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Clinical Observations

Rituximab Use in Pediatric Central Demyelinating Disease

Shannon J. Beres MD [a,*], Jennifer Graves MD, PhD [a], Emmanuelle Waubant MD, PhD [a,b]

[a] *Department of Neurology, University of California, San Francisco, California*
[b] *Department of Pediatrics, University of California, San Francisco, California*

ABSTRACT

BACKGROUND: Rituximab is a B-cell therapy used off-label to reduce relapses in adult demyelinating diseases. There is limited knowledge of its clinical use in pediatric neuromyelitis optica and multiple sclerosis. Demyelinating diseases in children can have high morbidity, and B-cell therapies hold promise for those with a severe course. Our study investigates the clinical experience of safety and efficacy with rituximab in children with demyelinating diseases of the central nervous system. **METHODS:** This is a retrospective case series of 11 patients with pediatric neuromyelitis optica and multiple sclerosis who received at least one rituximab infusion at the Pediatric Multiple Sclerosis Clinic, University of California, San Francisco. Each patient was infused up to 1000 mg twice 2 weeks apart. Patients were monitored prospectively, and relapse events, laboratories, and adverse reactions were recorded. **RESULTS:** Eight children with neuromyelitis optica, two with relapsing-remitting multiple sclerosis and one with secondary-progressive multiple sclerosis received rituximab treatment. The median number of cycles was 3. Most patients (82%, n = 9) experienced reduction of relapses after initiating rituximab. There were no serious infections. Infusion reactions were reported in three patients and managed successfully in subsequent infusions with increased pretreatment (dexamethasone and diphenhydramine) and use of slower infusion rates. Rituximab was not discontinued in any child because of side effects; two switched treatment therapy after 4.5 and 11 months because of relapses. **CONCLUSIONS:** The use of rituximab in our pediatric neuromyelitis optica and multiple sclerosis cohort was overall safe and effective. Larger studies should confirm our observations.

Keywords: multiple sclerosis, neuromyelitis optica, demyelinating diseases, rituximab, treatment, devic disease

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Introduction

Neuromyelitis optica (NMO) and multiple sclerosis (MS) are autoimmune inflammatory diseases of the central nervous system (CNS) that may result in severe and early disability even when they occur in childhood. NMO is associated with autoantibodies to the water channel aquaporin 4 (AQP4) expressed on astrocytes.[1] Evidence for B-cell mediated pathology is also reported in MS and includes the production of oligoclonal IgG antibody in the cerebrospinal fluid and the presence of B-cells in MS lesions. More recently, the significance of memory B-cell and B-cell cytokine responses have been highlighted in MS.[2] Rituximab is an anti-CD20 monoclonal chimeric antibody that dramatically reduces circulating memory and naïve B-cells while preserving mature plasma cells that do not express CD20 on their surface. The effect of rituximab in adults reveals great promise in small observational off-label treatment studies of NMO and in clinical trials in relapsing-remitting multiple sclerosis (RRMS).[3-9]

As a result of the perceived effectiveness of rituximab in adult CNS demyelinating disorders, it is now being used in children with demyelinating disease. However, very little is known about the use of this therapy in pediatric MS and NMO. Two case reports in children with NMO[4,10] and a case series of NMO including eight children[11] suggest rituximab is well tolerated and may reduce disease progression. There

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* Communications should be addressed to: Dr. Beres; Department of Neurology; University of California; Box 0114; 505 Parnassus Avenue; M798; San Francisco, CA 94143.
E-mail address: beress@neuropeds.ucsf.edu

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are no reports of rituximab therapy for MS treatment in children to date. Different than in adults, frequent childhood viral illnesses and routine vaccinations are unique safety concerns with the chronic use of B-cell targeting agents in this young population.

We sought to describe our longitudinal experience with rituximab therapy in 11 children with CNS demyelinating disease monitored at our center. We describe the relapse frequency of NMO and refractory MS in children before and during rituximab treatment, as well as medication tolerability in this population.

Methods

This is a retrospective case series of the use of rituximab in children with CNS demyelinating diseases observed at the Regional Pediatric MS Clinic, University of California, San Francisco between September 2005 and November 2013. We identified all patients treated at our center with rituximab through a search of our database and authorization records. This study is part of an Institutional Review Board-approved project ongoing at our institution. Inclusion criteria were a diagnosis of NMO or MS based on published disease criteria,[12] <18 years old at the time of disease onset, and at least 6-month follow-up after first rituximab dose.

