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Case Series

The Hammer and the Nail: Using Rituximab to Treat Pediatric Neuroimmunologic Diseases

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Abstract

Pediatric neuroimmunologic diseases are rare, autoinflammatory conditions affecting both the central and peripheral nervous systems. Treatment options are based on anecdotal evidence and adaptation from adult treatment protocols. Rituximab has emerged as a highly effective disease modifying therapy and immunomodulator across multiple neuroimmunologic diseases. Despite potential for serious side effects and cost related to rituximab use, when used appropriately rituximab is well tolerated, appears to have reasonable short- and long-term side effect profiles, and may be useful across a variety of neuroimmunologic conditions. Herein I report five different patients with distinct pediatric neuroimmunologic diseases including: chronic inflammatory demyelinating polyneuropathy (CIDP), pediatric onset multiple sclerosis (POMS), neuromyelitis optica immunoglobulin (NMO-IgG) positive NMO spectrum disorder (NMOSD), NMO-IgG negative NMOSD, and opsoclonus myoclonus ataxia syndrome (OMAS). Each patient responded well to rituximab with reduction of baseline disease activity and in some cases, disability. Rituximab was well tolerated, though there were three infusion-related reactions, none of which were life threatening or interfered with continued rituximab treatment. Two of the five received concomitant intravenous immunoglobulin therapy for baseline disease activity, but there was no hypogammaglobulinemia to date. These cases provide class D evidence of rituximab therapy and contribute to the growing literature supportive of wider off-label use of rituximab in pediatric neuroimmunologic diseases.

ABBREVIATIONS

AChR: Acetylcholine Receptor; ADEM: Acute Disseminated Encephalomyelitis; AIDP: Acute Inflammatory Demyelinating Polyneuropathy; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; CNS: Central Nervous System; DMT: Disease Modifying Therapy; GA: Glatiramer Acetate; IgG: Immunoglobulin G; INF: Interferon-beta-1a; IVIG: Intravenous Immunoglobulin; IVMP: Intravenous Methylprednisolone; MRI: Magnetic Resonance Imaging; MuSK: Muscle Specific Tyrosine Kinase; NEDA: No Evidence of Disease Activity; NMOSD: Neuromyelitis Optica Spectrum Disorder; POMS: Pediatric Onset Multiple Sclerosis; OD: Right Eye; OMAS: Opsoclonus Myoclonus Ataxia Syndrome; OS: Left Eye; PML: Progressive Multifocal Leukoencephalopathy; PNS: Peripheral Nervous System; RCT: Randomized Controlled Trial

INTRODUCTION

It is said that when one is a hammer all problems appear as nails. If the problem considered is pediatric neuroimmunologic disease, then rituximab, a murine monoclonal anti-CD 20 monoclonal antibody, has emerged as a very useful hammer. Far from a panacea for all such diseases, rituximab has its limitations and well characterized risk factors including infusion-related reactions, hypogammaglobulinemia, activation of latent chronic infections, and increased risk for acquired and potentially serious infections. However, for a variety of pediatric neuroimmunologic diseases for which B-cell depletion has been shown to be efficacious in limiting clinical disease, the off-label use of rituximab has become a valuable and reliable tool [1-3].

Pediatric neuroimmunologic and neuroinflammatory diseases affect the central and/or the peripheral nervous system (CNS and PNS, respectively) resulting in myriad clinical presentations and syndromes. Unlike adult patients whose nervous systems are intact at the time of disease onset, pediatric neuroimmunologic diseases have neurodevelopmental consequences that can affect the academic, social, and economic future of the patient and his or her family [4]. Presenting neurologic symptoms may mimic common pediatric maladies such as constipation

(myelitis), headache (optic neuritis), gastroenteritis (brainstem syndrome), or mood disorder (autoimmune encephalitis), among others, resulting in delayed recognition by parents and medical providers [5]. Once a diagnosis is made, patients and their parents are presented with immunosuppressive treatment options including steroids, intravenous immunoglobulins (IVIG), steroid-sparing immunosuppressive agents, and disease-specific disease modifying therapies (DMTs). These treatments have variable efficacies in neuroinflammatory diseases, and myriad side effects, some of which obviate chronic use in pediatric patients. Further, pediatric patients rely on their parents to make treatment choices on their behalf, and often these choices are made based on limiting medication side effects, rather than disease-specific risks and long-term disability [6]. The rarity of pediatric neuroimmunologic diseases makes large prospective, placebo-controlled, randomized clinical trials (RCTs) difficult [7]. Therefore, clinicians rely on case reports and experience to empirically treat pediatric neuroimmunologic diseases, with each patient serving as his or her own n=1 clinical trial. Treatment goals for these patients must include halting disease activity, minimizing symptoms as well as treatment-related side effects, preservation of neurodevelopment and improving quality of life [8]. These efforts are often limited by insurance denials for off-label use of expensive therapies, patient or family reservations about potential side effects, and difficulty with acquisition and administration of some agents due to class designations as chemotherapeutics (IR personal experience).

