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## Original Article

# Rituximab for Pediatric Central Nervous System Inflammatory Disorders in Alberta, Canada

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**ABSTRACT:** *Background:* Early and effective treatment of central nervous system (CNS) inflammatory disorders is vital to reduce neurologic morbidity and improve long-term outcomes in affected children. Rituximab is a B-cell-depleting monoclonal antibody whose off-label use for these disorders is funded in the province of Alberta, Canada, by the Short-Term Exceptional Drug Therapy (STEDT) program. This study describes the use of rituximab for pediatric CNS inflammatory disorders in Alberta. *Methods:* Rituximab applications for CNS inflammatory indications in patients <18 years of age were identified from the STEDT database between January 1, 2012, and December 31, 2019. Patient information was linked to other provincial datasets including the Discharge Abstract Database, Pharmaceutical Information Network, and Provincial Laboratory data. Analysis was descriptive. *Results:* Fifty-one unique rituximab applications were identified, of which 50 were approved. New applications increased from one in 2012 to a high of 12 in 2018. The most common indication was autoimmune encephalitis without a specified antibody ($n = 16$, 31%). Most children were approved for a two-dose ($n = 33$, 66%) or four-dose ($n = 16$, 32%) induction regimen. Physician-reported outcomes were available for 24 patients, of whom 14 (58%) were felt to have fully met outcome targets. *Conclusion:* The use of rituximab for pediatric CNS inflammatory disorders has increased, particularly for the indication of autoimmune encephalitis. This study identified significant heterogeneity in dosing practices and laboratory monitoring. Standardized protocols for the use of rituximab in these disorders and more robust outcome reporting will help better define the safety and efficacy of rituximab in this population

**RÉSUMÉ :** **L'emploi du rituximab pour des troubles inflammatoires du système nerveux central chez les enfants, en Alberta, au Canada**
*Contexte :* La mise en route précoce d'un traitement efficace des troubles inflammatoires du système nerveux central (SNC) est d'une importance capitale pour diminuer la morbidité neurologique et améliorer les résultats cliniques à long terme chez les enfants touchés. Le rituximab est un anticorps monoclonal à effet dépressif sur les lymphocytes B, dont l'emploi non conforme pour ce type de troubles est financé par le programme Short-Term Exceptional Drug Therapy (STEDT), en Alberta, au Canada. Il sera donc question dans l'étude de l'utilisation du rituximab chez des enfants présentant des troubles inflammatoires du SNC, en Alberta. *Méthode :* Les demandes exceptionnelles d'utilisation du rituximab dans les cas de troubles inflammatoires du SNC chez des patients < 18 ans ont été tirées de la base de données STEDT, pour la période s'échelonnant du 1er janvier 2012 au 31 décembre 2019. Les renseignements sur les patients étaient liés à d'autres ensembles de données provinciaux, dont la Discharge Abstract Database, le Pharmaceutical Information Network et la base de données Provincial Laboratory. Il s'agit d'une analyse descriptive. *Résultats :* Ont été relevées 51 demandes exceptionnelles d'utilisation du rituximab, parmi lesquelles 50 avaient été approuvées. Le nombre de nouvelles demandes est passé de 1 en 2012 à un sommet de 12 en 2018. L'indication la plus fréquente était une encéphalite auto-immune sans mention particulière d'anticorps (n = 16; 31 %). Le régime posologique d'induction approuvé, chez la plupart des enfants, était de 2 doses (n = 33; 66 %) ou de 4 doses (n = 16; 32 %). Nous disposions aussi de résultats cliniques déclarés par les médecins dans 24 cas et, dans 14 de ceux-ci (58 %), toutes les cibles de résultats avaient été atteintes. *Conclusion :* L'emploi du rituximab dans le traitement des troubles inflammatoires du SNC chez les enfants a augmenté, notamment dans les cas d'encéphalite auto-immune. Toutefois, des différences importantes ont été relevées dans l'étude en ce qui concerne la posologie et le suivi des résultats en laboratoire. L'élaboration de protocoles uniformes relatifs à l'utilisation du rituximab dans le traitement de ce type de troubles et une déclaration plus rigoureuse des résultats permettraient de mieux établir l'innocuité et l'efficacité du rituximab dans cette population particulière.

