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Rituximab Use for Relapse Prevention in Anti-NMDAR Antibody-Mediated Encephalitis

A Multicenter Cohort Study

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Abstract

Background and Objectives

Rituximab is an anti-CD20 monoclonal antibody used in patients with anti-NMDAR antibody (Ab)-mediated encephalitis as both an acute escalation therapy and a longer term relapse risk–reduction treatment. The potential long-term benefit of a single course administered during the acute disease phase on future relapse risk is uncertain. Moreover, the optimal dosing duration to reduce relapse risk is unknown. The aim of this study was to evaluate the effect of a single course of rituximab on relapse incidence. We also studied the duration of effect of a course of rituximab in adult patients with anti-NMDAR Ab-mediated encephalitis.

Methods

We recruited 67 patients with anti-NMDAR Ab-mediated encephalitis from 10 Australian hospitals. Rituximab exposure was quantified as a time-varying covariate in Cox proportional hazard models.

Results

A single course of rituximab was associated with longer time to first relapse (hazard ratio [HR] 0.11, 95% CI 0.02–0.70, $p = 0.02$). For patients in whom redosing is considered, rituximab was associated with longer time to first relapse at 6 months after the last infusion, after adjusting for concurrent immunotherapies and the presence of ovarian teratoma at disease onset (HR 0.05, 95% CI 0.00–0.48, $p = 0.005$). The treatment effect did not persist out to 12 months after a given course (HR 0.60, 95% CI 0.15–2.44, $p = 0.47$).

Discussion

A single course of rituximab reduces the risk of relapse of anti-NMDAR antibody-mediated encephalitis. In select patients for whom redosing of rituximab is considered, administration at 6 months delays relapses.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Supplementary Material

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Glossary

AE = autoimmune encephalitis; **AZA** = azathioprine; **DRE** = drug-resistant epilepsy; **ICD** = International Classification of Disease; **IQR** = interquartile range; **IVIg** = IV immunoglobulin; **NHMRC** = National Health and Medical Research Council; **NMDAR** = N-methyl-D-aspartate receptor.

Classification of Evidence

This study provides Class IV evidence that rituximab delays relapses in patients with anti-NMDAR antibody-mediated encephalitis.

Introduction

Anti–N-methyl-D-aspartate receptor (NMDAR) antibody (Ab)-mediated encephalitis has an estimated prevalence of 0.6 per 100,000.[1] Although a rare disease, it represents the most common form of autoimmune encephalitis (AE).[2] It most frequently occurs in children and young adults and is more prevalent in female patients,[3] with an approximate female-to-male ratio of 4:1.[4] Ovarian teratomas make up most of the associated tumors, occurring in up to one-third of female patients,[3,5] although nonparaneoplastic anti-NMDAR Ab-mediated encephalitis makes up most of the presentations. The acute clinical presentation is characterized typically by an abrupt onset of psychiatric disturbance, with rapid evolution to involve neurologic features. These include seizures, dyskinesias and other movement disorders, decreased conscious state, dysautonomia, and hypoventilation.[3] Most patients improve with immunotherapy, and earlier immunotherapy is associated with more favorable outcomes.[3,5] The acute and postacute disease phases are often protracted, and the recovery period can continue for many months to years.[3,5,6] Functional recovery is commonly measured as independence with daily activities—defined as a modified Rankin Scale[7] score of <2. This occurs in over 80% of patients after 2 years.[3,5] Despite this, long-term cognitive impairment across multiple domains occurs in two-thirds of patients, and it is increasingly recognized that a "good" mRS score of <2 does not adequately account for this.[8]

Relapses occur in 12%–16% of patients and can occur many years later.[3,5,9,10] Relapses are often milder than the initial disease, more often monosymptomatic, and associated with shorter duration of hospitalization.[3,5,9] Nonetheless, few studies have evaluated the impact of relapse on long-term outcomes.

Rituximab is a chimeric human and murine IgG1 anti-CD20 monoclonal antibody that rapidly depletes peripheral CD20-expressing B cells and also depletes CSF B cells.[11,12] B-cell reconstitution to approximately 30% of pre-rituximab levels occurs by 48 weeks from the last dose.[13] Rituximab as a second-line immunotherapy in anti-NMDAR Ab-mediated encephalitis reduced the odds of relapse at > 24 months from disease onset by 83% in a meta-analysis.[9] Still, it is unknown how long a course of treatment confers protection against disease recurrence. It is important to understand the impact of dosing regimens on relapse risk to guide postacute treatment strategies. Patients with persistence of residual deficits after the acute treatment period in particular may warrant further rituximab administration.

The aims of this study were to evaluate the effect of a single course of rituximab on relapse prevention. A secondary aim was to explore how long after a course of rituximab the risk of relapse is reduced in patients in whom redosing is considered. Specifically, the following research questions were addressed:

1. Whether a single course of rituximab delays time to first relapse in patients with anti-NMDAR Ab-mediated encephalitis
2. For a subset of patients in whom redosing is considered, whether the effect of rituximab on relapse prevention lasts 6 or 12 months after a treatment course.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the central Human Research Ethics Committee at Alfred Health (HREC/17/Alfred/168), with a waiver of consent for medical record access for retrospectively recruited patients. All prospectively recruited patients provided informed consent.