The goal of the following case reports is to demonstrate five patients with five unique disease states for which rituximab has limited or resolved disease activity: chronic inflammatory demyelinating polyneuropathy (CIDP), pediatric onset multiple sclerosis (POMS), neuromyelitis optica immunoglobulin (NMO-IgG) positive NMO spectrum disorder (NMOSD), NMO-IgG negative NMOSD, and opsoclonus myoclonus ataxia syndrome (OMAS). While not a replacement for prospective RCTs, these patients' experiences can be added to the growing body of literature supporting the off-label use of rituximab in pediatric neuroinflammatory disease.

MATERIALS AND METHODS

Retrospective chart review of patients known to the treating neurologist. Inclusion criteria were diagnosis with a pediatric neuroimmunologic disease, and treatment with at least two doses of rituximab after August 2016 but before April 1, 2018. IRB approval was sought and obtained through Akron Children's Hospital. Patient/guardian assent was obtained when available.

CASE PRESENTATIONS

Case 1: CIDP

RL was a previously healthy, developmentally normal girl who presented at age 11 with slowly progressive left sided weakness and tingling. She initially presented to an emergency department with onset of symptoms over two weeks, and was found to have a left foot drop, decreased reflexes in the left patella and ankle, and some decreased sensation to pain and light touch in the lateral aspect of the left foot. She was discharged without further work up due to an up-coming family vacation. Upon her return two weeks later, symptoms had progressed to include left hand weakness and painful paresthesias, as well as more impaired gait and recent falls. Initial MRI of the brain and cervical spine was negative, but lumbar puncture showed elevated protein (79, normal 15-45 mg/dL) with normal white blood cell count (4, normal 0-5/μL). A nerve conduction study was performed approximately 5 weeks after onset of symptoms which revealed a diffuse demyelinating motor and sensory polyneuropathy affecting all limbs, including asymptomatic limbs. MRI of the lumbar spine with gadolinium demonstrated nerve root enhancement, affecting the left sided nerve roots more diffusely, consistent with the clinical picture. She was diagnosed with acute inflammatory demyelinating polyneuropathy (AIDP), or Guillain-Barre Syndrome, and was admitted for intravenous immunoglobulin (IVIG) treatment 2 gram (g)/kilogram (kg) body weight divided into two consecutive daily doses.

The patient's symptom progression halted with IVIG treatment, achieving a nadir about 5 to 6 weeks from onset, and began to improve dramatically in the week following IVIG. The patient received intensive rehabilitation as an outpatient and recovered function essentially back to baseline by 9 months. She failed to return to neurology for follow up but followed up with physiatry who documented her clinical and functional recovery.

Approximately 19 months following her initial presentation, RL (2 weeks from her 13th birthday) presented with 5 days of progressive left leg numbness, tingling, and weakness, similar to her initial presentation. Upon neurologic exam, she was found to have weakness predominantly affecting the left arm, hand, and both proximal and distal left leg, but also affecting right ankle dorsiflexion. There was also decreased sensation to light touch, pain, and vibration predominantly in the left hand and left lower leg. MRI lumbar spine again showed mild contrast enhancement of the left sided nerve roots; repeat lumbar puncture was attempted but failed, and given the history, exam and MRI findings no further attempts were made. A comprehensive work up failed to identify infectious or inflammatory etiologies for RL's symptoms, including anti-ganglioside antibody panel, which was negative. RL was again treated with IVIG 1g/kg body weight daily for two doses, which halted symptom progression and allowed recovery of some function. Upon follow up at 4 weeks, RL continued to show significant left sided weakness, though she no longer had painful paresthesias or numbness, and sensory testing was essentially normal. Three weeks later, RL had a third clinical relapse with progressive worsening of left sided numbness and tingling, painful paresthesias and left leg weakness, approximately 7 weeks from her last IVIG. Based on the initial slow nadir, paraclinical testing demonstrating demyelinating senosorimotor polyneuropathy, acute MRI imaging demonstrating nerve root enhancement, and cerebrospinal fluid cytoalbuminologic dissociation, RL met criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) and began on maintenance IVIG 1 gram/kg every 4 weeks.