## Background

The understanding of the phenotypic spectrum and pathophysiology of inflammatory disorders of the central nervous system (CNS) in children has been evolving. Many of these disorders are now defined by biomarkers such as antibodies that have a diagnostic and/or pathogenic role.[1] Along with this has come the development of an increasing array of therapeutic options directed towards specific immunologic targets, increasing the complexity of treatment decisions for clinicians. Rituximab is a monoclonal antibody targeting CD20 that results in B-cell depletion and has been reported beneficial in a variety of CNS inflammatory disorders including autoimmune encephalitis,[2–4] myelin oligodendrocyte glycoprotein antibody-associated disease,[5] multiple sclerosis (MS),[6] and opsoclonus-myoclonus syndrome.[7] However, evidence in children is largely limited to open-label or retrospective studies.

Rituximab use in children has increased over time across a variety of indications.[8] While rituximab is generally well-tolerated in children, risks include infusion reactions, hematologic abnormalities (such as neutropenia), and infectious complications, including rare lethal infections in children treated for CNS inflammatory disorders.[9,10] Children treated with a single cycle of rituximab can show reduced B-cell populations and hypogammaglobulinemia one year or more after treatment, which may be more prominent in younger children and those treated for CNS inflammatory disorders compared to other indications.[11,12] However, data on the long-term immunologic effects of rituximab in children treated for CNS inflammatory disorders – particularly those receiving repeated dosing – remain limited. Thus, it is important to continue to evaluate the effectiveness and safety of rituximab in treating this diverse group of disorders, particularly as new CNS inflammatory disorders are defined and new treatments emerge. The aim of this study was to describe trends in the use of rituximab – including measures related to safety and efficacy – for pediatric CNS inflammatory disorders in the province of Alberta, Canada.

## Methods

### Study Population

This study was approved by the University of Alberta Health Research Ethics Board. The province of Alberta, Canada, administers a universal publicly funded healthcare system to a population of approximately 4.4 million residents. Access to rituximab for off-label indications (including pediatric CNS inflammatory disorders) in Alberta is funded through the Short-Term Exceptional Drug Therapy (STEDT) program. The STEDT program has maintained a database of requests for rituximab use since 2012 that includes patient demographic information, clinical indication, approved dosing, and prescriber information. This database was screened to identify individuals meeting the following inclusion criteria: 1) Application for rituximab between January 1, 2012, and December 31, 2019; 2) Age <18 years at the time of initial application; 3) Indication for rituximab related to CNS inflammation, including (but not limited to) autoimmune encephalitis, neuromyelitis optica spectrum disorder (NMOSD), MS, and opsoclonus-myoclonus syndrome. Children with a systemic inflammatory disorder were excluded if CNS inflammation was not specified as the primary indication.

### Data Sources

The STEDT database was used to describe baseline information provided by the prescriber in relation to the rituximab request including patient demographic information, clinical indication for rituximab use, prior therapies, and approved rituximab dosing. Prescriber's name was used to identify the prescriber's medical specialty, as reported by the College of Physicians and Surgeons of Alberta.

Unique patient identifying information was used to link the study population identified from the STEDT database to other provincial datasets. The Discharge Abstract Database records information related to inpatient admissions and was used to identify the number, duration, and associated diagnoses (by ICD10-CA code) for hospitalizations in each participant. The Pharmaceutical Information Network captures outpatient prescription dispensing information, with approximately 95% of Alberta pharmacies submitting records. Pharmaceutical Information Network data were used to identify the use of immunomodulating agents by anatomic therapeutic chemical classification code. The Population Registry contains demographic information for all Albertans with Alberta Health Care Insurance Plan coverage and was used to identify participants lost to provincial out-migration or death. Provincial laboratory data were screened to identify CD19 counts and immunoglobulin (Ig) levels (IgG, IgA, and/or IgM). Data were included from these datasets for a period beginning two years prior to initial rituximab approval in each patient until March 31, 2020.