Participant Identification

We identified adult patients aged 18 years and older with a diagnosis of anti-NMDAR Ab-mediated encephalitis who had an acute hospital admission and/or outpatient neurology clinic review between January 2008 and April 2024. The study was performed in 10 Australian hospitals, all members of the Australian Autoimmune Encephalitis Consortium Study: in Victoria (Alfred Health, Melbourne Health, Eastern Health, Monash Health, Austin Health, St Vincent's Health, Barwon Health, Peninsula Health), New South Wales (Concord Repatriation General Hospital), and Queensland (Princess Alexandra Hospital). We identified patients using Health

Information Systems discharge codes matching the following International Classification of Diseases (ICD) codes: G048, G258, G608, G049, and M359.

Anti-NMDAR Ab-mediated encephalitis was defined both phenotypically and by recorded anti-NMDAR IgG detection in the CSF. We also included 2 patients who met the 2016 Lancet Neurology "probable anti-NMDA encephalitis" criteria. One had positive anti-NMDAR antibodies in serum, but their CSF was not evaluated, and the other had a recorded positive anti-NMDAR antibody test, but the sample source (i.e., serum vs CSF) was not specified. Serum and CSF anti-NMDAR antibodies were generally detected by indirect immunofluorescence using a commercial fixed human embryonic kidney 293 cell-based assay (Autoimmune Encephalitis Mosaic 6 or glutamate receptor–type NMDAR slides, Euroimmun, Lübeck, Germany). In 1 case, the test was performed in an overseas laboratory with no further information available.

Data Collection

We retrospectively collated data from medical records including patient demographics, clinical features, and ancillary investigation results including CSF results and presence/absence of a tumor. We retrospectively assigned initial admission and 12-month mRS scores and clinical assessment scale in autoimmune encephalitis[14] scores. The assigners were one of 3 subspecialist neurologists assigned (N.S., R.W., J.B.). For prospectively evaluated patients, scores were recorded during outpatient reviews. MRI T2/fluid attenuated inversion recovery scan hyperintensities were classified by a blinded neuroradiologist (P.B.) as AE-related if no better explanation was evident. Commencement and cessation dates for all immunotherapies were recorded. Clinical data were collated using the Research Electronic Data Capture database.[15,16]

Study Definitions

Cognitive symptoms included memory disturbance, attentional deficits, and frank confusion, as determined retrospectively from review of relevant medical records. **Consciousness disturbance** was defined as a Glasgow Coma Scale score of <13. **Speech disturbance** encompassed impairment of language and articulation. **Psychiatric disturbance** was defined as hallucinations or delusions and altered mood or behavior. **Drug-resistant epilepsy (DRE)** and **status epilepticus** were defined as per International League Against Epilepsy (ILAE) definitions.[17,18]

First-line immunotherapy included IV methylprednisolone, IV immunoglobulin (IVIg), and/or plasma exchange, and **second-line immunotherapies** included rituximab or cyclophosphamide. Bortezomib was the only therapy used as **third-line**. **Steroid-sparing** agents were mycophenolate, azathioprine (AZA), and methotrexate. **IVIg maintenance** was defined as IVIg duration spanning at least 2 treatment courses, 28 days or more apart. Courses of IVIg not followed by further doses within 1 month were assigned as having a duration of 28 days. **Time to first-line immunotherapy** was recorded as days from symptom onset to start of the first-line immunotherapy agent. **Treatment delay** was defined as delay of first-line immunotherapy beyond 30 days from symptom onset. Various rituximab dosing regimens were all defined as a single course, including 1 g administered 2 weeks apart, a single dose, and 4 weekly doses based on body surface area. Subsequent treatments, independent of actual dose administered (e.g., 500 mg cf. 1 g or otherwise), were also treated as separate courses. We grouped cyclophosphamide and bortezomib exposure together and considered their effect to last until the end of follow-up irrespective of the number of cycles or dose.

For evaluation of the efficacy of a single course of rituximab, we treated all follow-up time after the single course as exposed to rituximab. Patients who received more than 1 treatment course of rituximab but relapsed between the first and second treatment courses were included in the single-treatment group, and patients who relapsed before receiving any rituximab were included in the untreated group. Furthermore, 2 models of rituximab effect were defined. The first model considered effect lasting for a period of 6 months after the last course of rituximab, with no more than 6 months separating successive treatment courses. The second considered the effect as lasting 12 months after the last course of rituximab, with no more than 12 months separating courses (Figure 1). The following time intervals were defined as being "unexposed" to rituximab: (1) the time from initial admission until first rituximab treatment course, if rituximab was administered before a relapse in relapsing cases; (2) the time from initial admission until first relapse if no rituximab was administered or rituximab was administered after the first relapse; (3) the time from admission until the final follow-up if no rituximab was administered and no relapses occurred; (4) the time from either 6 or 12 months after a rituximab treatment course (depending on the treatment-effect model), if no further rituximab was administered by 6 or 12 months, until the first of either relapse, delayed rituximab retreatment, or final follow-up.

