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Evaluating Rituximab Failure Rates in Neuromyelitis Optica Spectrum Disorder: A Nationwide Real-World Study From South Korea

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Background and Purpose Treatments for neuromyelitis optica spectrum disorder (NMOSD) such as eculizumab, ravulizumab, satralizumab, and inebilizumab have significantly advanced relapse prevention, but they remain expensive. Rituximab is an off-label yet popular alternative that offers a cost-effective solution, but its real-world efficacy needs better quantification for guiding the application of newer approved NMOSD treatments (ANTs). This study aimed to determine real-world rituximab failure rates to anticipate the demand for ANTs and aid in resource allocation.

Methods We conducted a nationwide retrospective study involving 605 aquaporin-4-antibody-positive NMOSD patients from 22 centers in South Korea that assessed the efficacy and safety of rituximab over a median follow-up of 47 months.

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Results The 605 patients treated with rituximab included 525 (87%) who received continuous therapy throughout the follow-up period (median=47 months, interquartile range=15–87 months). During this period, 117 patients (19%) experienced at least 1 relapse. Notably, 68 of these patients (11% of the total cohort) experienced multiple relapses or at least 1 severe relapse. Additionally, 2% of the patients discontinued rituximab due to adverse events, which included severe infusion reactions, neutropenia, and infections.

Conclusions This study has confirmed the efficacy of rituximab in treating NMOSD, as evidenced by an 87% continuation rate among patients over a 4-year follow-up period. Nevertheless, the occurrence of at least one relapse in 19% of the cohort, including 11% who experienced multiple or severe relapses, and a 2% discontinuation rate due to adverse events highlight the urgent need for alternative therapeutic options.

Key Words neuromyelitis optica; rituximab; eculizumab; satralizumab; inebilizumab.

INTRODUCTION

Eculizumab, ravulizumab, satralizumab, and inebilizumab were recently approved for preventing relapses in neuromyelitis optica spectrum disorder (NMOSD).[1,2] Despite their proven efficacy, the high cost of the approved NMOSD treatments (ANTs) have restricted their widespread use as a first-line therapy.[3] Rituximab is an off-label option for NMOSD that has been widely adopted due to its efficacy in preventing NMOSD relapse, its long-term safety profile, and its significantly lower cost that has been facilitated by the availability of biosimilars.[2,4,5] This cost advantage makes rituximab the preferred first-line treatment in countries with low healthcare budgets, with ANTs reserved for patients who do not respond to rituximab.

In this context, understanding the actual failure rate of rituximab is crucial for shaping national rare-disease policies and optimizing resource allocation for patients who are rituximab-refractory and in need of ANTs. To address this situation, we conducted a nationwide study in South Korea to assess the real-world failure rate of rituximab in patients with NMOSD.

METHODS

We retrospectively collected clinical data on aquaporin-4-antibody-positive NMOSD patients who received rituximab treatment from 22 centers in South Korea between January 1, 2006, and February 28, 2024. All included patients met the 2015 diagnostic criteria for NMOSD.[6] The aquaporin-4-antibody serostatus was determined through a cell-based assay conducted at each respective center. A data analysis was conducted from May to August 2024. The study was approved by the Institutional Review Board of the National Cancer Center, South Korea (NCC2014 0146). All patients at the National Cancer Center provided written informed consent, while data from other institutions were de-identified, exempting IRB approval.