### Outcomes

Physician-reported outcomes following rituximab approval were collected from the STEDT database, where provided. Prescribing physicians reported whether the patient had subjectively met, partially met, or not met the desired clinical outcome following rituximab use (with the parameters of the desired outcome determined by the prescriber for each individual patient). Free-text comments describing the outcome were also reviewed, where provided, in addition to whether renewal of rituximab was requested (and, if applicable, the number of renewals). The Discharge Abstract Database was used to identify the occurrence and duration of inpatient admissions associated with any neurologic or psychiatric diagnostic code prior to and more than 30 days following rituximab approval. The Pharmaceutical Information Network was used to identify the use of other immunomodulating agents following rituximab approval.

### Safety and Laboratory Monitoring

Physician reports of adverse outcomes related to rituximab infusion were collected from the STEDT database, identified by a yes/no response and free-text physician comments in cases where an adverse outcome was noted. Deaths following rituximab approval were identified from the Population Registry. The provincial Laboratory Database was used to identify CD19 counts performed within 180 days after rituximab approval and classified as zero or greater than zero. Where a CD19 count of zero was identified, the timing of the next CD19 count greater than zero was recorded. Measurement of IgG, IgA, and/or IgM levels more than 30 days after rituximab approval was also identified, and values below the lower limit of normal were identified.

### Statistical Analysis

Analysis is descriptive, with categorical variables summarized as number (percentage) and continuous variables summarized as median (range).

## Results

Fifty-one unique applications were identified during the study period (Table 1). New applications increased from one in 2012 to 11 in 2019, with the highest number (12) occurring in 2018 (Figure 1). The most common indication over the study period was autoimmune encephalitis without a specified associated antibody ($n = 16$, 31%), and in the final two years of the study, this indication accounted for more applications than all other indications combined. The most common indication for antibody-associated autoimmune encephalitis was anti-NMDA encephalitis ($n = 14$, 28%), while other antibody-associated autoimmune encephalitis was uncommon including anti-GAD65 ($n = 2$), anti-LGI1 ($n = 1$), and anti-MOG ($n = 1$) (Figure 2). Other neuroinflammatory indications included epilepsy ($n = 2$), neurodegenerative Langerhans cell histiocytosis ($n = 1$), and neurosarcoidosis ($n = 1$, diagnosis made after initial rituximab approval). The majority of requests came from neurologists ($n = 21$, 41%), rheumatologists ($n = 11$, 22%), or psychiatrists ($n = 10$, 20%).

One application for a diagnosis of autoimmune encephalitis associated with anti-GAD65 antibody was denied. Fifty applications received approval and were included in subsequent analyses. Forty-eight children could be linked to provincial datasets, with a median time from initial rituximab approval to the end of data collection of 2.65 (range 0.3–7.3) years. Rituximab administration was considered confirmed in 34 children (68%) based on physician report, pharmacy dispense, or documented CD19 count of 0.

### *Therapies Prior to Rituximab*

Use of at least one immune therapy prior to rituximab approval was documented in 45 children (90%), including 37 (74%) who received two or more different therapies prior to rituximab approval. The most common therapies prior to rituximab were corticosteroids ($n = 38$), IVIG ($n = 31$), and PLEX ($n = 12$) (Table 2).

In the two years prior to rituximab approval, 42 children had at least one inpatient admission associated with a neurologic or psychiatric diagnosis, with a median 22 (range 3–350) total inpatient days. The highest number of inpatient days prior to rituximab application was in the non-NMDA autoimmune encephalitis group (Table 2), almost half of whom ($n = 9$) had an admission with a psychiatric diagnosis prior to rituximab. Two children with anti-NMDA encephalitis had admissions associated with a psychiatric diagnosis prior to rituximab application, while the remainder of admissions prior to rituximab were associated with neurologic diagnoses.

### *Dosing*

The most common induction regimen approved was two doses ($n = 33$), with variation in the amount per dose, including 500 mg/m$^2$ ($n = 9$), 375 mg/m$^2$ ($n = 7$), 500 mg ($n = 3$), 1000 mg ($n = 2$), or another specified dose ($n = 12$). The majority of remaining induction regimens consisted of four doses ($n = 16$), while one child was approved for an induction regimen of six doses.