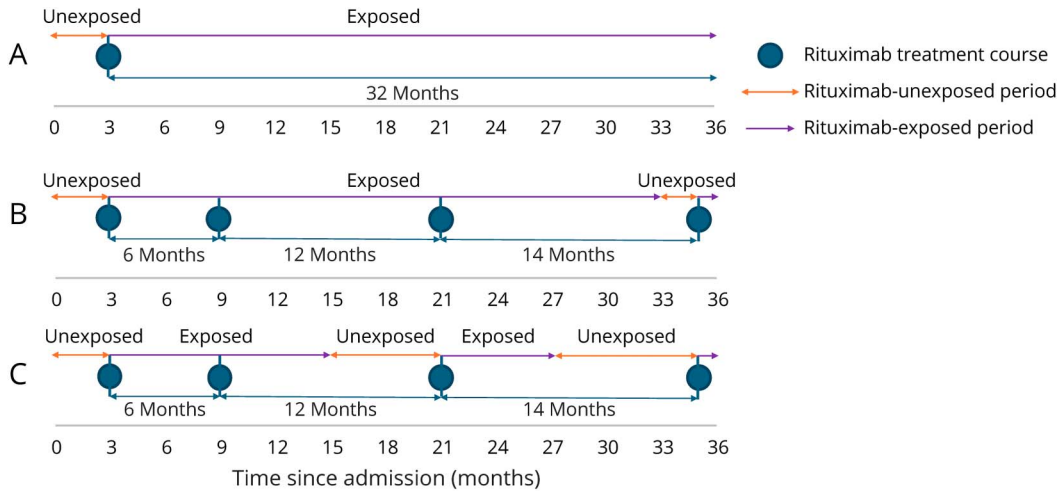
Relapse was defined as the presence of new or worsening clinical features after at least 2 months of stability or improvement. **Follow-up time** was defined as the time from initial admission until the final study visit.

Statistical Analysis

All analyses were performed using R version 4.2.0. Descriptive statistics were expressed as median with interquartile range (IQR). We used the Wilcoxon signed rank test (2-tailed p values, significance threshold of 0.05) to compare paired variables with non-Gaussian distributions. We used Wilcoxon rank-sum and χ^2 tests as appropriate for nonpaired comparisons. For these analyses, immunotherapies in relapsing patients were only included if administered before the first relapse.

For relapse analyses, time to first clinical relapse or censoring at last follow-up or death was the outcome of interest. Patients

Figure 1 Schematic of Hypothetical Patients Evaluated Using Rituximab Treatment-Effect Models



(A) Single-course rituximab model; (B) 6-month effect model; (C) 12-month effect model.

were included if they had at least 2 months of follow-up data available. The association between non–time-varying covariates and relapse was evaluated using Cox proportional hazard regression models. The effect of rituximab on relapse risk was analyzed as a time-varying covariate in Cox regression models, with each exposed and unexposed period contributing separately to analyses as per the previous rituximab effect definitions. In multivariable analyses, only concomitant immunotherapies and presence of ovarian teratoma were included as covariates. The following immunotherapies were evaluated as covariates expressed as the proportion of each rituximab-exposed and unexposed period: prednisolone, steroid-sparing agents, IVIg, and cyclophosphamide or bortezomib. If no relapses occurred in rituximab-exposed periods, we used Cox proportional hazard regression with Firth penalized likelihood[19] to calculate hazard ratios for time to first relapse.

Data Availability

Anonymized data are available to any qualified investigator by the corresponding author on reasonable requests.

Results

Baseline Variables

We included a total of 67 patients with anti-NMDAR Ab-mediated encephalitis. The median age at onset was 27.3 years (IQR 22.3, 38.7), and 52 patients (78%) were female (Table 1). Acute clinical features are provided in Table 1. An underlying ovarian teratoma was found and removed in 13 patients (19%). A further ovarian mass with inconclusive pathology was identified in another patient, with no further information available (eTable 1).

In total, 66 (99%) and 47 (70%) patients received first-line and second-line immunotherapy, respectively (Table 2). The median time from symptom onset to first-line immunotherapy was 30 days (IQR 14, 53), and median time to rituximab was 58 days (IQR 30, 366). All patients who received second-line immunotherapy received rituximab. Rituximab was administered in 33 patients (49%) during their acute admission, 5 (7%) after discharge from hospital because of ongoing clinical features not deemed to be a definable relapse, and 9 (13%) after a relapse. A total of 23 patients (34%) received only a single course of rituximab. A further 15 patients (22%) received multiple courses, excluding treatment after first relapse. The median treatment interval was 251 (IQR 187, 352) days (eFigure 1). The rituximab dosing regimens are presented in eTable 2. Cyclophosphamide and bortezomib were administered to 12 (18%) and 5 (8%) patients, respectively. Oral prednisolone was administered in 43 (64%) and maintenance IVIg in 19 (28%) patients. Mycophenolate mofetil was prescribed to 18 patients (27%) and AZA to 7 (10%). The temporal relation of second-line and maintenance immunotherapies to relapses are presented for each patient in Figure 2 and the temporal relation of all immunotherapies and teratoma removal to relapses in eFigure 2. Acutely, the median nadir mRS score was 4 (IQR 3, 5), and at 12 months, 41 patients (75%) had an mRS score of 2 or less. DRE occurred in 3 (6%) and 4 (8%) patients at 12 months and the final follow-up. Four patients died during the study period: 1 died by suicide, 1 died from acute myeloid leukemia, 1 died from neuroendocrine carcinoma, and in 1 patient, the cause of death was unknown.

