelination

Autoimmune diseases of the pediatric nervous system constitute a diverse group of uncommon disorders that can involve any region of the central and / or peripheral nervous system including brain, spinal cord, nerve roots, peripheral nerves, neuromuscular junction, and muscle. Accordingly, children of any age may present with various symptoms and signs with acute or subacute course in onset. It is important to determination of an

autoimmune process as the pathogenesis of clinical presentation, as it may result in early diagnosis of disease and timely initiation of immunotherapy with subsequently improved long-term prognosis (16). The antigen–antibody interactions are the basic mechanism in the primary pathogenesis of autoimmune neurological diseases that can lead to nervous system involvement with demyelination (e.g. NMOSD, ON and MS) or without demyelination (e.g. OMS) (17). In this study, there were 8 patients (89 %) with demyelinating disorders including NMOSD and chronic relapsing idiopathic ON, and one patient (11%) with OMS, non- demyelinating autoimmune nervous system disorder.

1) NMOSD/NMO: Neuromyelitis optica spectrum disorder (Devic's disease) is one of the DDCNS, notably involving the optic nerves and spinal cord (18). The characteristic features include recurrent episodes of longitudinally extensive transverse myelitis (LETM), extending ≥ 3 vertebral segments, as well as optic neuritis. Some patients with NMOSD/NMO may have an autoantibody against aquaporin-4 (AQP4) in serology (19-21).

Available literature about pediatric NMOSD/NMO originates some case series. In children and adults, the incidence and prevalence of NMOSD/NMO range from 0.05 to 4 and from 0.52 to 4.4, respectively but up to 3-5% of cases have childhood onset and between 4-10% of cases occur before the age of 18 years (22-25).Interestingly, NMOSD/NMO have been reported in children as young as 12-16 months; however, the typical age of onset is 10 to 12 years (26). In Japan, the incidence of children with NMOSD/NMO was reported as 0.06 per 100,000 persons (27). In our country, there is no epidemiologic study determining the incidence and prevalence of children NMOSD/NMO, although the current study showed that 78 percent of patients had NMOSD/NMO.

Females are more likely to be affected than males at a ratio of 3:1 in the pediatric population but up to 9:1 in adults (28). In many regions of the world, there is a pattern of female predominance in adults and children: east Brazil 5:1, Iran 5.9:1, 2.8:1 in Germany, 7:1 in Pediatric patients treated at Mayo Clinic, Spain 2.4:1, Southern Denmark 2.8:1, and in Japan 6.4:1. The disease predilection for females in NMOSD/NMO is stronger than in MS, in which gender ratio varies from 1.1:1 to 3.4:1 in Europe and 3.1:1 in United States. Due to the high prevalence in females, some investigators suggest the possibility of hormones influencing the development of NMOSD/NMO (29).

This ratio was 1.25: 1 in our study that was not similar to results of other studies, indicating more studies with more cases needed to be done. In a similar Iranian study conducted on adult NMOSD/NMO, female/male ratio was 5.4:1.

In our study, the mean age at the initiation of RTX therapy was 8.6 ± 3.4 years (range of 4 to 13 years). In similar studies of children NMOSD/NMO, the mean age at Rituximab administration was 9.6 (30), 9.9 (31), and 13.7 (32) years, suggesting comparable ages at the initiation of RTX therapy.

NMO-IgG (AQP4) is an antibody directed against the aquaporin-4 water channel located on astrocyte end feet. This serum biomarker has a sensitivity of 73% and a specificity of 91% in differentiating NMO from other demyelinating disorders, such as MS, in adult NMO patients and is detected in up to 78% of children with relapsing NMO (33). Approximately 65% of pediatric patients with NMOSD are AQP4 antibody seropositive; however, seropositivity may not occur at the time of the initial attack but up to 4 years later.