Twenty children (40%) were approved for more than one cycle of rituximab (Table 3), with the majority ($n = 13$) having the second cycle approved within one year of initial dosing. Repeat dosing regimens were variable, with the second cycle consisting of one ($n = 5$), two ($n = 9$), or four ($n = 6$) doses. Only seven children were approved for more than two cycles, with a maximum of five cycles approved during the study period. At the time of data collection, 11 children were continuing rituximab therapy or within six months

**Table 1:** Study cohort

| | $N = 51$[1] |
|---|---|
| Female, *n* (%) | 33 (65) |
| Age, median (range) | 13.9 (0.8–17.9) years |
| **Indication, *n* (%)** | |
| *NMDA Encephalitis* | 14 (28) |
| *Other Autoimmune Encephalitis* | 20 (39) |
| *MS* | 5 (10) |
| *NMOSD* | 3 (6) |
| *OMS* | 5 (10) |
| *Other Neuroinflammatory* | 4 (8) |
| **Prescriber Specialty, *n* (%)** | |
| *Neurology* | 21 (41) |
| *Rheumatology* | 11 (22) |
| *Psychiatry* | 10 (20) |
| *Other Pediatric Specialty* | 9 (18) |
| **Number of Doses Approved at Induction, *n* (%)** | |
| *Two* | 33 (66) |
| *Four* | 16 (32) |
| *Six* | 1 (2) |
| **Number of Rituximab Cycles Approved, *n* (%)** | |
| *One* | 30 (60) |
| *Two* | 13 (26) |
| *Three or More* | 7 (14) |

Abbreviations: MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorder, OMS = opsoclonus-myoclonus syndrome.
[1]50 applications approved

of their last approved cycle, while two children had switched to ocrelizumab.

### *Response to Treatment*

Subjective physician-reported outcomes were available for 24 children at a median 0.67 (range 0.07–4.15) years from initial approval. Of these, 14 were reported to have fully met the desired clinical outcome, while 10 were reported to have partially met the desired outcome. When comparing induction regimens, 8/13 (62%) of those with a two-dose induction regimen having outcome data available were reported to have fully met the desired outcome compared to 6/11 (55%) receiving four or more doses at induction. Twenty-nine children had inpatient hospital days associated with a neurologic or psychiatric diagnostic code more than 30 days following rituximab approval, with a median 39 (range 2–252) total inpatient days (Table 3).

All five children with a demyelinating diagnosis and outcome data were reported to have fully met the desired outcome. In those with autoimmune encephalitis, 7/14 (50%) with outcome data were reported to fully meet the desired outcome, including 3/5 (60%) with anti-NMDA encephalitis and 4/9 (44%) with autoimmune encephalitis associated with another antibody or without a specified antibody. Within the autoimmune encephalitis group, fully meeting outcomes were reported in 3/5 (60%) receiving one cycle of rituximab vs 4/9 (44%) receiving multiple cycles.