A total of 19 patients (28%) had at least 1 relapse, which occurred at a median of 764 (IQR 355, 1,193) days from the initial admission (Table 2). In relapsing patients, the nadir mRS score was lower at relapse compared with acute presentation and the number of clinical features was lower at relapse compared with acute presentation (eTable 3, eFigures 3 and 4). Of 38 patients who received rituximab as a second-line immunotherapy (i.e., not due to a relapse), 7 subsequently relapsed, at

Table 1 Cohort Demographics

Characteristic	N = 67
Age at onset, median (IQR), y	27.3 (22.3, 38.7)
Female, n (%)	52 (78)
Clinical features, n (%)	
Cognitive	61 (91)
Seizures	42 (63)
Status epilepticus	9 (14)
Psychiatric	64 (96)
Consciousness disturbance	35 (52)
Speech disturbance	31 (46)
Movement disorders	38 (57)
Sleep disorder	26 (39)
Mechanical ventilation, n (%)	19 (28)
Tumour, number of patients (%)	17 (25)
Ovarian teratoma[a]	13 (19)
Ovarian mass, pathology inconclusive	1 (1)
Ovarian teratoma resected historically before encephalitis[b]	2 (3)
Ovarian fibrothecoma (during relapse)	1 (1)
Primary neuroendocrine carcinoma of the esophagus	1 (1)
Serum anti-NMDAR antibody positive, n (%)	38/49 (78)
CSF anti-NMDAR antibody positive,[c] n (%)	65/65 (100)
CSF white cell count, median (IQR), cells/mm^3	15.5 (2.0, 41.8)
CSF pleocytosis (>4 cells/mm^3)	43 (67)
CSF total protein, median (IQR), g/L	0.38 (0.28, 0.55)
CSF-restricted oligoclonal bands, n (%)	14 (78)
Associated T2/FLAIR hyperintensity on initial MRI, n (%)	7 (11)

Abbreviations: IQR = interquartile range; NMDAR = NMDA receptor; FLAIR = fluid attenuated inversion recovery.
[a] Including 1 patient who had dermoid removed overseas, the details of which were not available in medical records.
[b] One patient had a teratoma resected from the left before encephalitis and then had teratoma recurrence on the right found during the encephalitis workup.
[c] One patient did not have CSF evaluated, and in another, the sample source was not specified.

a median of 353 days (IQR 306, 1,028) from the previous rituximab treatment course (eTable 4). Of these 7 patients, no patients relapsed within 6 months of the last rituximab treatment course, 4 patients relapsed between 6 and 12 months, and the remaining 3 patients relapsed at 24 months or more after the last rituximab treatment course. Relapse clinical features, and if available, serum and CSF antibody status and CSF results are presented in eTable 5.

Comparison of Relapsing and Nonrelapsing Patients

Overall, time to first-line immunotherapy was longer in patients who relapsed compared with patients who did not relapse (76 days; IQR 32, 122, cf. 18 days; IQR 12, 41; $p < 0.001$), and patients who relapsed were more likely to experience initial treatment delay (79% cf. 47%, $p = 0.004$) (Table 3). Similarly, there was a longer time to rituximab in relapsing patients (156 days; IQR 123, 339, cf. 35 days, IQR 27, 62; $p = 0.003$). Relapsing patients were more likely to receive maintenance IVIg compared with nonrelapsing patients (58% cf. 15%, $p < 0.001$). There were no significant differences between baseline clinical and treatment covariates in relapsing and nonrelapsing patients.

A greater time to immunotherapy was again observed in relapsing rituximab-treated patients (excluding patients who received rituximab after a relapse), compared with nonrelapsing rituximab-treated patients (97 days; IQR 26, 122, cf. 18 days;

Table 2 Treatment and Clinical Outcomes

Characteristic	N = 67
1st-line,[a] n (%)	66 (99)
2nd-line, n (%)	47 (70)
Pulsed IV methylprednisolone, n (%)	59 (88)
Induction IVIg, n (%)	65 (97)
Plasma exchange, n (%)	13 (19)
Rituximab, n (%)	47 (70)
Timing of initial rituximab administration, n (%)	
During acute admission	33 (49)
Ongoing clinical features after hospitalisation	5 (7)
After relapse	9 (13)
Number rituximab courses, median (IQR)	1 (0, 2)
Single course only	23 (34)
More than 1 course[b]	15 (22)
Dosing interval, median (IQR), d[c]	251 (187, 352)
Cyclophosphamide, n (%)	12 (18)
Bortezomib, n (%)	5 (8)
Oral prednisolone, n (%)	43 (64)
Maintenance IVIg, n (%)	19 (28)
Maintenance IVIg duration,[d] median (IQR), d	584 (304, 818)
Mycophenolate mofetil, n (%)	18 (27)
Azathioprine, n (%)	7 (10)
Methotrexate, n (%)	1 (1)
Time symptom onset to 1st-line therapy, median (IQR), d	30 (14.53)
Time symptom onset to rituximab, median (IQR), d	58 (30, 366)
mRS nadir score	4 (3.5)
12m mRS score, median (IQR)	2 (1.3)
12m mRS score <3, n (%)	41 (75)
DRE final, n (%)	4 (8)
DRE 12 mo, n (%)	3 (6)
Initial CASE score, median (IQR)	5 (3, 7)
12m CASE score	2 (1, 3)
Follow-up time, median (IQR), mo	45 (15, 75)
Total relapses (%)	
0	48 (72)
1	11 (16)
2	7 (10)
3	1 (1.5)

Continued

Table 2 Treatment and Clinical Outcomes *(continued)*

Characteristic	N = 67
Time from first day of initial admission to first relapse, median (IQR), d	764 (355, 1,193)
Follow-up time,[e] median (IQR), mo	45 (15, 75)
Mortality, n (%)	4 (6)

Abbreviations: CASE = clinical assessment scale in autoimmune encephalitis; DRE = drug-resistant epilepsy; IVIg = IV immunoglobulin; mRS = modified Rankin Scale.
[a] Two patients received first-line immunotherapy after a relapse.
[b] Excluding treatment courses after first relapse in relapsing cases.
[c] Interval between rituximab courses, excluding courses after first relapse.
[d] Maintenance IVIg duration, excluding patients who only received induction IVIg dosing.
[e] From admission until last visit follow-up, independent of relapses.

