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Clinical Observation

Rituximab as Adjunct Maintenance Therapy for Refractory Juvenile Myasthenia Gravis

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ABSTRACT

Background: Juvenile myasthenia gravis is a pediatric autoimmune disorder of the neuromuscular junction associated with substantial morbidity, for which standard therapies are not always efficacious. The objective of our study was to assess the tolerability and efficacy of rituximab use in children with refractory juvenile myasthenia gravis.
Methods: We conduced a retrospective cohort study at a single tertiary care referral center to evaluate children with juvenile myasthenia gravis who were treated with rituximab. The clinical status of these participants before and after initiation of rituximab therapy was measured, focusing on numbers of hospital admissions, numbers of immunomodulatory or immunosuppressive medications needed, and Myasthenia Gravis Foundation of America severity class.
Results: Five children with juvenile myasthenia gravis were ascertained who received rituximab as part of their regimen, four of whom had elevated acetylcholine receptor antibodies and one of whom had elevated muscle-specific kinase antibodies. After initiation of rituximab therapy, all participants experienced reduced numbers of immunomodulatory medications during the follow-up period (mean 11.6 months). Four of the five subjects experienced fewer juvenile myasthenia gravis-related hospital admissions and reduced (improved) Myasthenia Gravis Foundation of America classes, with no subjects having moderate or severe symptoms following treatment with rituximab. No significant adverse events were recorded for any of the participants.
Conclusion: Rituximab was well-tolerated and efficacious in this juvenile myasthenia gravis cohort. The beneficial effect of rituximab was most pronounced in the one participant with muscle-specific kinase antibodies.

Introduction

Juvenile myasthenia gravis (JMG) is a pediatric autoimmune disorder of the neuromuscular junction for which standard therapies are not always efficacious. Common pathogenic antibodies target the postsynaptic acetylcholine receptor (AChR) and muscle-specific kinase (MuSK). Remission is often but not always induced by standard treatments.[1,2] The first-line treatment in most cases is the acetylcholinesterase inhibitor pyridostigmine. Many children require immunomodulation as well, traditionally with prednisone, plasmapheresis/plasma exchange, and/or intravenous immunoglobulins (IVIG). The use of steroid-sparing immunosuppressants such as azathioprine, mycophenolate, cyclosporine, and cyclophosphamide has been reported sporadically for JMG.

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Rituximab is a chimeric monoclonal antibody directed against CD20 on mature B cells that depletes this cell population. Autoreactive B cells have demonstrated pathogenicity in the development of autoimmune myasthenia gravis.[3] Rituximab has been well-studied for the treatment of adult myasthenia gravis,[3-6] but its use has been documented sparsely in JMG.[7-9] The objective of our study was to assess the tolerability and efficacy of rituximab use in children with refractory JMG.

Methods

This retrospective study was approved by the University of Florida Institutional Review Board. The institution's Integrated Data Repository was mined using the Informatics for Integrating Biology & the Bedside tool[10] with the following criteria for the years 2011 to 2019: (1) patients younger than 18 years and (2) diagnosis of myasthenia gravis. Ascertained individuals were manually screened for (1) persistent symptoms despite therapy with pyridostigmine and at least one immunomodulatory medication and (2) therapy with rituximab. Relevant clinical data were abstracted from the medical record. The rituximab initiation regimen used in all cases was 750 mg/m^2 (maximum 1000 mg), two doses two weeks apart. Maintenance dosing was 375 mg/m^2 every 12 weeks. Each dose was administered intravenously and was followed by rescue IVIG, dosed at 1 g/kg. Complete blood cell counts and CD19/20 counts were monitored. Participants were advised to receive annual influenza vaccines, but not live viral vaccines.