Excluding two children who switched to ocrelizumab, eight children filled outpatient prescriptions for other immune therapies following rituximab approval consisting of mycophenolate alone in six and mycophenolate plus multiple agents in two. In these children, the last outcomes reported for rituximab were fully met in two, partially met in three, and not available in three.
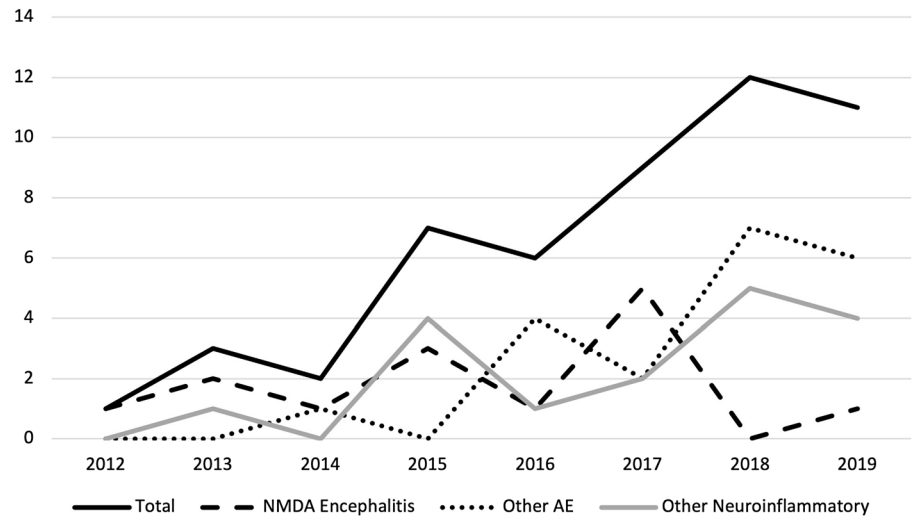
**Fig. 1:** New rituximab applications by year of application and indication. AE = autoimmune encephalitis.
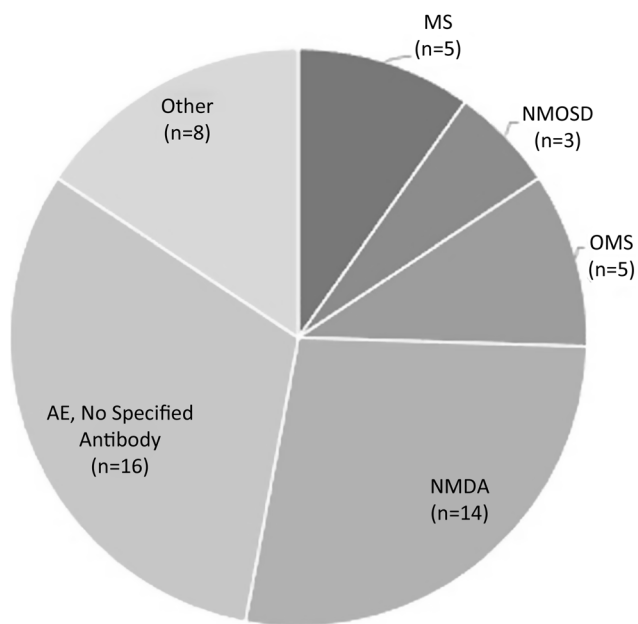


**Fig. 2:** Diagnostic indications for pediatric rituximab applications. Other diagnoses included anti-LGI1 encephalitis ($n = 1$), stiff-person syndrome associated with anti-GAD65 antibody ($n = 1$), encephalitis associated with anti-GAD65 antibody ($n = 1$), encephalitis associated with anti-MOG antibody ($n = 1$), epilepsy ($n = 2$), neurodegenerative Langerhans Cell Histiocytosis ($n = 1$), and neurosarcoidosis ($n = 1$, diagnosis made after initial rituximab approval). AE = autoimmune encephalitis, MS = multiple sclerosis, NMDA = anti-NMDA receptor encephalitis, NMOSD = neuromyelitis optica spectrum disorder, OMS = opsoclonus-myoclonus syndrome.

### Safety and Laboratory Monitoring

An adverse reaction was reported in 1/24 children (4%) in whom this data was reported, with the child (age 16 years) described as developing rash, nausea, and chills four days following their third rituximab infusion and resulting in discontinuation of rituximab. Three children had a hospital admission associated with an infectious diagnosis in the year following initial rituximab approval (range 20–114 days following approval) with diagnostic codes corresponding to bacteremia, viraemia, and acute upper respiratory infection. All three were approved for a four-dose induction cycle. No deaths occurred during the study period.

Immunoglobulin results 30 days or more after initial rituximab approval were identified for 14 children. Of these, six had at least one immunoglobulin subset below the lower limit of normal at one or more timepoints (range 98–1239 days from initial rituximab approval to first abnormal immunoglobulin result), half of which had isolated low IgM levels. Two children had reduced IgG levels (<2.00 g/L and 3.45 g/L at nadir) first identified 664 and 1239 days following initial rituximab approval. The median age at first abnormal immunoglobulin result was 12.8 years (range 1.1–18.7). Five children had only been approved for a single rituximab cycle at the time of first abnormal immunoglobulin result. One child had a hospital admission associated with a diagnostic code of viraemia at the time of low IgM levels.