Despite IVIG treatment and on-going physical therapy, RL continued to have symptom exacerbation requiring more frequent IVIG treatments. At age 13.5 years, approximately 2 years from her initial presentation, RL was requiring IVIG every 2 weeks, including at least one additional relapse in which IVIG treatment was needed twice in 3 days (total 2g/kg) to halt

symptom progression. Her IVIG treatments required frequent missed school days and lost work productivity for her parents. She was developing chronic left leg weakness affecting her gait and she continued to have left-sided hyporeflexia; she had paresthesias that disrupted her sleep, requiring treatment with gabapentin for a short time. Given her on-going symptoms and need for frequent IVIG the decision was made to escalate therapy to include Rituximab.

RL received Rituximab 500mg/m2 doses each on day 1 and day 15, approximately 27 months after her initial CIDP symptom onset. She tolerated both infusions without side effects or infusion reaction. She continued to tolerate every 4 weeks IVIG treatments without recurrence of symptoms, and by three months following her Rituximab treatment RL had recovered significant function in the left leg, with only mild left hip flexion and left dorsiflexion weakness. She requested to space out IVIG treatments to avoid interference with school. At the time of writing, RL has received an additional rituximab treatment 6 months after the initial treatments, and is tolerating IVIG every 8 weeks without symptom recurrence. She is three years from her initial CIDP symptom onset, has an essentially normal neurologic exam with normal reflexes, normal sensory exam, and very subtle fatigable left hip flexion and left dorsiflexion. She has had one mild rituximab infusion reaction (infusion #3) consisting of oral itching and mild pharyngeal urticaria that responded well to diphenhydramine and a slower infusion rate. There have been no concerns for recurrent infections or other rituximab side effects. She is 14 years old, participates in volleyball, and has missed very few school days in 8th grade due to doctor's visits or treatments. Given the success of rituximab, this will be continued q6 months for an additional 3 doses (i.e. 2 years), during which time IVIG will be weaned to every 3 months dosing, and then stopped. Given the potential for some CIDP patients to go into remission, RL will be challenged with cessation of treatments after her fourth q6 month rituximab treatment.

Case 2: NMO-IgG positive NMOSD

EB was a previously healthy, neurodevelopmentally normal 7-year-old girl when she presented with progressive vision loss in the left eye (OS) associated with a sensation of retroorbital pressure, but no pain with eye movement. Her symptoms progressed over 3 weeks to complete vision loss OS. One month later she was evaluated by ophthalmology who found no abnormalities on fundoscopic exam, but did document complete vision loss, and abnormal visual evoked potentials bilaterally, but worse OS. One month following loss her visual symptoms, EB developed numbness and tingling bilaterally in the hands and the lower extremities and had some difficulty with balance and gait due to sensory impairment. An MRI of the brain and orbits was obtained about 4 months following onset of vision loss, but both were unremarkable; no cervical spine imaging was obtained at that time.

EB's sensory symptoms persisted with mild daily fluctuations, but there were no new neurologic symptoms until 9 months later, now age 8 years old. At that time EB developed rapidly progressing bilateral hand dysfunction and bilateral leg weakness resulting in significant disability over the course of a couple of days. She also noted new vision loss in the right eye (OD), which prompted her presentation to the emergency department. Upon presentation, there was mild weakness noted in her hands and moderate weakness distally in the lower extremities, associated with hyperreflexia including ankle clonus, decreased range of motion at the knees, and up-going plantar reflexes. These findings were concerning for acute and chronic upper motor neuron signs. MRI of the brain was unremarkable (no dedicated orbit study), but MRI of the spine revealed a longitudinally extensive transverse myelitis (LETM) from the medulla distal to the upper boundary of T2, and a second smaller focus of myelitis opposite spinal level T3. The cord was T2 hyperintense, expansile, and demonstrated contrast enhancement from the medulla to spinal level C7, with distinct enhancing lesions at T1 and T3. Given the history of likely optic neuritis OS, and additional relapse with optic neuritis OD as well as clinical and MRI evidence of LETM, a clinical diagnosis of neuromyelitis optica spectrum disorder (NMOSD) was made [9]. Lumbar puncture and CSF analysis was negative for oligoclonal bands or evidence of infection or neoplasm. No other inflammatory or infections etiologies were uncovered with routine serologic testing. Anti-aquaporin-4 (AQ4) IgG was sent and eventually returned positive, confirming the diagnosis of NMO-IgG positive NMOSD. EB was treated with methylprednisolone 30mg/kg/day for 5 days followed by a very slow prednisolone oral taper. Her vision stabilized OD with only partial visual field loss, and her bilateral weakness and spasticity mildly improved. Given the severity of her symptoms she was admitted to inpatient rehabilitation for three weeks, followed by three weeks of outpatient day rehabilitation services, through which she regained functional strength, balance, and ambulation without assistance. She did not recover full strength, and she remained blind OS.

