Rituximab as a first-line preventive treatment in pediatric NMOSDs
Preliminary results in 5 children

ABSTRACT

Objective: No established therapeutic protocol has been proposed to date for childhood-onset neuromyelitis optica (NMO) spectrum disorders (NMOSDs). We report the response of 5 NMO immunoglobulin (IgG)-positive pediatric cases to a standardized B-cell–targeted first-line immunosuppressive protocol with rituximab for prevention of relapses.

Methods: Retrospective observational cohort study.

Results: All patients included in the study showed disease remission after rituximab induction. Relapses always occurred in conjunction with CD19+ B-cell repopulation and appeared less severe than prior to treatment. At the end of follow-up, neurologic disability and MRI findings stabilized or improved in all the patients, with only minor and transient side effects. Oral steroid discontinuation was possible in all the patients.

Conclusions: Our protocol is well-tolerated and has provided encouraging results in terms of control of relapses and progression of disability. An early intervention with rituximab might affect the disease course in pediatric NMO-IgG-positive NMOSDs.

Classification of evidence: This study provides Class IV evidence that for children with NMOSDs, rituximab is well-tolerated and stabilizes or improves neurologic disability. Neurology Neuroimmunol Neuroinflamm 2014;1:e46; doi: 10.1212/NXI.0000000000000046

GLOSSARY

AQP4 = aquaporin-4; EDSS = Expanded Disability Status Scale; Ig = immunoglobulin; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder.

Neuromyelitis optica (NMO) spectrum disorders (NMOSDs) are a group of highly disabling inflammatory conditions of the CNS encompassing the definite form of NMO and a rapidly expanding spectrum of syndromes characterized by various combinations of symptoms and signs explained by the presence of lesions at sites of high aquaporin-4 (AQP4) expression.1

To date, the therapeutic management of pediatric NMOSDs has been largely based on Class IV evidence, and current practice follows studies of adult NMO (table 1).2 It is generally accepted that immunosuppression is necessary to prevent relapses and incremental attack-related disability, but no established therapeutic protocol has been proposed thus far.

Anti-AQP4 immunoglobulin (IgG) (NMO-IgG), detected in 78% of children with relapsing NMO,3 is considered to have a crucial role in the pathogenesis of the vast majority of these disorders, providing a strong rationale for the use of antibody-depleting therapies. An increasing number of studies have described the role of rituximab, a genetically engineered IgG1 targeting the circulating CD20+ B lymphocytes, in the long-term preventive immunotherapy of adult patients with NMOSDs.4-6 Rituximab may also ameliorate the course of these conditions in the pediatric population,7-10 but no standardized treatment approach has been proposed thus far.
METHODS Primary research aim. The primary research aim was to report the clinical outcomes and the tolerability profile of a standardized B-cell–targeted immunosuppressive protocol with rituximab as the first-line treatment for long-term relapse prevention in NMOSDs in a cohort of pediatric patients (Class IV evidence).

Patients and methods. We performed a single-center retrospective analysis of consecutive patients followed at the Hospital for Sick Children, Toronto, Canada from 2009 to 2014 and included in the Hospital for Sick Children Demyelinating Disorders Database. We included children who (1) had an established diagnosis of NMO or NMOSDs; (2) had a positive NMO-IgG status (ELISA assay); (3) were treated with a standardized protocol using rituximab (induction therapy with 500 mg/m², 2 doses 2 weeks apart; immunophenotyping with CD19⁺ B-lymphocyte count 2 weeks and 6 months after the second infusion and monthly thereafter; individualized retreatment timing at B-cell reconstitution [using a threshold of cell counts over 0.01 × 10⁹/L] or at a fixed maximum interval of 9 months from previous cycle, administered using the same induction course); and (4) had not received previous immunosuppressive treatments for relapse prevention. Patients were clinically and radiologically assessed at onset, 1 and 3 months from onset, every 6 months thereafter, and at the time of suspected clinical relapses; all the MRI scans were acquired on a 1.5T scanner using nonstandardized sequences used in routine clinical practice.