Seventeen children had a CD19 count of 0 documented within 180 days of initial rituximab approval. Of these, 10 subsequently had a CD19 >0 documented at a time ranging from 163 to 608 days following initial rituximab approval, six of whom received more than one cycle of rituximab. No results within the specified time windows for either immunoglobulins or CD19 count could be identified for 26 children, including 13 children with confirmed rituximab administration. The proportion of children with at least one available lab result was highest when neurologists were the prescriber (13/21, 62%) compared to rheumatologists (4/11, 44%), psychiatrists (4/10, 40%), and other pediatric subspecialties (3/8, 38%).

### Discussion

Using provincial administrative health datasets, this study identified an increase over time in the utilization of rituximab for CNS inflammatory disorders in children. The greatest increase in rituximab utilization was for the indication of autoimmune encephalitis, to the extent that this diagnosis accounted for more rituximab applications in the final two years of the study than all other indications combined. Previous studies have identified anti-NMDA encephalitis and opsoclonus-myoclonus syndrome as the most common indications for rituximab use in pediatric neuroinflammatory cohorts.[9,13] The diagnostic subgroup of autoimmune encephalitis was heterogeneous, with the majority not specified as having an antibody associated with autoimmune encephalitis, followed by those reported as anti-NMDA receptor encephalitis. However, since antibody results were not uniformly reported as part of the application, it is unclear what proportion of this

**Table 2:** Characteristics of the study population by indication

| Indication | Female, *n* | Age at Rituximab Approval, years (median, [range]) | Prior Immune Therapies (*n*) | Hospitalized Prior to Rituximab Approval[1] (*n*) | Days Admitted Prior to Rituximab Approval (median, [range]) |
|---|---|---|---|---|---|
| Other AE (*n* = 19) | 15 | 16.1 (0.8–17.9) | Steroids (14), IVIG (14), PLEX (2), cyclosporine (1) | 17 | 39 (7–350) |
| NMDA Encephalitis (*n* = 14) | 10 | 11.9 (2.3–16.5) | Steroids (10), IVIG (9), PLEX (7), cyclophosphamide (1), chemotherapy not specified (1) | 13 | 21 (4–44) |
| MS (*n* = 5) | 3 | 15.9 (13.2–17.7) | Steroids (5), dimethyl fumarate (1), glatiramer acetate (1) | 4 | 9 (5–22) |
| OMS (*n* = 5) | 1 | 1.4 (1.2–5.1) | Steroids (4), IVIG (5), cyclophosphamide (2), chemotherapy not specified (1) | 3 | 11 (3–39) |
| NMOSD (*n* = 3) | 3 | 17.1 (13.4–17.6) | Steroids (3), PLEX (2) | 3 | 13 (8–27) |
| Other Neuroinflammatory Disorders (*n* = 4) | 1 | 9.6 (4.2–16.3) | IVIG (3), Steroids (2), PLEX (1), cytarabine (1), methotrexate (1) | 2 | 6.5 (6–7) |

Abbreviations: AE = autoimmune encephalitis, IVIG = intravenous immunoglobulin; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; OMS = opsoclonus-myoclonus syndrome; PLEX = plasma exchange.
Hospitalization indicates an inpatient admission associated with a neurologic or psychiatric diagnostic code in the two years prior to rituximab approval.
[1]Hospitalization data not available for one child with other AE indication and one child with NMDA encephalitis.