IQR 14, 39; $p = 0.05$). Maintenance IVIg was more frequently administered in relapsing patients than in nonrelapsing patients (71% cf. 13%, $p = 0.005$). Other covariates were not significantly different between the 2 groups (eTable 6).

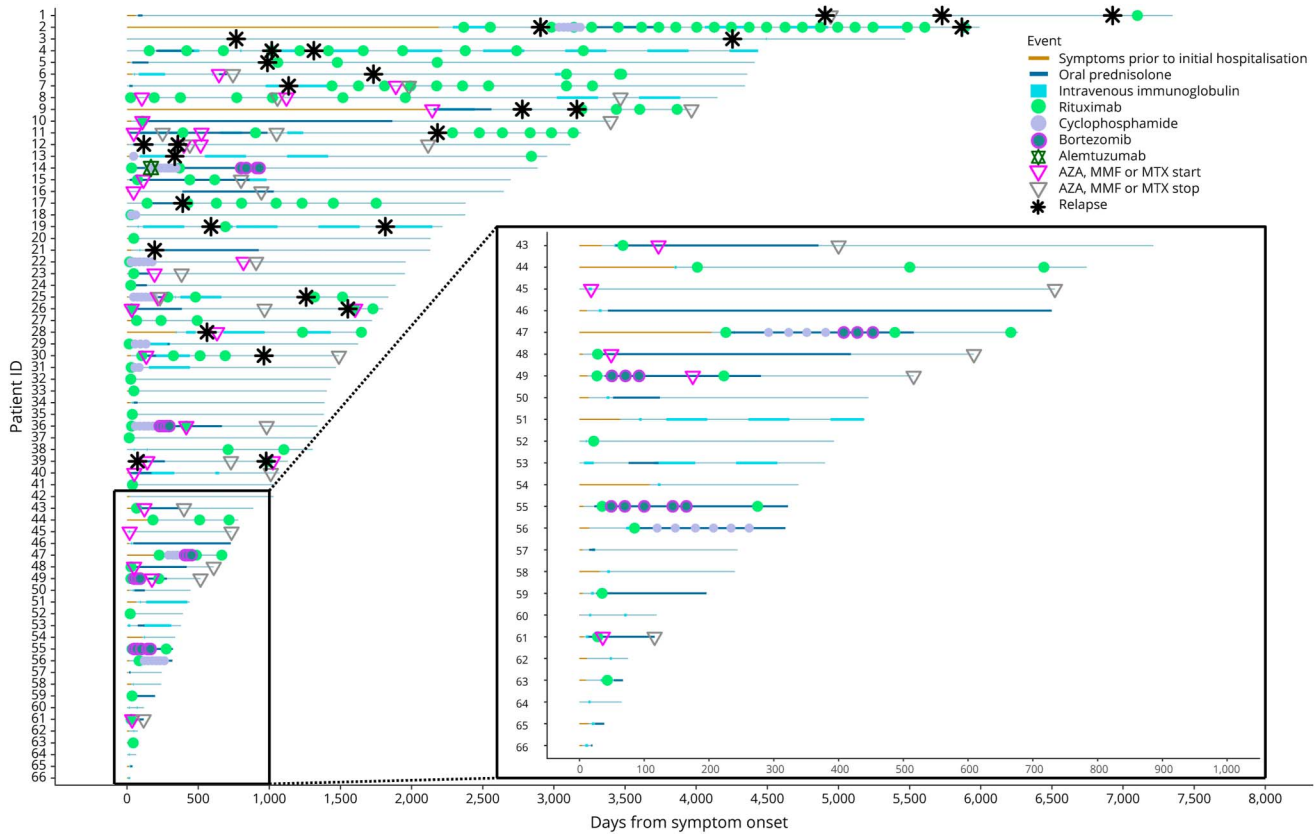
Univariable Cox Regression Analyses (Baseline Covariates)

Delay to first-line immunotherapy was associated with shorter time to first relapse (hazard ratio [HR] 5.81, 95% CI 1.89–17.82, $p = 0.002$). None of the baseline clinical parameters was associated with time to first relapse (eTable 7).

Rituximab Cox Regression Analyses for Single-Course Rituximab

A single course of rituximab was associated with significantly longer time to first relapse, corresponding to an 89% reduction in the risk of relapse in multivariable analysis (HR 0.11, 95% CI 0.02–0.70, $p = 0.02$, n = 51) (Table 4).