Given her history of at least two relapses in the first year of disease onset, EB was at high risk for additional NMOSD relapse, and thus required treatment with a disease modifying therapy (DMT). At the time of diagnosis, EB had significant social upheaval with unstable housing, and there was concern for non-compliance with orally administered DMT. EB experienced rapid weight gain with oral steroids, thus there was great need for steroid-sparing therapy. In the absence of approved DMT for pediatric or adult NMOSD, the decision was made to begin Rituximab 500mg/m2 day 1 and day 15 followed by every 6 months treatments. During the initial treatment, despite routine pre-treatment with acetaminophen, diphenhydramine, and methylprednisolone, EB experienced an infusion reaction consisting of difficulty breathing with mild drop in pulse oximetry to 90%, and throat and mouth itching. She responded well to high flow oxygen and additional diphenhydramine and methylprednisolone but did not require any epinephrine. She was able to complete the infusion at a slower rate without additional reactions. She has since completed four subsequent rituximab infusions and remains relapse-free with significant improvement in motor function. She remains entirely blind OS with visual acuity 20/250 OD, but has no residual weakness, and her gait and balance have recovered essentially to normal. She has mild proprioceptive and two-point discrimination deficits that have manifested with some difficulty learning Braille. There have been no concerns for recurrent infection or other rituximab side effects.

Case 3: NMO-IgG negative NMOSD

DC was a previously healthy neurodevelopmentally normal 14-year-old boy who developed progressive bilateral vision blurring and loss of visual acuity over a 2-week period. There was no pain at that time. He was evaluated by two ophthalmologists who documented bilateral afferent pupillary defects (APDs), optic disc pallor bilaterally (OU), loss of color vision and visual acuity of 20/800 OU. An MRI of the orbits with and without contrast two months after symptom onset was negative. DC was referred to pediatric neurology about three months after onset of symptoms at which time he also complained of new onset bilateral foot numbness and was found to have significantly reduced vibration sense bilaterally at the great toes; other than optic pallor on fundoscopy and decreased vibration sense, the neurologic exam was normal. Additional MRI of the orbits, brain, and entire spine about 4 months after symptom onset revealed subtle contrast enhancement bilaterally in the pre-chiasmatic portion of the optic nerves, forniceal T2 hyperintensity with associated restricted diffusion (of unclear clinical significance), and a longitudinally extensive T2 hyperintense lesion mostly restricted to the dorsal cord from C2 distal to T11 with some areas of anterior and lateral T2 hyperintensity and mild contrast enhancement throughout the cervical cord and punctuate enhancement in the thoracic cord. Given the atypical nature of DC's presentation and MRI findings, an extensive work up was undertaken to include inflammatory, infectious, toxic, metabolic, mitochondrial, and genetic etiologies to explain these findings. He was NMO-IgG negative, and no other etiology was identified through testing. Five months after symptom onset, DC was treated empirically with high-dose methylprednisolone 1000mg daily x 3 days; surprisingly this was reported to improve vision slightly. Based on this improvement DC was subsequently treated with plasma exchange with 6 total volume exchanges over 2 weeks. He tolerated this well, had resolution of foot numbness, and reported very mild improvement in visual acuity and scotoma OD. Follow up visual acuity by ophthalmology found OD 20/500, but OS hand movements only.