**Table 3:** Outcomes following rituximab approval

| Indication (*n*) | Desired Outcome Met by Physician Report (*n*) | Time to Last Reported Outcome, years (median, [range]) | Number of Approved Rituximab Cycles (*n*) | Immune Therapy After Rituximab[1] (*n*) | Hospitalized Following Rituximab Approval[1] (*n*) | Admission Days Following Rituximab Approval (median, [range]) |
|---|---|---|---|---|---|---|
| Other AE (19) | Fully (4), Partially (5), Not Available (10) | 0.5 (0.1–1.5) | 1 cycle (14), 2 cycles (4), 3 cycles (1) | MMF alone (4), MMF/Cyclosporine/Tofacitinib (1) | 14 | 36.5 (2–252) |
| NMDA Encephalitis (14) | Fully (3), Partially (2), Not Available (9) | 1.7 (0.5–2.3) | 1 cycle (9), 2 cycles (4), 5 cycles (1) | MMF (1) | 9 | 53 (2–187) |
| MS (5) | Fully (3), Not Available (2) | 1.0 (0.9–1.7) | 1 cycle (2), 2 cycles (1), 4 cycles (1), 5 cycles (1) | Ocrelizumab (2) | 0 | N/A |
| OMS (5) | Fully (1), Partially (2), Not Available (2) | 0.9 (0.7–3.0) | 1 cycle (2), 2 cycles (3) | MMF (1) | 1 | 4 |
| NMOSD (3) | Fully (2), Not Available (1) | 0.4 (0.4–0.5) | 1 cycle (1), 3 cycles (2) | N/A | 3 | 6 (2–71) |
| Other Neuroinflammatory Disorders (4) | Fully (1), Partially (1), Not Available (1) | 2.6 (1.0–4.1) | 1 cycle (2), 2 cycles (1), 4 cycles (1) | MMF/Azathioprine/Methotrexate/Adalimumab (1) | 2 | 63.5 (2–125) |

Abbreviations: AE = autoimmune encephalitis, IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; OMS = opsoclonus-myoclonus syndrome; PLEX = plasma exchange.
Hospitalization indicates an inpatient admission associated with a neurologic or psychiatric diagnostic code from 30 days following rituximab approval until the end of the study period.
[1]Hospitalization and pharmacy data not available for one child with other AE indication and one child with NMDA encephalitis.

subgroup was truly seronegative or whether some may have had a positive antibody result omitted or not available at the time of application (e.g., due to delays in antibody result reporting). Interestingly, the subgroup of autoimmune encephalitis without a specified associated antibody also had the highest number of hospital admission days prior to rituximab application and a higher proportion admitted with a psychiatric diagnosis. Whether this may reflect diagnostic uncertainty/delay in this subgroup – potentially in the context of complex psychiatric presentations – or the use of other therapies prior to proceeding to rituximab application is unclear.

Most children in this study received at least one immune therapy prior to rituximab, including approximately three-quarters receiving multiple therapies. The majority of therapies prior to rituximab were those typically considered acute therapies, namely corticosteroids, IVIG, and/or PLEX. The use of other disease-modifying or immunosuppressive therapies prior to rituximab was uncommon, particularly in the subgroups with NMOSD or autoimmune encephalitis, which aligns with adult studies supporting the use of rituximab as initial long-term therapy in these diseases.[14,15] Similar to previous pediatric studies,[9] we found significant variability in rituximab dosing – in the number

of doses per cycle, the amount of each dose, and re-dosing practices – reflecting lack of consensus in the optimal dose and duration of rituximab therapy in these disorders.

Where physician-reported outcomes were available, the most consistent benefit was noted in those with MS or NMOSD, with all children in these subgroups reported to fully meet the desired outcomes where this information was provided. No children with MS or NMOSD filled outpatient prescriptions for other immune therapies (except for the alternative B-cell therapy ocrelizumab). Outcomes for other indications were mixed, with hospitalizations more than 30 days after rituximab approval being common in those with autoimmune encephalitis. While the two children with outcome data available who were classified as autoimmune encephalitis without a specified associated antibody and had a preceding admission associated with a psychiatric diagnosis were reported to meet the desired outcome only partially, the lack of outcome data for the remaining children in this subgroup limits the ability to draw conclusions regarding efficacy. Despite this, the use of other immune therapies after rituximab was uncommon, with mycophenolate being the most common agent prescribed. Since only outpatient pharmacy data were collected, the use of additional immune therapies during inpatient stays cannot be excluded.