Figure 2 Swimmer Plot Demonstrating Temporal Relation of Second-Line and Maintenance Immunotherapies to Relapses



(A) Rituximab dosing: 2 induction doses of 1 g over a fortnightly period and weekly body surface area dosing up to 4 weeks treated as a single course and represented by a single symbol; cyclophosphamide dosing: 750 mg/m^2 or 15 mg/kg dosing per treatment, with reductions in dose as necessary; bortezomib dosing: each cycle represented by a cycle of subcutaneous dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle. (B) One patient excluded because of missing data for immunotherapy administered overseas. Abbreviations: IVIg = IV immunoglobulin; AZA = azathioprine; MMF = mycophenolate mofetil; MTX = methotrexate.

Table 3 Comparison of Baseline Clinical and Treatment Covariates Between Nonrelapsing and Relapsing Cases

	No relapses (n = 48)	Relapses (n = 19)	*p* Value
Age at onset	28.1 (23.8, 37.1)	26.0 (20.6, 40.1)	0.36
Sex (male) (%)	10 (21)	5 (26)	0.87
Admission mRS score[a]	3 (2.4)	3 (2, 3)	0.32
Admission CASE score[a]	5 (3.7)	5 (3, 7)	0.65
Teratoma (%)	12 (25%)	1 (5)	0.13
Clinical features[a] **(no)**	5.5 (3.8, 6)	5 (4, 6)	0.42
CSF pleocytosis,[a] **n (%)**	33 (69)	10 (63)	0.88
MRI abnormal,[a] **n (%)**	4 (9)	3 (17)	0.58
Mechanical ventilation,[a] **n (%)**	16 (33)	3 (16)	0.26
Time to immunotherapy (d)[b]	18 (12, 41)	76 (32, 122)	<0.001
Treatment delay,[b] **n (%)**	16 (47)	15 (79)	0.004
Pulse steroids,[c,d] **n (%)**	42 (88)	13 (68)	0.14
Induction IVIg,[c,e] **n (%)**	46 (96)	15 (79)	0.09
Plasma exchange,[c,f] **n (%)**	10 (21)	2 (11)	0.52
Rituximab,[c] **n (%)**	31 (65)	7 (37)	0.07
Rituximab courses[c] **(total)**	1 (0, 1)	0 (0, 1.5)	0.25
Time to rituximab[b,c] **(d)**	35 (27, 62)	156 (123, 339)	0.003
Cyclophosphamide,[c] **n (%)**	9 (19)	3 (16)	1
Bortezomib,[c] **n (%)**	5 (10)	0 (0)	0.34
Maintenance IVIg, n (%)	7 (15)	11 (58)	<0.001
Prednisolone, n (%)	29 (60)	12 (63)	1
Mycophenolate, n (%)	9 (19)	5 (26)	0.72
Azathioprine, n (%)	4 (6)	2 (11)	1

Abbreviations: mRS = modified Rankin Scale; CASE = clinical assessment scale in autoimmune encephalitis; IVIg = IV immunoglobulin.
[a] During acute presentation.
[b] One patient treated overseas without information on dates for overseas immunotherapies excluded from time to immunotherapy, treatment delay, and time to rituximab analyses.
[c] Immunotherapies before first relapse in relapsing patients.
[d] Four patients received pulse steroids after a relapse.
[e] Four patients received IVIg induction after a relapse.
[f] One patient received PLEX after a relapse.

Rituximab Cox Regression Analyses of 6-Monthly and 12-Monthly Treatment Effect for Patients in Whom Redosing Is Considered

Univariable analyses of rituximab treatment effect of 6 months and 12 months, respectively, in relation to time to first relapse, are presented in eTable 8.

In multivariable analysis (Table 5), for treatment effect lasting 6 months after a treatment course, rituximab use was associated with greater time to first relapse (HR 0.08, 95% CI 0.00–0.64, p = 0.01, n = 66), using Firth penalized likelihood. When the treatment effect was extended to 12 months after a treatment course, the effect was lost (HR 0.93, 95% 0.28–3.10, p = 0.91, n = 66).

Classification of Evidence

This study provides Class IV evidence that rituximab delays relapses in patients with anti-NMDAR antibody-mediated encephalitis.

Discussion

In this cohort of adult patients with anti-NMDAR Ab-mediated encephalitis, we studied the effect of rituximab treatment on relapse. We show that a single course of rituximab is protective against relapses. Furthermore, we show that treatment with rituximab delays time to first relapse for 6 months after a treatment course, irrespective of other

Table 4 Multivariable Model of Single-Course Rituximab in Relation to Time to First Relapse[a]

	HR	95% CI	*p* Value
Rituximab exposure	0.11	0.02–0.70	0.02
IVIg	1.02	1.00–1.04	0.13
Prednisolone	1.03	1.00–1.05	0.06
Steroid-sparing	0.98	0.95–1.01	0.13
Cyclophosphamide/bortezomib	1.00	0.98–1.03	0.92
Ovarian teratoma	0.14	0.01–1.49	0.10

Abbreviation: IVIg = IV immunoglobulin.
[a] n = 48.

immunotherapies, but this effectiveness seems to be lost after 6 months.