Approximately 10% to 15% of cases of pediatric NMOSD are MOG antibody seropositive, which has implications for both prognosis and treatment, and they may be considered separately from AQP4 antibody–seropositive cases. Dual seropositivity has not been reported in children. Approximately 15% of pediatric NMOSD cases are both AQP4 and MOG antibody seronegative. Moreover, seropositivity may not occur at the time of the initial attack but up to 4 years later. Therefore, serial testing is recommended for highly suspicious cases (34). In a study of 37 patients with NMOSD in the U.S. Network of Pediatric MS Centers, serum testing for NMO-IgG was positive in 60% of those tested. The timing of testing showed that, of the seropositive patients, 57% tested positive within 12 months of disease onset, 13% at 12 to 23 months, 13% at 24 to 35 months, and 17% at more than 36 months after disease onset (25). It has been recognized that a proportion of individuals with an NMO phenotype,are NMO IgG seronegative repeatedly even when sensitive cell-based assays are employed. A large retrospective study of 175 Caucasian NMO patients reported that compared with seronegative patients, seropositive patients were more likely to be female, to harbor additional serum autoantibodies, to have more severe clinical attacks, and to have a greater spinal cord lesion load, including an increased likelihood of having spinal lesions greater than six spinal segments in length. In the same study, seronegative patients were more likely to have bilateral ON or simultaneous ON and TM at presentation and were more likely to experience a monophasic (as opposed to relapsing) disease course (35).

In our study, 43% of cases were AQP4 antibody seropositive that was inconsistent with results of similar studies; this can be due to poor assay techniques or reduced number of patients. Also, it can be due to measurement of antibody during seronegativity period. A subset of children and adults with clinical NMO who are seronegative for NMO-IgG display serum anti-MOG antibodies. The two antibodies rarely coexist in the same patient, suggesting that anti-MOG antibodies are not simply a reflection of heightened autoimmunity in NMO patients (36-38).In our study, all patients were anti-MOG seronegative.

The VEP are frequently abnormal in NMO patients and typically display a prolongation or absence of the P100 response, in keeping with anterior visual pathway involvement. In adults with NMO, markedly abnormal or absent visual-evoked potential responses at baseline are associated with worse longer-term visual outcomes. Delayed P100 responses may be observed in the absence of a clear history of ON, suggesting subclinical optic nerve involvement for some patients (39, 40). In current study, a VEP was abnormal in all patients.

2) ON: Optic neuritis is one of the most common presentations of acquired

demyelinating syndromes in childhood and should be considered in the differential

diagnosis of any child presenting with acute or subacute visual.

3) OMS: Opsoclonus-myoclonus syndrome (OMS) is a rare and primarily immune-mediated non-demyelinating disease in children and adults. The main symptoms include opsoclonus, myoclonus and ataxia. In children, the symptoms also include irritability, and, over a long-term course, learning and behavioral disturbances. OMS can be idiopathic, parainfectious or occur as a paraneoplastic (tumor-associated) syndrome. Paraneoplastic OMS in children is almost exclusively associated with neuroblastoma,

whereas in adults, small cell lung cancer and breast cancer are the main underlying tumors. An autoimmune pathophysiology is suspected because childhood OMS patients have functionally active autoantibodies, proinflammatory changes in the cytokine network and immunotherapy responses. Children appear to respond regularly to immunosuppressive treatment. However, although the neurological symptoms show a good response, most children continue to show neuropsychological disturbances (42). In present study, one patient (11%) had OMS.

B) Rituximab therapy in autoimmune neurological diseases

1) Overview: Similarly to systemic autoimmune diseases, autoimmune neurological diseases may be mediated by all elements of the immune system, including B cells (43). Rituximab (Mabthera, Rituxan) is a chimeric human/murine monoclonal antibody against CD-20 surface antigen expressed on B-cells. Rituximab, by causing B-cell depletion, appears to be effective in several autoimmune disorders (44). Rituximab induces both apoptotic and cytotoxic (ADCC and CDC) cell death in CD20-expressing B cells (43). A triggered reduction of antibody formation is presumably the RTX mechanism of action (45).