We performed a chart review of all available medical records for these patients and recorded demographic data (gender age at onset, and National Institute of Health definitions of self-reported race and ethnicity), relapse event dates with clinical features, laboratory data (cell counts pre- and post-rituximab and AQP4 antibody status performed at the Mayo Clinic laboratory by enzyme-linked immunosorbent assay), previous treatments, vaccinations, and adverse events. Relapse events were new neurological deficits lasting >24 hours in the absence of fever or other findings suggestive of pseudoexacerbation and >30 days after a previous relapse.

A standard rituximab regimen was adapted from adult and pediatric rheumatology studies[13] for all patients, and an infusion (maximum 1000 mg per infusion) was administered twice, 2 weeks apart. For patients who initially started at a dose lower than the maximum, dose escalation was considered if there was early B-cell reconstitution (≤6 months after the last rituximab infusion). Dose escalation was generally an increase of 500 mg per cycle. Cell blood count with differential, CD4, CD8, and CD19 counts were monitored every 2-4 months. Retreatment with rituximab was administered either yearly or more frequent, if CD19 B-cell counts recovered before a year.

Results

Patient characteristics

We identified 11 children treated with rituximab at our center, all of who met inclusion criteria. There were two male and nine female patients. Eight patients (Patients 1-8) met the currently published clinical criteria for NMO.[12] Most (75%, n = 6) were seropositive for AQP4 antibodies. The median age of NMO disease onset was 8.6 years old (range, 2.8-16.2 years). One patient (Patient 9) had onset of MS at an age of 17.9 years (progression to secondary-progressive multiple sclerosis) and two had RRMS (Patients 10 and 11) with respective disease onset at ages 10.8 and 11.8 years. The median disease duration before the first rituximab infusion was 9 months (range, 3 months to 8 years) for the NMO cases and 3.7 years for the MS cases (range, 3.0-3.8 years). The median treatment duration (calculated by the time between the initial rituximab treatment dose to the date of manuscript submission for those still in treatment, the date of therapy change [Patients 4 and 7], or the date of last rituximab dose [Patients 1 and 9]) was 19 months, and the median number of rituximab cycles was 3. At the initiation of rituximab, 10 patients were on monotherapy and one patient (Patient 2) continued pre-rituximab treatment, mycophenolate mofetil (1000 mg twice daily). The clinical and demographic characteristics of the patients are outlined in Table 1.

Infusion regimen

An infusion dose of 208-584 mg/m^2 (maximum dose 1000 mg per infusion, total dose per cycle range, 416-1168 mg/m^2) was administered twice, 2 weeks apart. The details of the exact infusions are depicted in Table 2. Two of the patients with MS started with higher dose per body surface area at initiation (approximately 580 mg/m^2). Premedication included oral acetaminophen (15 mg/kg, maximum 650 mg) and oral diphenhydramine (0.5 mg/kg, maximum 50 mg) 30 minutes before starting the infusion. In some cases, intravenous dexamethasone (0.2-0.5 mg/kg, maximum 50 mg) was given during pretreatment. The standard rate protocol for the first infusion includes starting at 50 mg/hr and increasing by 50 mg/hr every 30 minutes until 400 mg/hr.

Disease activity on treatment with rituximab

Before the initiation of rituximab, the patients experienced a mean of 4 relapses per year (range, 0.3-10.2), with

TABLE 1.
Demographic and clinical characteristics of patients

Variable	n	Median (Range)	%
Gender			
Female	9		82
Ethnicity			
Exclusively Hispanic	3		27
In-part Hispanic	1		9
Non-Hispanic	7		64
Race			
Exclusively white	5		45
In-part white	2		18
Non-white	4		36
Disease type (% of patients)			
NMO	8		73
RRMS	2		18
SPMS	1		9
Age (yr) at disease onset		10.1 (2.8-17.9)	
NMO		8.6 (2.8-16.2)	
RRMS and SPMS		11.8 (10.8-17.9)	
Age (yr) at first rituximab infusion		14.7 (3.1-21.0)	
NMO		10.4 (3.1-16.6)	
RRMS and SPMS		15.5 (14.7-21.0)	
Disease duration (mo) at first rituximab infusion		9 (3-94)	
NMO		6 (3-94)	
RRMS and SPMS		45 (36-46)	
Time (mo) between cycles* of rituximab		7 (3-12)	
Number of cycles* of rituximab		2†	

Abbreviations:
NMO = Neuromyelitis optica
RRMS = Relapsing-remitting multiple sclerosis
SPMS = Secondary-progressive multiple sclerosis
* Cycle includes two infusion of rituximab spaced about 2 weeks apart.
† Six patients currently in ongoing rituximab treatment.