One child was reported to discontinue rituximab due to an adverse reaction, consistent with other published cohorts of pediatric CNS inflammatory disorders that have found a low rate of rituximab discontinuation due to infusion reactions.[9,13] Although this study did not assess the occurrence of mild infections, hospital admissions associated with an infectious diagnosis were uncommon, with only four children being admitted to hospital with an infectious diagnosis in the year following rituximab approval and no deaths occurring in the study period. Previous studies have identified serious infections in approximately 10–15% of children treated for CNS inflammatory or other autoimmune diseases, with the highest rate of serious infections in the month after rituximab administration.[9,10,12]

Only a minority of children in our study were identified to have a CD19 count and/or immunoglobulin levels assessed following initial rituximab approval. In those with immunoglobulin levels available, almost half had at least one immunoglobulin subset fall below the lower limit of normal at least once after rituximab approval. This is consistent with the rate of hypogammaglobulinemia reported following rituximab in previous pediatric studies, which can be identified one year or longer after a single rituximab cycle and may occur at a higher rate in children treated with rituximab for CNS autoimmune diseases.[11,12] The variability in laboratory monitoring seen in this study may reflect the variability in practice between different prescribing subspecialties, the fact that most applications were for a single cycle of rituximab, and the lack of consensus guidelines for rituximab use and monitoring in pediatric CNS inflammatory disorders. The lack of standardized laboratory monitoring in relation to rituximab dosing limited the ability to evaluate other potential adverse effects of rituximab, such as neutropenia. However, as experience with rituximab in these disorders continues to grow, practices for routine laboratory monitoring may become better defined.[16]

This study has several limitations, most notably the reliance on data supplied by prescribers as part of application for rituximab funding. Diagnoses for rituximab indication were provided by prescribers and not independently verified. Furthermore, established diagnostic criteria for CNS inflammatory disorders evolved over the course of the study.[17–20] As such, standardized diagnostic criteria could not be applied in this study. Prescribers may also have a bias to present the clinical information supporting their diagnosis and omit or diminish information that may suggest an alternate diagnosis or other therapeutic avenues. Similarly, physician-reported outcomes were subjective, not standardized between patients, and predominantly collected in the context of application for rituximab re-dosing and reflected relatively short-term follow-up. As a result, physician-reported outcomes were not available for approximately half of the study cohort and those outcomes provided are expected to be biased towards those patients in whom rituximab was felt to be beneficial. The study's relatively small sample size and missing outcome data also preclude analysis of the efficacy of different rituximab dosing regimens in different CNS inflammatory disorders. Rituximab administration also could only be confirmed in approximately two-thirds of the study cohort, and thus, it is possible that some children did not ultimately receive rituximab despite being granted funding approval.

Subsequent to this study, classification criteria and diagnostic algorithms for pediatric autoimmune encephalitis – including probable antibody-negative autoimmune encephalitis – have been proposed.[20] Evidence is lacking for the use of rituximab in antibody-negative autoimmune encephalitis, particularly in children, although a recent observational study in adults suggested possible clinical benefit to rituximab as a component of an immunotherapy regimen for antibody-negative autoimmune encephalitis.[4] Future studies of the use of rituximab in pediatric autoimmune encephalitis will benefit from incorporating these classification criteria, with particular attention required to the patterns of use and effect of rituximab in antibody-negative disease.

In conclusion, we identified increasing use of rituximab for pediatric CNS inflammatory disorders in the province of Alberta, Canada, particularly for the indication of autoimmune encephalitis. The STEDT program has subsequently moved to applying consistent diagnostic criteria for autoimmune encephalitis at the time of rituximab application, which should help standardize this diagnostic subgroup in future clinical use and research studies. Variability in dosing and laboratory monitoring practices also highlights the need for standardized treatment protocols in this population. While the STEDT program has since moved to standardized rituximab dosing regimens in the adult population, evidence to define specific dosing regimens in the pediatric population is lacking and will require prospective, multicenter studies to establish. Ongoing assessment of rituximab treatment in this population using standardized outcome measures is required to assist in determining the efficacy and safety of rituximab across the growing spectrum of CNS inflammatory disorders. This will be better addressed through the prospective collection of clinical data, rather than administrative datasets.

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