Relevant demographic information and clinical data (including the clinical history) were obtained from medical records, including the date of disease onset, aquaporin-4-antibody serostatus, attack history before and after rituximab administration, current treatment status, Expanded Disability Status Scale (EDSS) score, reasons for discontinuing rituximab, and occurrence of mortality. Attacks were defined as the occurrence of new symptoms or the worsening of previous symptoms not attributed to other causes, and occurring more than 30 days following the onset of a preceding attack.[7] Attacks were confirmed by a neurological examination and magnetic resonance imaging (MRI) revealing new T2 high lesions or contrast-enhanced lesions. A severe relapse was defined as an EDSS score of ≥6 (requiring a walking aid to walk 100 m with or without resting) at the nadir of the attack, or an increase in the EDSS score of ≥0.5 points if the patient had a baseline score of ≥6. For optic neuritis cases, a severe relapse was defined as a new worsening of visual acuity of ≤0.1 in patients with a baseline visual acuity of >0.1. If the baseline visual acuity was light perception, hand motion, or counting fingers, a severe relapse was defined as any decrease in visual acuity that was accompanied by MRI evidence of optic neuritis.[7] Clinically significant worsening on the EDSS was defined according to the baseline EDSS score. To reduce the inherent variability in EDSS transitions, particularly the measurement fluctuations between scores of 0 and 1.0, increases in the EDSS score of ≥1.5, ≥1.0, and ≥0.5 points were required for patients with baseline EDSS scores of 0, 1.0–5.0, and >5.0, respectively.[8]

The applied rituximab protocols varied among the included centers. Induction therapy consisted of either 1,000 mg administered twice at a 2-week interval, or 375 mg/m^2 ad-

ministered weekly for 4 weeks. Redosing was performed every 4–8 months, or when $CD19^+$ B cells constituted >1% of the peripheral blood mononuclear cells (PBMCs) or when $CD19^+CD27^+$ memory B cells constituted >0.05% of PBMCs, with a single dose of either 1,000 mg or 375 mg/m^2.

Data are presented as median and interquartile range (IQR) or mean±standard-deviation values for continuous variables, and as numbers and percentages for categorical variables. To minimize the risk of overestimating the annualized relapse rate (ARR) due to short follow-up durations, patients with pre- or posttreatment periods shorter than 6 months were excluded from the ARR analysis. Group comparisons were performed using a *t*-test for continuous variables and Fisher's exact test for categorical variables. Statistical significance was defined as $p<0.05$. All analyses were performed using GraphPad Prism and STATA (version 15, StataCorp).

RESULTS

Rituximab treatment was initiated in 605 (49.6%) of 1,218 seropositive NMOSD patients, with 75 (12.4%) using it as a first-line treatment. The clinical data of these 605 patients are detailed in Table 1. The total follow-up period for rituximab-treated patients was 3,161 patient-years, with a median treatment duration of 47 months (IQR=15–87 months). By February 2024, 525 (86.7%) of the patients were still on rituximab, 41 (6.7%) had discontinued rituximab, 11 (1.8%) had died, and 28 (4.6%) were lost to follow-up. Patients were treated according to the redosing protocols of their respective centers. Most centers (13 out of 22, 59%) administered a dose when $CD19^+$ B cells constituted >1% of PBMCs. Seven centers (31.8%) redosed rituximab every 4–8 months, while two centers (9%) did this when $CD19^+CD27^+$ memory B cells constituted >0.05% of PBMCs.

While receiving rituximab treatment, 117 patients (19.3%) experienced at least 1 relapse; of these, 112 continued therapy, with 68 (61%) remaining relapse-free for a median of 43 months (IQR=15–127 months), while 44 (39%) experienced a second relapse after a median of 6 months (IQR=2–10 months). B-cell monitoring was conducted in 150 of the 216 total relapse cases, with 106 (70.7%) relapses occurring when $CD19^+$ B cells constituted <1% of the PBMCs. The median time to the first relapse after rituximab initiation was 8 months (IQR=3–23 months), and 42% of relapsing patients experienced their first relapse within 6 months. Severe relapse occurred at least once in 45 (7.4%) patients, and EDSS worsening at the last follow-up was observed in 27 (4.4%) patients. Two or more relapses or at least 1 severe relapse occurred in 68 (11.2%) patients. Rituximab was discontinued in 41 patients due to relapse in 17 (2.8%) patients, adverse events in 13 (2.1%), and other reasons (mainly cost) in 11 (1.8%). Among these patients, those who discontinued due to relapse had a median of 2 relapses (IQR=1–4), and their median rituximab treatment duration was 17 months (IQR=6–38 months).