We found relapse to be more common than previously described. Relapses in anti-NMDAR Ab-mediated encephalitis occur in approximately 12%–16% of pediatric and adult patients in reported studies.[3,5,9] Rituximab use ranged from 2% to 25% in these cohorts. This variability in rituximab use may have influenced the reported frequency of relapses, given the known association of rituximab with a monophasic disease course.[9] In our study, a higher proportion of patients (28%) had a relapsing course, despite relatively frequent use of rituximab (65% of patients overall). We found a median time of 764 days (IQR 355, 1,193) from initial admission to first relapse, over a median follow-up period of 45 (IQR 15, 75) months, which is longer than in previous studies. Logically, longer follow-up is associated with a higher incidence of relapse.[20] It is possible that owing to selection bias, relapsing patients were more likely to receive follow-up compared with milder cases in our cohort. Use of ICD codes, however, as in our study, would have prevented nonrelapsing cases from being missed because all cases coded as AE were captured. Relapses were only assigned in our study if no better medical etiology was identified. The higher incidence of relapse observed in our study warrants exploration in future cohorts with adult patients and longer follow-up intervals, given the implications for long-term outcomes.

Table 5 Multivariable Models of 6-Monthly and 12-Monthly Rituximab Treatment Effect in Relation to Time to First Relapse

	HR	95% CI	*p* Value
6-monthly treatment effect[a] (n = 63)			
Rituximab exposure	0.05	0.00–0.48	0.005
IVIg	1.02	1.00–1.03	0.06
Prednisolone	1.01	0.99–1.03	0.20
Steroid-sparing	0.99	0.97–1.00	0.11
Cyclophosphamide/bortezomib	0.99	0.98–1.01	0.42
Ovarian teratoma	0.32	0.04 1.33	0.13
12-monthly treatment effect (n = 63)			
Rituximab exposure	0.60	0.15–2.44	0.47
IVIg	1.02	1.01–1.04	0.007
Prednisolone	1.01	0.99–1.03	0.27
Steroid-sparing	0.98	0.97–1.00	0.09
Cyclophosphamide/bortezomib	0.99	0.98–1.01	0.33
Ovarian teratoma	0.22	0.03–1.70	0.15

Abbreviation: IVIg = IV immunoglobulin.
[a] Using penalized likelihood.

There was a greater time to immunotherapy and rituximab administration in relapsing patients overall and in rituximab-treated patients specifically in our cohort. Delayed immunotherapy and increased relapse risk were also reported in a study from Western China.[5] In that study, however, few patients received rituximab. A previous meta-analysis conversely showed only a trend toward a long-term relapsing disease course after immunotherapy delay beyond 30 days.[9] To our knowledge, previous studies have not evaluated the association of rituximab timing with relapse risk. Given our treatment of rituximab as a time-varying covariate, we were unable to specifically explore rituximab timing and relapse risk in regression models. Furthermore, it is possible in our cohort that treatment delay was associated with increased relapse risk because of delayed rituximab administration. In clinical practice, however, when indicated, rituximab use typically follows soon after first-line immunotherapy.[21] The importance of prompt immunotherapy administration is, therefore, emphasized by our findings, and future studies should aim to compare early and late rituximab administration and relapse risk.

We observed more frequent use of maintenance IVIg regimens in patients who relapsed compared with those who did not. In post hoc analysis, of 11 patients who received maintenance IVIg therapy and relapsed, 8 relapsed after the last dose of maintenance IVIg, at a median of 426 days (IQR 67, 671), i.e., were not receiving maintenance IVIg at the time of relapse (data not shown). Therefore, this finding does not exclude the possibility that maintenance IVIg is effective at relapse prevention. In a meta-analysis, maintenance IVIg, defined as at least 6 months of therapy, was associated with a nonrelapsing disease course. This study, however, included a high proportion of individual case reports and small series, and only 24 patients received maintenance IVIg.[9] Taken together, there is currently insufficient evidence to substantiate either efficacy or inefficacy of IVIg maintenance in relapse prevention.

The reduction of relapse risk associated with a single treatment course in our cohort builds on preexisting knowledge

concerning rituximab efficacy. This may be of most relevance to circumstances where a patient has had substantial recovery after the initial encephalitis by the time redosing of rituximab is considered, whereby a discussion about treatment cessation could be considered. In addition, patients with comparatively milder initial disease may also be considered for a single treatment course followed by an observation period.[3,5,9]

A recent meta-analysis of studies that assessed the benefit of early rituximab use on relapse risk showed a 5.9-fold reduction of relapse at 24 months in pediatric and adult patients.[9] An observational study of pediatric and adult patients found that second-line immunotherapy was associated with lower frequency of relapses in nontumor patients. This included 71 patients treated with rituximab. Furthermore, relapsing patients experienced fewer relapses subsequent to second-line immunotherapy.[3] However, none of these studies specifically explored the effect of a single course of rituximab on overall relapse risk.

In some patients with anti-NMDAR Ab-mediated encephalitis, rituximab redosing to prevent further relapses may be considered, and our results suggest that the most effective dosing strategy is a 6-monthly dosing interval. After the initial encephalitis, a proportion of patients continue to recover at 12 months and beyond.[3,5] In 1 study, approximately one-third of patients had an mRS score of 3 or more at 8 months of follow-up.[3] We found 25% of patients at 12 months to have an mRS score of 3 or more. Therefore, clinical deficits can persist at a functionally disabling level well after the clinical effect of rituximab has subsided. In this context, relapse prevention may be particularly crucial. Some patients, especially those with a predominantly psychiatric presentation, are diagnosed late and, therefore, treated late. Because treatment delay was associated with higher relapse risk in our cohort, we would recommend this group of patients be considered for redosing with rituximab.