While atypical, DC met criteria for NMO-IgG negative NMOSD [9]; he was also noted to have elevated serum eosinophils 11.9% (normal 0-3%), IgE 648 (normal < 100), and had class 5 responses to dustmites D. farinae and D. pteronyssinus. These latter results suggested an alternative diagnosis of atopic myelitis, which can present similarly to NMOSD, though does not typically involve the optic nerves [10,11]. However, in the paucity of cases in the literature, some showed relapsing diseases similar to MS or NMOSD [12]. Thus, given DC's clinical and radiographic findings consistent with NMO-IgG negative NMOSD, and the risk for permanent disability with relapse, the decision was made to treat with rituximab 500mg/m2. At the time of writing, DL has received four doses of rituximab, which he has tolerated well. He had a mild infusion reaction when an automated IV pump failed and he received a rapid infusion. This was immediately identified and stopped, and he responded well to diphenhydramine, without subsequent reactions upon resumption of normal infusion rates. DC remains relapse free and post-rituximab MRIs show resolution of contrast enhancement in the optic nerves and the spinal cord. Additionally, there has been interval improvement in the LETM T2 hyperintensity along the dorsal columns of the entire spinal cord, and follow up ophthalmologic evaluation found visual acuity to be slightly improved to 20/400 OD, but hand movements only OS.

Case 4: POMS

OB had her first demyelinating event at 18 months old, presenting to another institution with bilateral optic neuritis. Prior to this OB was a normally developing, healthy toddler girl. Her vision recovered with high dose IVMP and work up at the time was negative for infectious etiology. There was no alteration in sensorium, or other CNS lesions to suggest alternative diagnoses including acute disseminated encephalomyelitis (ADEM), POMS, or NMOSD at this presentation. She had a second clinical demyelinating event at age 2.5 years, with MRI evidence of dissemination in space, thus satisfying diagnostic criteria for POMS at the time [13]. Following high dose IVMP and moderate symptom improvement, DMT was initiated using once weekly intramuscular interferon-beta 1a (INF). However, OB did not tolerate the injections due to pain and INF-related flu-like symptoms. Thus, over the one year of her treatment there was breakthrough MS disease activity associated with DMT non-compliance. She was switched to every other day subcutaneous glatiramer acetate (GA) 20mg injections (modified dosing protocol) which she continued for approximately four years from age 4 to 8 years old. OB had idiosyncratic drug reactions to GA, injection site reactions, poor compliance, and frequent clinical relapses.

At age 8 years old she was prescribed dimethyl fumarate (DMF), but due to parental concerns this was never started. OB remained off DMT through age 9 years when she had an additional clinical relapse presenting with diplopia and found to have intranuclear ophthalmoplegia (INO). These symptoms responded to high dose IVMP, and she was referred to my clinic for further management recommendations. Based on her highly active POMS, the decision was made to start rituximab 500mg/m2. At the age of 10 years, 9 months old, OB has completed four doses of rituximab with no side effects, no infections, and normal serum IgG and IgM levels. Further, she has had no clinical or radiographic disease activity, and no disability progression since starting rituximab, satisfying current criteria for "no evidence of disease activity-3" or NEDA-3.

Case 5: OMAS

EC was a developmentally normal 11 month 2-week-old, infant girl with a history of congenital mild to moderate bilateral hearing loss of unclear etiology, who presented to the emergency department with several days of progressive clumsiness, head tilt, and abnormal/chaotic eye movements consistent with opsoclonus. She was found to have elevated blood pressure and urine metanephrines rising concerns for neuroblastoma and associated paraneoplastic OMAS. Computed tomography (CT) of the abdomen revealed an adrenal mass, which was resected and pathology was found to be consistent with stage III intermediate risk neuroblastoma. Following surgical resection EC was treated with chemotherapy (COG-ANBL00P3 x 4 rounds, as well as COG-ANBL0531 x 4 cycles with 6 cycles of isotretinoin [14,15]), which she completed at approximately 16 months of age. At the time of OMAS symptom onset, her Mitchell-Pike OMS severity

scale was 18/18 (https://omslifefoundation.org/wp-content/uploads/2018/01/Mitchell-Pike-OMS-Rating-Scales-full-from-Wendy-Mitchell-Sept-15-2017.pdf). Despite tumor resection and chemotherapy, EC suffered developmental motor regression with profound hypotonia, milder but on-going opsoclonus, and behavioral problems. At 17 months of age EC had a febrile illness due to acute otitis media and developed febrile status epilepticus which stopped with intravenous lorazepam; subsequent EEG and brain MRI were normal.