Data analysis. Standardized demographic and clinical data points were collected on all patients using an established case report form, with subsequent chart review to confirm the data. MRI data were reviewed and assessed for the presence of worsening or improvements of T2/fluid-attenuated inversion recovery hyperintense and/or T1 hypointense lesions over time.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethics committee as part of the ongoing Hospital for Sick Children Demyelinating Disorders Registry. Informed consent was obtained from all patients and caregivers.

RESULTS All the patients at our institution diagnosed with an NMOSD since 2009 were treated with rituximab according to the specified protocol and satisfied the inclusion criteria for the study. Table 2 details the clinical characteristics of the 5 included

### Table 1  Immunosuppressive agents for preventive therapy in neuromyelitis optica

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Poor efficacy or harmful effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>β-Interferons</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td></td>
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<tr>
<td>Mitoxantrone</td>
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<td>Methotrexate</td>
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</tbody>
</table>

### Table 2  Clinical characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at onset, y</th>
<th>Clinical features at presentation</th>
<th>Acute-phase treatment</th>
<th>MRI findings at presentation</th>
<th>Time from symptom onset to rituximab induction therapy, mo</th>
<th>Side effects</th>
<th>Time from rituximab induction to B-cell repopulation, mo</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>15.9</td>
<td>Intractable nausea and vomiting with severe progressive encephalopathy and coma</td>
<td>IVmp, PA, IVlg, P</td>
<td>Deep WM/GM, optic chiasm, brainstem; LETM</td>
<td>3.6</td>
<td>Facial rash; mild transitory leukocytopenia 10 days after first infusion</td>
<td>6.0</td>
<td>27.7</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>10.9</td>
<td>Gait disturbances, back pain</td>
<td>IVmp, PA, IVlg, P</td>
<td>Subcortical and periventricular WM lesions; multicystic LETM</td>
<td>2.9</td>
<td>Urticaria, transitory hypotension</td>
<td>5.3</td>
<td>16.7</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>11.6</td>
<td>ON</td>
<td>IVmp, PA, IVlg, P</td>
<td>Periventricular WM, optic nerve, chiasm; 2 foci of subtle intramedullary signal change</td>
<td>3.0</td>
<td>None</td>
<td>NA</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>12.9</td>
<td>Intractable hiccups, nausea, and vomiting</td>
<td>IVmp</td>
<td>Bilateral hypothalamic, optic chiasm, area postrema</td>
<td>3.2</td>
<td>Facial rash</td>
<td>7.5</td>
<td>16.2</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>17.0</td>
<td>Intractable hiccups, nausea, and vomiting; sinus bradycardia</td>
<td>IVmp, P</td>
<td>Area postrema</td>
<td>3.2</td>
<td>Facial rash, transitory hypertension</td>
<td>8.5</td>
<td>32.8</td>
</tr>
</tbody>
</table>

Abbreviations: GM – gray matter; IVlg – IV immunoglobulin (2 g/kg over 2–5 days); IVmp – IV methylprednisolone (20–30 mg/kg daily for 3–5 days); LETM – longitudinally extensive transverse myelitis; NA – not applicable (therapeutic depletion up to 8.5 months after induction when retreated according to protocol); ON – optic neuritis; P – oral prednisone taper (starting at 2 mg/kg); PA – plasmapheresis (5–7 treatments on alternate days); WM – white matter.

See text for further details.
patients. The figure provides an overview of the clinical course and the treatment protocols. All the patients were treated with a standardized course of high-dose IV methylprednisolone (20–30 mg/kg daily for 3–5 days) for the acute control of relapses, followed by an oral corticosteroid taper starting at 2 mg/kg (maximum 60 mg/day). Those patients not showing signs of clinical improvement within 48–72 hours of beginning IV corticosteroid treatment (patients 1, 2, and 3) were treated with additional plasmapheresis (5–7 treatments on alternate days, median volume exchanged 1:1–1:1.5) and/or IV immunoglobulin (2 g/kg over 2–5 days, maximum 70 g) as escalation therapy.