Results

The Informatics for Integrating Biology & the Bedside search revealed 65 unique pediatric patients, of whom five received rituximab therapy. Four of these individuals had elevated AChR antibodies, and one had elevated MuSK antibodies (Table). They were treated between 2014 and 2019 and initiated rituximab therapy between 2017 and 2019. Mean age at diagnosis was 11.6 years. All subjects with AChR-positive JMG had ptosis and variable proximal weakness, with three of the four also reporting diplopia (baseline Myasthenia Gravis Foundation of America [MGFA] classes IIa-IIIa). The subject with MuSK-positive JMG had asymmetric facial weakness, ophthalmoplegia, and dysphagia (baseline MGFA class IVb). Before rituximab, mean disease duration was 15.1 months (range 4.5 to 27.5), mean immunomodulatory medications were 2.8, and mean JMG-related hospitalizations were 2.8 (range 0 to 8) (Fig). Initial therapies included IVIG (five of five), plasma exchange (three of five), prednisone (two of five), and mycophenolate (two of five). Four of the five had thymectomy before rituximab, including the MuSK-positive participant. None had comorbid autoimmune disorders amenable to treatment with rituximab. Subjects 1 and 2 had normal barium swallow study evaluations. Subject 1 had a normal documented ophthalmologic examination. Subjects 1 and 4 were evaluated by physical therapy during their respective hospital admissions. Subjects 3 and 5 did not have any documentation of dysphagia or evaluations by ophthalmology or physical therapy. All five subjects had normal serum thyroid-stimulating hormone levels at the time of diagnosis.

All participants received two induction doses of rituximab spaced two to three weeks apart, followed by at least one maintenance dose (mean 3.2, range 1 to 6 doses). Infusions were well-tolerated, with no reported adverse effects. At mean follow-up of 11.6 months (range 4 to 24 months), participants were taking on average 1.6 immunomodulatory medications, with no JMG-related hospitalizations (Fig). Subjects reported reduction in symptoms of diplopia, dysphagia, and muscle weakness, with four of the five participants showing reductions (improvement) in their MGFA classes. Ptosis tended to persist. All subjects had decreased AChR or MuSK antibody titers following rituximab, with antibodies becoming undetectable in three of the five cases. Two participants were able to space rituximab infusion intervals to every four to six months. Two subjects taking prednisone when initiating rituximab were able to taper or discontinue prednisone. The beneficial effects of rituximab were most pronounced in the one MuSK antibody subject who had previously failed five immunomodulatory therapies and had eight prior myasthenia gravis-related

TABLE
Patient Characteristics

ID	Age (y) Sex/Race	MGFA Class*	Ab Status	Prior Therapies	Time to RTX (mo)	Doses (n)	Follow-up (mo)	Therapies at Last Visit
1	6 F/Af	IVb	MuSK	T, Py, P, IVIG PLEX, MM, Bz	27.5	I+6	24	MM, RTX
2	16 M/C	IIb	AChR	T, Py, IVIG, PLEX	21	I+3	9	Py, RTX
3	16 M/As	IIb	AChR†	T, Py, P,IVIG, PLEX	10	I+1	4	Py,‡ P, RTX
4	12 F/Bi	IIa	AChR†	T, Py, P,IVIG, MM	12.5	I+4	13	Az, RTX
5	8 F/Af	IIIa	AChR	Py, IVIG	4.5	I+2	8	Py, RTX

Abbreviations:
AChR = Acetylcholine receptor
Af = African American
As = Asian American
Az = Azathioprine
Bi = Biracial
Bz = Bortezomib
C = Caucasian
I = Induction doses of rituximab
IVIG = Intravenous immunoglobulin
MG = Myasthenia gravis
MGFA = Myasthenia Gravis Foundation of America
MM = Mycophenolate mofetil
MuSK = Muscle-specific tyrosine kinase
P = Prednisone
PLEX = Plasma exchange
Py = Pyridostigmine
RTX = Rituximab
T = Thymectomy
* See Figure C for MGFA class at follow-up.
† AChR binding antibodies only.
‡ Prednisone taper.