Following this febrile illness, OMAS symptoms recurred and EC's hypotonia, developmental regression/delays, and opsoclonus returned with severe disease burden. Monthly IVIG treatment was initiated about 2 months following the OMAS relapse, and EC was referred to my clinic at 19 months old having received a single dose of IVIG. Per her parents, EC showed mild improvement in opsoclonus following three monthly doses of IVIG, but no improvement in development. Based on her relapsing disease and severe symptom burden, rituximab was initiated in addition to monthly IVIG, using once weekly rituximab IV 375mg/m2 x 4 weeks. No high dose IVMP or adrenocorticotropin hormone (ACTH) was utilized. EC showed dramatic recovery of function within two months of rituximab dosing. To date she has tolerated rituximab with four loading doses and a subsequent 600mg/m2 treatment 6 months after the starting doses, without infusion reactions or frequent infections. EC is now 2 years 8 months old and making developmental progress with supportive physical, occupational, and speech therapies. She no longer has opsoclonus and while hypotonia persists she is now pushing up to sit without assistance, pulling into a kneeling position, and scooting on her buttocks to "ambulate". She is no longer ataxic or dysmetric with reaching or grasping, and her language is beginning to develop. Given the recent evidence supporting better developmental outcomes with IVIG and risk of hypogammaglobulinemia with rituximab, EC remains on monthly IVIG 1g/kg, which will be slowly weaned now that she is greater than one year from her most recent relapse. Her current OMS severity scale is 9/18, a 50% reduction from presentation.

DISCUSSION

While anecdotal, these five cases demonstrate a range of PNS and CNS neuroimmunologic diseases for which rituximab treatment halted disease activity, and in some cases reversed accrued disability. These findings are similar to previous reports in both pediatric and adult neuroimmunologic and autoinflammatory diseases [1,2,16,17]. Autoinflammatory B-cells have been shown to play roles in antigen presentation, cytokine production, T-cell co-stimulation, and disease activity if not pathogenesis, in a variety of humoral- and T-cell mediated autoimmune diseases [18]. Thus mechanistically, it should be no surprise that rituximab treatment was useful in these five cases. The question remains if rituximab is the best choice of treatment for these conditions.

Several advantages support the use of rituximab over other DMTs in pediatric neuroimmunological diseases. Body surface area dosing of rituximab is one advantage, allowing patient-specific treatment, rather than using full adult doses, or modified adult doses to mitigate side effects. Adult-dosing strategies have been the standard of care as first-line therapies in POMS [19], but were ineffective for the POMS patient reported here who suffered significant side effects to her standard injectable DMTs; side effects and injection avoidance lead to treatment non-compliance and thus breakthrough disease. Steroids and many steroid-sparing immunosuppressive agents used in autoimmune disease require self-administration via oral liquids or pills, or parenteral injections. Thus, issues of non-compliance complicate efficacy when treatment is not directly observed. As an intravenously infused medication, rituximab compliance is either zero, or 100%, thereby eliminating questions of treatment compliance if issues of efficacy arise [4,20].

While long-term outcomes and sequelae are not available for these five patients, compared to their baseline disease activity, left untreated each patient's disease is known to carry risk of life-long disability. Three of the five patients did have mild infusion reactions, but these were treated with protocol-based reaction therapies including diphenhydramine and in one case IVMP, and all five tolerated on-going treatment with rituximab. In this case series none of the patients exhibited clinical or laboratory side effects resulting in morbidity, mortality, or cessation of rituximab treatment. Two of the five patients received IVIG co-treatment for baseline immunomodulation, but no hypogammaglobulinemia has occurred at the time of writing in any of the five patients. These case reports offer class D evidence at best for the use of rituximab in neuroimmunologic diseases. Other limitations include a biased inclusion criteria, retrospective review, and a small number of patients. These cases do not represent all rituximab-receiving patients in our institution and were chosen to illustrate rituximab's efficacy in rare pediatric neuroimmunologic diseases. Admittedly, rituximab is not useful for all patients, and there may be disease-related limitations to its efficacy, as well as patient-specific reasons for not choosing this medication. In autoimmune myasthenia gravis, for example, rituximab has been shown to be effective in anti-muscle specific tyrosine kinase (anti-MuSK) related disease [21], though classical myasthenia gravis associated with anti-acetylcholine receptor (AChR) modulating antibodies responds less well [22]. This data is largely adult patient driven, and anecdotal evidence in pediatric patients suggests rituximab may play a role in treatment [23]. Anti-myelin oligodendrocyte glycoprotein (anti-MOG) associated relapsing CNS demyelinating diseases have also been shown to be less responsive to rituximab [24,25]; this has been true in my practice as well.