Table 1. Characteristics of 605 NMOSD patients treated with rituximab

Characteristic	Value
Using rituximab as first-line treatment	75 (12.4)
Age at onset (yr)	38 [28–47]
Sex, female	536 (88.5)
Time from disease onset to initiation of rituximab (months)	51 [12–120]
ARR before rituximab	0.95 [0.48–1.87]
Total rituximab treatment period (patient-years)	3,161
Rituximab treatment duration (months)	47 [15–87]
Current treatment status since rituximab initiation	
Still taking rituximab	525 (86.7)
Discontinued	41 (6.7)
Due to relapse (*n*=17)	
Due to adverse events (*n*=13)	
Due to other reasons (e.g., cost) (*n*=11)	
Death	11 (1.8)
Due to pneumonia (*n*=3)	
Due to concurrent cancer progression (*n*=2)	
Due to COVID-19 (*n*=1)	
Due to aspiration (*n*=1)	
Due to suicide (*n*=1)	
Unknown cause (*n*=3)	
Lost to follow-up	28 (4.6)
Treatment outcomes	
ARR on rituximab	0 [0–0]
≥1 relapse	117 (19.3)
≥2 relapses	44 (7.2)
≥3 relapses	10 (1.6)
≥1 severe relapse	45 (7.4)
Time to first relapse (months)	8 [3–23]
≥2 relapses or ≥1 severe relapse	68 (11.2)
EDSS worsening	27 (4.4)

Data are *n* (%), median [interquartile range], or numbers only.
ARR, annual relapse rate; EDSS, Expanded Disability Status Scale; NMOSD, neuromyelitis optica spectrum disorder.

The duration of rituximab treatment was significantly longer in patients who took rituximab as a first-line treatment (*n*=85, 104±73 months) than in those who took it as part of an escalation strategy (*n*=520, 5±51 months). The ARR prior to administering rituximab did not differ significantly between the first-line group (median=1.47, IQR=0.93–2.67) and the escalation group (median=0.93, IQR=0.46–1.71; $p=0.36$). Additionally, the following outcomes after administering ritux-

imab did not differ significantly between the first-line and escalation groups: relapse-free rate (81% vs. 80%, p=0.88), median ARR (0 vs. 0, p=0.93), and the proportion of patients with severe relapses (2% vs. 8%, p=0.07).

The adverse events that resulted in 13 (2.1%) patients discontinuing rituximab treatment after a median of 3 months (IQR=0–23 months) included neutropenia with/without thrombocytopenia (n=4), infection (n=5), and severe infusion reactions (n=4). Causes of death included pneumonia (n=3), concurrent cancer progression (n=2), COVID-19 (n=1), aspiration (n=1), suicide (n=1), and unknown causes (n=3).

DISCUSSION

This nationwide cohort study using real-world data found that rituximab was effective in preventing relapses among seropositive NMOSD patients, with 87% of 605 patients continuing treatment over 4 years. We evaluated treatment failure from multiple perspectives since there is no standardized definition for this in NMOSD therapy. In our cohort, 19% of patients experienced at least 1 relapse, while 7% had multiple relapses. Another 7% experienced severe relapses, and 2% discontinued rituximab due to intolerable adverse events, underscoring concerns about treatment tolerability and safety. Overall, our comprehensive failure metric—which incorporates patients with two or more relapses, at least one severe relapse, or discontinuation due to adverse events—affected approximately 13% of the cohort.