Circulating B-cell reconstitution begins from approximately 6 months after last rituximab infusion, but $CD27^+$ memory B-cell reconstitution is considerably slower.[22] There is less known about findings within the lymphoid organs.[23] Anti-NMDAR Ab-mediated encephalitis is mediated by pathogenic autoantibodies, which are likely formed both in the periphery and in the CNS.[4] Given that plasma cells do not express CD20, the mechanism of action of rituximab in both the acute disease and in reducing relapse risk is not understood. It may in part, however, be facilitated by B-cell depletion in germinal centers.[24] Overall, our study affirms a central pathogenic role of B cells in the disease pathogenesis and relapses. Future studies could assess differences in the rate of B-cell reconstitution in individual patients.

For patients who require third-line acute therapy,[3,25] options include cyclophosphamide, bortezomib, and tocilizumab.[25,26] These therapies may affect the need for further rituximab doses, but this has not been clarified. A meta-analysis did not find cyclophosphamide to reduce the risk of relapses.[9] Cyclophosphamide usage is usually reserved for more severe cases, which may have confound these results. Furthermore, rituximab is commonly used overall, and cyclophosphamide is rarely used in isolation. These practices make it difficult to discern the true impact of cyclophosphamide on relapses, given the known effectiveness of rituximab. In the aforementioned study, the bortezomib group was too small to be evaluated.[9] Of interest, none of the 5 patients treated with bortezomib in our cohort relapsed (Figure 2 and eFigure 4). Bortezomib has a short-lived effect on plasma cells.[27] When combined with rituximab, there lies the possibility of a synergistic effect.[28] Rituximab could deplete potentially pathogenic B cells before they become anti-NMDAR Ab-secreting plasma cells, and bortezomib remove pathogenic plasma cells. Whether this therapeutic combination has potential to further delay recurrence of disease activity compared with rituximab alone remains to be seen and warrants further evaluation. Ultimately, however, too few patients in our cohort were treated with either cyclophosphamide or bortezomib to perform specific analyses.

Our study has several limitations. These include the predominantly retrospective nature of our data collection, modest sample size, and variable follow-up period. The clinical definition of relapse used in this article and previous publications is limited. In 14 of 28 relapses where CSF antibodies were available, 14 were positive for anti-NMDAR IgG (100%), but titers were not available, and 2 patients had recurrence of CSF antibodies at time of relapse (eTable 2). Given antibodies are known to persist in the CSF in the absence of clinical activity, the former is largely of uncertain significance.[29] Our analyses may be subject to indication bias, given that rituximab is typically used initially as a second-line immunotherapy in this disease and, therefore, may be commenced in more clinically severe patients. Illness severity itself may influence relapse risk. These factors could have caused an underestimation of its relapse-preventing effect. We were unable to analyze the effect of the number of courses of rituximab on relapse risk, or compare patients who received a single course with those who received multiple courses. We did not have data available on peripheral lymphocyte subsets, which would be of potential interest regarding rituximab clinical activity. We could not adjust for the dose or timing of doses of concomitant immunotherapies in regression models. We did not collect data on treatment-related adverse effects, which are of importance regarding initial and ongoing treatment with rituximab.

Our study evaluates the therapeutic implications of a single course of rituximab with treatment effect analyzed as a time-varying covariate. We substantiate that the effectiveness of rituximab in reducing relapse risk applies to a single treatment course, building on the results of a recent meta-analysis.[9] This may benefit a large proportion of patients with this disease.

Rituximab effectively delays occurrence of relapses in patients with anti-NMDAR Ab-mediated encephalitis. A single course

of rituximab (compared with no rituximab) reduces the risk of first relapse, which is likely sufficient in most patients. In the select population of patients who require redosing, six-monthly treatment is superior to less frequent dosing regimens.

Author Contributions

N. Seery: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. R. Wesselingh: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P. Beech: major role in the acquisition of data. L. McLaughlin: major role in the acquisition of data. T. Rushen: major role in the acquisition of data; study concept or design. A.J. Halliday: drafting/revision of the manuscript for content, including medical writing for content liora ter horst: major role in the acquisition of data. S.P. Griffith: major role in the acquisition of data; study concept or design. M. Forcadela: major role in the acquisition of data. T.H. Tan: drafting/revision of the manuscript for content, including medical writing for content. C. Kazzi: drafting/revision of the manuscript for content, including medical writing for content. C. Nesbitt: major role in the acquisition of data. J. Broadley: study concept or design. K. Buzzard: major role in the acquisition of data. A. Duncan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. W.J. D'Souza: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. Y. Tran: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Van Der Walt: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. Skinner: major role in the acquisition of data. B.V. Taylor: drafting/revision of the manuscript for content, including medical writing for content. A. Swayne: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Brodtmann: drafting/revision of the manuscript for content, including medical writing for content. D. Gillis: drafting/revision of the manuscript for content, including medical writing for content. E.G. Butler: major role in the acquisition of data. T. Kalincik: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. U.K. Seneviratne: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. R.A. Macdonell: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S Blum: major role in the acquisition of data. S. Ramanathan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C.B. Malpas: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S.W. Reddel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T.A. Hardy: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T.J. O'Brien: drafting/revision of the manuscript for content, including medical writing for content. P.G. Sanfilippo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. H. Butzkueven: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Monif: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Appendix Coinvestigators

Coinvestigators are listed at Neurology.org/NN

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