Other challenges to the use of rituximab in a pediatric neurologic diseases include its cost and chemotherapeutic designation. The former represents a challenge in obtaining insurance approval for use as an off-label therapy, particularly as a first line agent. In emergent cases, such as an inpatient with a fulminant demyelinating crisis, or autoimmune encephalitis, institutions may wind up absorbing the cost of rituximab therapy. The United States patent for rituximab expired in 2016, and several generic biosimilars are currently in various stages of development and approval by regulatory agencies [26]. Less expensive biosimilars have been in use in other neuroimmunologic diseases including MS (glatiramer acetate) [27], and may help redu.ce cost of treatment and improve access to therapy as insurance providers adopt policies favorable to these lower-cost agents. Beyond cost, designation

as a chemotherapeutic agent limits rituximab administration to nurses with specialized training in oncology and safe handling of chemotherapeutic agents. However, similar B-cell targeted monoclonal antibodies do not share this designation, and thus are not similarly restricted. Reclassification of rituximab would permit broader use within institutions where chemotherapy designation limits staffing and thus patient accessibility.

Short- and long-term safety issues regarding rituximab use in pediatric neuroimmunologic patients continue to be raised by parents and clinicians alike. While tumor lysis syndrome is a concern in B-cell tumor treatment, this risk does not exist in neuroimmunologic diseases, thereby reducing some of the acute risk associated with rituximab administration in this population. Appropriate screening for infectious disease prior to starting rituximab helps to mitigate issues of chronic mycobacterial and viral reactivation such as with hepatitis B [28]; the risk for serious infection does remain due to chronic immunosuppression. However, without prior chemotherapy, there appears to be a relatively low risk for progressive multifocal leukoencephalopathy (PML) in rituximab-treated patients, even after many years of B-cell suppression [29]. Taken together, the growing body of evidence favors rituximab treatment over poorly controlled disease activity in pediatric neuroimmunologic disease. Future prospective clinical trials pitting rituximab against other active comparators will be necessary to quantify efficacy and safety across pediatric neuroimmunologic diseases. However, while waiting for these trials to be commenced across disease states, in my practice I will continue to wield the hammer of rituximab while combatting pediatric neuroimmunologic disease.

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CONFLICT OF INTEREST

I.R. attended advisory boards for Novartis, January 2018, Sarepta January 2017, and Genzyme October 2016.