Relapse rate. Rituximab resulted in disease control in 3 patients who experienced catastrophic clinical manifestations with repeated relapses and steroid-refractory clinicoradiologic exacerbations prior to initiation of treatment (patients 1, 2, and 5). All the relapses after rituximab initiation occurred before therapeutic CD19+ B-cell depletion (patient 2) or in strict conjunction with B-cell repopulation (patients 1 and 5). None of these patients required additional treatment for relapse control outside of IV corticosteroids. Patients 3 and 4 were relapse-free until the most recent follow-up. Oral steroid discontinuation was possible in all patients a median of 6.5 months (range 6.0–18.4) after rituximab initiation. Time to B-cell repopulation was variable, ranging from 5.3 to greater than 9.6 months after infusion (table 2).

Progression of disability. Median Expanded Disability Status Scale (EDSS) score in the 5 patients decreased
from 3.0 (range: 3–7) at initiation of rituximab therapy to 2.0 (range: 0–4.5) at 6 months from onset and 0.8 (range: 0–4.5) at 12 months from onset. Of note, none of the 3 patients who relapsed showed the accrual of further permanent disability. Only 2 patients had permanent neurologic deficits at the last follow-up (patients 2 and 3; EDSS = 3 due to impaired visual function and EDSS = 4.5 due to chronic spinal cord syndrome, respectively).

**Neuroimaging data.** None of the patients showed any further extension of brain or spine lesions after rituximab-induced B-cell depletion (table 2).

**Tolerability.** No adverse events were reported during and after rituximab initiation outside of transient side effects at the time of infusion (table 2).

**DISCUSSION** Growing evidence in adult patients supports the safety and efficacy of rituximab for the chronic management of NMOSDs,4–6 but few published articles report its use in the pediatric population.7–9 To the best of our knowledge, our study is the first to report a standardized approach to rituximab treatment for pediatric NMOSDs. Our protocol appears to be well-tolerated and has provided encouraging results in terms of control of relapses and progression of disability in pediatric NMOSDs.

Common practice includes repeated rituximab administration at fixed time intervals every 6–12 months.5,9 However, given the strict relationship between B-cell restoration and disease recurrence and the high interpersonal and intrapersonal variability of B-cell depletion (which can be sustained from a few months to more than a year),4–6 recently proposed approaches have suggested the individualization of retreatment frequency by regular monitoring of B lymphocytes every 6–8 weeks.4,6 Advantages of such approaches include prompt detection of early B-cell reconstitution and minimization of cumulative doses of rituximab. In our cohort, immunophenotyping was performed 2 weeks after the second rituximab infusion, then 6 months afterwards, and monthly thereafter. Notably, disease relapses occurred in strict association with CD19+ B-cell reconstitution in all cases. Because B-cell count assessment at a fixed interval of 6 months from previous infusion appeared to be insufficient to prevent 2 of the 3 relapses that occurred in our cohort after rituximab induction, our data support a more individualized monitoring approach with more frequent periodic immunophenotyping and retreatment as soon as B-cell reemergence is detected.

The early initiation of immunosuppressive treatment with rituximab may be of paramount importance in preventing further relapses and the accrual of permanent disability in NMO-IgG–seropositive cases (considered at high risk for developing a chronic relapsing disease5,7), challenging the current “step-up” approach, which tends to reserve rituximab for treatment-refractory cases. Unfortunately, the small sample size and the relatively short follow-up limit our results. Future safety and efficacy studies will be crucial in addressing these issues in the long term.

**AUTHOR CONTRIBUTIONS** Drs. Longoni and Yeh had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Longoni, Yeh. Analysis and interpretation of data: Longoni, Yeh. Drafting of the manuscript: Longoni. Critical revision of the manuscript for important intellectual content: All authors. Study supervision: Yeh, Banwell.

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**REFERENCES**

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