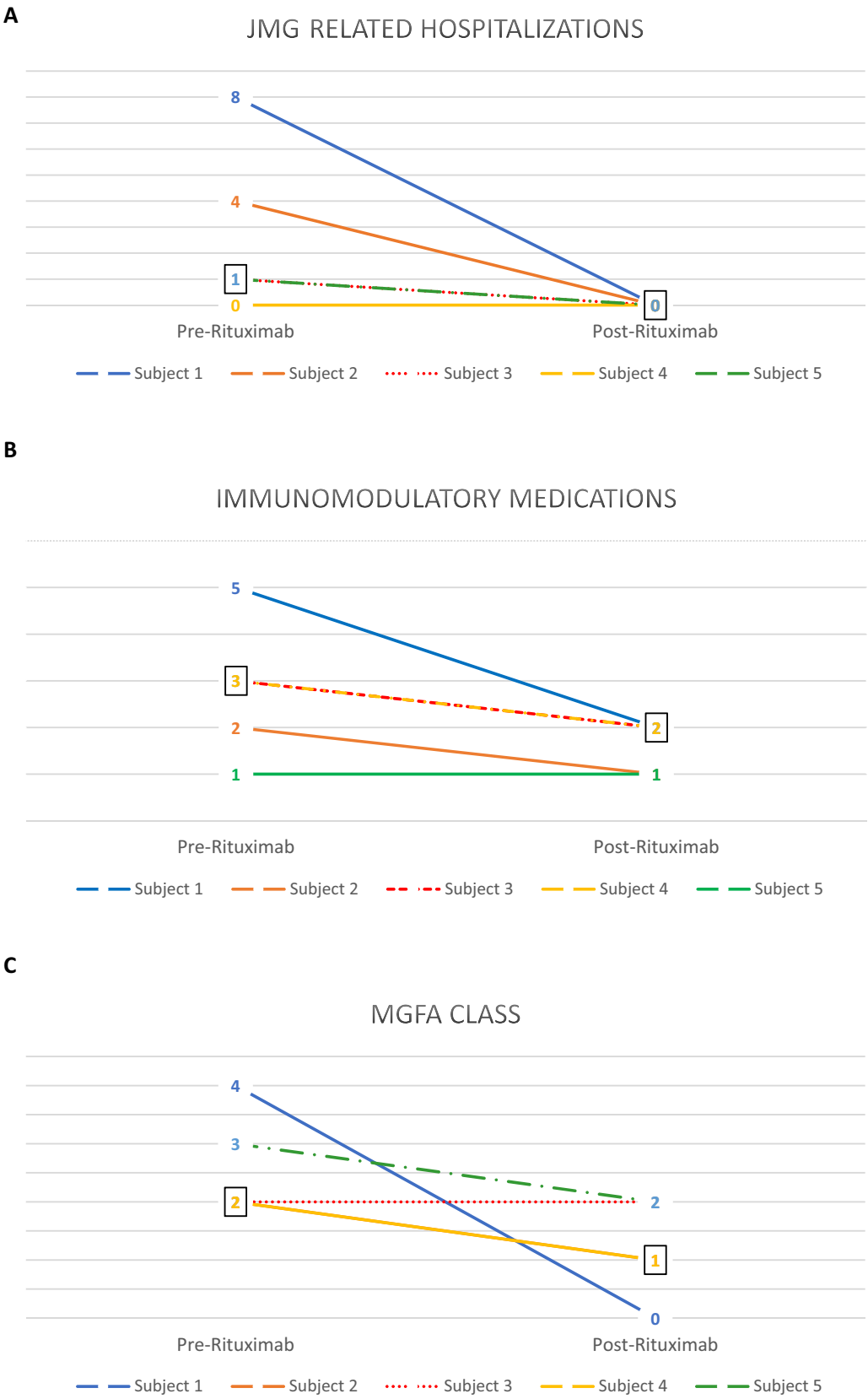

FIGURE. Clinical status before and after initiation of rituximab therapy for the five individual JMG subjects. (A) Hospital admissions related to JMG pre-rituximab and post-rituximab. Note that subjects 3 and 5 have the same numbers of hospital admissions at both time points and thus their plots overlap. All five subjects had zero hospital admissions post-rituximab at last follow-up appointment. (B) Number of immunomodulatory medications prescribed pre-ritixumab and post-rituximab. Note that subjects 3 and 4 have the same number of medications at both time points and thus their plots overlap. All five subjects were on fewer immunomodulatory medications post-rituximab compared with pre-ritixumab. (C) Myasthenia Gravis Foundation of America (MGFA) class pre-rituximab and post-rituximab. Note that subjects 2 and 4 have the same MGFA class at both time points and thus their plots overlap. Four of the five subjects had a decrease in JMG symptoms corresponding to a decrease (improvement) in MGFA class.

hospitalizations. Following rituximab, she had no hospitalizations over a two-year period, even after developing influenza.

Discussion

In this retrospective analysis of five children and adolescents with refractory JMG, rituximab was well-tolerated and efficacious without any serious reported side effects during the follow-up period. All patients received at least one maintenance dose and were followed for at least four months, with all showing reduction of JMG symptoms. Although ptosis tended to persist, this has been previously documented in patients with JMG with stable disease.[11] The beneficial effects of rituximab were most pronounced in the one MuSK antibody subject who had previously failed five immunomodulatory therapies and had eight prior myasthenia gravis-related hospitalizations. Following rituximab, she had no hospitalizations over a two-year period, even after developing influenza.

The use of rituximab in JMG is sparsely documented, in contrast to the adult literature. In one pediatric cohort, there was significant benefit in two of five patients with JMG treated with rituximab (one AChR, one MuSK) and partial benefit in the others (two AChR, one MuSK).[7] Clinical benefit was also reported in two patients with JMG treated with rituximab (one AChR, one seronegative—MuSK not tested).[9] A single case report documented efficacy in a child with MuSK-JMG.[8]