2) RTX and NMOSD: NMO is a relapsing disease with a high early mortality

rate. More than 50% of patients with NMO will be functionally blind or will progress to wheelchair dependence within 5 years without employing appropriate immunosuppressant treatment (46,47). Treatment options for NMO are based on case series and expert opinion; among which, immunosuppressive therapy is the main method used to prevent recurrence and disability. Successful use of RTX has been widely reported in NMO. However, randomized controlled trials in NMO are relatively few, and no established guidelines have been established for RTX treatment. Although RTX is expensive, it can offset the cost of recurrence and plasma exchange due to its good therapeutic effect (48, 49)

In 2005, an open label study described for the first time a significant reduction in disease activity in eight NMO patients treated with RTX (50). In this study, RTX was infused weekly at 375 mg/m2 for 4 weeks followed by 1,000 mg reinfusion if CD19+ B cells were detectable in the peripheral blood. Positive curative effect was observed in all cases. Since then, an increasing number of patients were treated with RTX. However, to date only a few prospective studies investigating the effect of RTX on NMOSD exist (45).

The therapeutic effects of RTX last weeks to begin due to its long half-life which include observed benefits such as reduced relapse rates and maintained or improved patients' neurological health (50, 51). Despite these claims, not all patients respond favorably to this medication, as several cases report relapse episodes after therapy initiation (51, 52). This can happen due to a sudden increment of the anti AQP4 antibodies expressed by the patients after a 2 week period (52). In another 5-year prospective study, researchers reported that 26 of 30 patients benefited from the treatment (53). Generally, as mentioned in methods, there are two different regimens (15). In most studies, Rituximab was administered at regular 6-month intervals beginning with four weekly doses of 375 mg/m2 followed by two biweekly doses of 1 g (50, 53-55). Other studies used more frequent infusions (usually 1 g every 12 months) (56, 57) or administration depending on circulating B-cell numbers (54-57). In each study, patients

treated with Rituximab demonstrated a significant stabilization of disability.

In a retrospective analysis, 25 patients with Devic's disease, who were unresponsive to other treatments, showed significant improvement with RTX therapy. Patients were followed for 19 months after receiving the standard regimen of 2g in 1 month. This study although retrospective and uncontrolled showed that up to 80% of patients with Devic's disease may benefit from RTX therapy (54).A Multicenter retrospective study of 16 children with NMO/NMOSD receiving ≥ 2 RTX courses showed that Rituximab is effective in relapse prevention (30). Similar to results of other studies(30,50-57), our patients had a high relapse rate (41 episodes) and a long disease course (6-18 months) before RTX therapy but both reduced significantly following treatment initiation, suggesting competent preventive effectiveness of Rituximab.

All patients received immunosuppressive therapies before RXT therapy. All received IV Methylprednisolone and IVIG, 89% received Azathioprine and 67% received plasma exchange. History of immunosuppressive therapy before RTX therapy in our study was comparable to other studies (54-58). In present study, Rituximab was generally initiated after ≥ 3 relapse episodes while in the most studies it was initiated after ≥ 1-2 relapse episodes (50-58).This delay in the initiation of RXT therapy compared to similar pediatric studies can be due to a variety of factors including loss of adapted guideline in Iran, poor socioeconomic state of patients' family, misdiagnosis of affected patients in the early visits and inadequate drug deposit and / or drug delivery in Iran, emphasizing evaluation of the causes of delayed treatment in another study and solving problems based on the results.

3) RTX and OMS: The first successful treatment of pediatric OMS patients using Rituximab was done by M. Pranzatelli in 2005 (64). The same investigator showed the efficiency of Rituximab in a group of 16 children with OMS with an increased subset of B-cells in the CSF after unsuccessful treatment with ACTH, IVIG or both (59).

In a study mainly investigated the safety of Rituximab in pediatric neurological autoimmune diseases, which included more than 30 pediatric OMS patients. Whereas all OMS patients had a modified ranking scale (MRS) of 3 that was worse before treatment, Rituximab led to a significant improvement (60). Other studies confirm the beneficial effects of Rituximab (59, 42, and 61).

In Conclusion

RTX has acceptable tolerance, reduces the relapse frequency, and improves disability in most patients with NMO/NMOSD and other AINDs such as OMS. Future studies should focus on reducing the health-care costs, improving the functional outcomes, and reducing the adverse effects associated with RTX treatment.

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All authors declare that they have no conflicts of interest.

The research was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1397.1331)

Author's Contribution

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Conflict of interest

None

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