Meta-analyses of clinical trials and observational studies in NMOSD have found that rituximab therapy significantly reduced the ARR by 0.79–1.57 and improved EDSS scores by 0.55–1.34.[4,9,10] Furthermore, previous research has revealed relapse-free rates for rituximab ranging from 40% to 100%.[4,5] However, many previous observational studies involved small samples and analyzed treatment outcomes over follow-up periods shorter than 2 years, which makes it challenging to generalize their findings due to various factors such as patient-specific variability (e.g., genetic polymorphisms[11]), differences in disease severity, and differences in retreatment protocols. Two large studies on long-term rituximab treatment in NMOSD, each involving around 100 patients, found that 28%–30% of patients experienced at least 1 relapse.[11,12] Most relapses (77%) occurred within the first 6 months after initiating rituximab treatment or in the context of delayed retreatment and/or B-cell reconstitution.[11,12] In contrast, our study—which included a larger cohort and a longer follow-up period—has provided a more comprehensive and generalizable representation of the real-world effectiveness and safety of rituximab. During rituximab treatment, 42% of relapses occurred within the first 6 months of therapy, and 39% of these patients experienced a second relapse after a median of 6 months. Adverse events during rituximab treatment have been found in 23%–26% of patients with NMOSD in previous studies, with most such events being minor.[9,10] Severe adverse events led to treatment discontinuation in only 0.7% of patients, and the reported mortality rate was 1.5%.[9,10] Despite the larger cohort and longer follow-up, our study did not show a substantial increase in treatment discontinuation due to adverse events or mortality, underscoring the safety and tolerability of rituximab in real-world settings.

The risk of treatment failure in our cohort did not differ significantly between the rituximab first-line and escalation groups. However, the reimbursement policies in South Korea restrict rituximab use to second-line treatment, resulting in first-line use being concentrated in a few institutions and primarily involving patients treated before these policies were implemented. Consequently, in addition to disease activity, the choice of first-line rituximab was likely influenced by institutional practices, clinician preferences, and the financial status of patients. For these reasons, the comparison performed in our cohort between patients who took rituximab as a first-line treatment and those who received it as a second-line treatment did not allow us to determine whether rituximab effectiveness differs with the disease activity.

The relapse-free rates for ANTs are notably high: 92.9% for eculizumab over 4.1 years, 72% for satralizumab over 5.5 years, and 83% for inebilizumab over 4 years.[13] While directly comparing the efficacy of rituximab and ANTs in preventing relapses between is impossible, the available evidence suggests that ANTs are effective for patients who do not respond to rituximab treatment.[2,14] The cost disparity between rituximab and ANTs is significant. In the United States, the annual cost of ANTs ranges from USD 219,000 to USD 710,000, compared with USD 18,000 for rituximab.[13] In South Korea, government insurance coverage for satralizumab began in December 2023 and for eculizumab in April 2024, with first-year costs of USD 80,000 and USD 280,000, respectively, versus USD 5,000 for rituximab. In multiple sclerosis treatment, the high costs of newer medications have increased calls for off-label rituximab use—known for its efficacy and safety in multiple sclerosis—to reduce healthcare costs.[15] Similarly, for NMOSD, clinicians and other experts advocate the use of rituximab or ANTs as first-line treatments based on their proven effectiveness, cost-effectiveness, and capacity to make treatment more accessible.[2,16] Currently, the United States, Japan, and Germany employ ANTs as first-line treatments, while other countries including South Korea, Canada, France, and Australia reimburse them as a second-line option after attempted off-label therapy has been unsuccessful. This situation underscores the need to evaluate how many patients require ANTs

after rituximab failure in order to support effective government policies for NMOSD and ensure the judicious allocation of healthcare resources, particularly in settings with low resources. Despite the inherent limitations of retrospective multicenter studies, such as interrater variability and observer bias, as well as the obtained data being restricted to a single country, our study has provided valuable insights into the probability of rituximab failure in large multicenter cohorts. These data are essential for refining economic models related to treatment strategies, improving accuracy estimates of costs and health outcomes, and improving the ability of decision-makers to perform cost-effectiveness analyses.

Availability of Data and Material

The raw data generated in this study are available upon request from the corresponding author.

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Conflicts of Interest

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