REFERENCES

1. Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory cns disease. Neurol. 2014; 83: 142-150.
2. Beres SJ, Graves J, Waubant E. Rituximab use in pediatric central demyelinating disease. Pediatr Neurol. 2014; 51: 114-118.
3. Salzer J, Lycke J, Wickstrom R, Naver H, Piehl F, Svenningsson A. Rituximab in paediatric onset multiple sclerosis: A case series. J Neurol. 2016; 263: 322-326.
4. McGinley M, Rossman IT. Bringing the heet: The argument for high-efficacy early treatment for pediatric-onset multiple sclerosis. Neurotherapeutics. 2017; 14: 985-998.
5. 5. Wang CX, Greenberg BM. Pediatric multiple sclerosis: From recognition to practical clinical management. Neurol Clin. 2018; 36: 135-149.
6. Jarmolowicz DP, Bruce AS, Glusman M, Lim SL, Lynch S, Thelen J, et al. On how patients with multiple sclerosis weigh side effect severity and treatment efficacy when making treatment decisions. Exp Clin Psychopharmacol. 2017; 25: 479-484.
7. Chitnis T, Tardieu M, Amato MP, Banwell B, Bar-Or A, Ghezzi A, et al. International pediatric ms study group clinical trials summit: Meeting report. Neurology. 2013; 80: 1161-1168.
8. Simone M, Chitnis T. Use of disease-modifying therapies in pediatric MS. Curr Treat Options Neurol. 2016; 18: 36.
9. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015; 85: 177-189.
10. Kira J, Kawano Y, Horiuchi I, Yamada T, Imayama S, Furue M, et al. Clinical, immunological and MRI features of myelitis with atopic dermatitis (atopic myelitis). J Neurol Sci. 1999; 162: 56-61.
11. Yoon JH, Joo IS, Li WY, Sohn SY. Clinical and laboratory characteristics of atopic myelitis: Korean experience. J Neurol Sci. 2009; 285: 154-158.
12. Itoh K, UmeharaF, Osame M. Multifocal relapsing-remitting myelitis in a patient with atopic dermatitis: Multiple sclerosis or atopic myelitis? Intern Med. 2002; 41: 495-497.
13. Krupp LB, Banwell B, Tenembaum S. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology. 2007; 68: S7-12.
14. Davidoff AM. Neuroblastoma. Semin Pediatr Surg. 2012; 21: 2-14.
15. de Alarcon PA, Matthay KK, London WB, Naranjo A, Tenney SC, Panzer JA, et al. Intravenous immunoglobulin with prednisone and risk-adapted chemotherapy for children with opsoclonus myoclonus ataxia syndrome associated with neuroblastoma (anbl00p3): A randomised, open-label, phase 3 trial. Lancet Child Adolesc Health. 2018; 2: 25-34.
16. Kim SH, Huh SY, Lee SJ, Joung A, Kim HJ. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurol. 2013; 70: 1110-1117.
17. Ramos-Casals M, Garcia-Hernandez FJ, de Ramon E, Callejas JL, Martinez-Berriotxoa A, Pallares L, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol. 2010; 28: 468-476.
18. Claes N, Fraussen J, Stinissen P, Hupperts R, Somers V. B cells are multifunctional players in multiple sclerosis pathogenesis: Insights from therapeutic interventions. Front Immunol. 2015; 6: 642.
19. Ghezzi A, Amato MP, Makhani N, Shreiner T, Gartner J, Tenembaum S. Pediatric multiple sclerosis: Conventional first-line treatment and general management. Neurology. 2016; 87: S97-S102.
20. Schwartz CE, Grover SA, Powell VE, Noguera A, Mah JK, Mar S, et al. Risk factors for non-adherence to disease-modifying therapy in pediatric multiple sclerosis. Mult Scler. 2018; 24: 175-185.
21. Hehir MK, Hobson-Webb LD, Benatar M, Barnett C, Silvestri NJ, Howard JF Jr, et al. Rituximab as treatment for anti-musk myasthenia gravis: Multicenter blinded prospective review. Neurology. 2017; 89: 1069-1077.
22. Tandan R, Hehir MK 2nd, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: A systematic review. Muscle Nerve. 2017; 56: 185-196.
23. Barraud C, Desguerre I, Barnerias C, Gitiaux C, Boulay C, Chabrol B. Clinical features and evolution of juvenile myasthenia gravis in a french cohort. Muscle Nerve. 2018; 57: 603-609.
24. Wong YYM, Hacohen Y, Armangue T, Wassmer E, Verhelst H,

Hemingway C, et al. Paediatric acute disseminated encephalomyelitis followed by optic neuritis: Disease course, treatment response and outcome. Eur J Neurol. 2018; 25: 782-786.

25. Ramanathan S, Mohammad S, Tantsis E, Nguyen TK, Merheb V, Fung VSC, et al. Clinical course, therapeutic responses and outcomes in relapsing mog antibody-associated demyelination. J Neurol Neurosurg Psychiatry. 2018; 89: 127-137.

26. Greenwald M, Tesser J, Sewell KL. Biosimilars have arrived: Rituximab. Arthritis. 2018; 3762864.

27. Cohen J, Belova A, Selmaj K, Wolf C, Sormani MP, Oberye J, et al. Equivalence of generic glatiramer acetate in multiple sclerosis: A randomized clinical trial. JAMA Neurol. 2015; 72: 1433-1441.

28. Hall SA, Shaikh A, Kailin Teh, Tantiongco M, Coghlan D, Karapetis CS, et al. Hepatitis b screening before rituximab therapy: A multicentre south australian study of adherence. Intern Med J. 2018.

29. Memon AB, Javed A, Caon C, Srivastawa S, Bao F, Bernitsas E, et al. Long-term safety of rituximab induced peripheral b-cell depletion in autoimmune neurological diseases. PLoS One. 2018; 13: e0190425.

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