There is not sufficient evidence at this time to indicate whether rituximab should be considered before thymectomy in some patients. Patients with anti-MuSK myasthenia may especially benefit from another therapeutic option as their responses to thymectomies are not as robust as for AChR antibody-positive myasthenia; prior literature suggests that a few anti-MuSK patients do respond to thymectomies,[12] whereas a newer study's findings are less optimistic on this point.[13] Our one anti-MuSK patient received a thymectomy in the context of older literature, before we implemented the use of rituximab for this disease at our center.

Currently, no standardized protocol exists for determining the initiation of rituximab therapy in JMG. Our dosing protocol is similar to those used in adults, with the exception of two versus four induction doses. It is worth considering whether the rescue IVIG that our participants received had a confounding therapeutic effect, as IVIG is also used to treat JMG. However, the intervals between maintenance rituximab doses are longer than the standard intervals for IVIG therapy, and the response to IVIG has been found to be inconsistent for JMG,[14] thus making it unlikely that IVIG had a perceptible therapeutic effect in these participants.

Eculizumab, a terminal complement inhibitor, was approved by the US Food and Drug Administration in 2017 for the treatment of generalized myasthenia gravis in adults with elevated anti-AchR antibodies.[15] Eculizumab has not been studied in JMG, but has been used for the treatment of other pediatric diseases and may bear examination as a potential treatment option for JMG in the future.

Based on our cohort analysis, rituximab appears to be well-tolerated and potentially efficacious for children with JMG, including those who have already had thymectomy. With respect to its safety profile, rituximab does not affect B-cell recovery, plasma cells, or antibody production.[11] Rituximab has the potential to fill a significant therapeutic gap for refractory JMG, but should be studied more rigorously in a larger cohort before more definitive recommendations can be made. Such an investigation will require the assembly of a multicenter consortium of pediatric neuromuscular clinics, perhaps modeled after ones that have already been established for inherited pediatric neuromuscular diseases such as spinal muscular atrophy and Duchenne muscular dystrophy.

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