RESEARCH ARTICLE OPEN ACCESS

Rituximab-Induced Hypogammaglobulinemia and Risk of Infection in Neuromyelitis Optica Spectrum Disorders

A 14-Year Real-Life Experience

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Neurol Neuroimmunol Neuroinflamm 2022;9:e1179. doi:10.1212/NXI.0000000000001179

Abstract

Background and Objectives

To investigate the frequency and predictors of hypogammaglobulinemia during long-term rituximab (RTX) treatment in patients with neuromyelitis optica spectrum disorder (NMOSD) and its association with infections.

Methods

We retrospectively reviewed the data of patients with NMOSD who received RTX through the maintenance regimen based on memory B-cell detection for at least 1 year from 2006 to 2021 at an institutional referral center for NMOSD.

Results

A total of 169 patients received a median of 10 courses (range 1–27) of RTX reinfusion after induction over a median of 8 (range, 1–15) years. Their mean serum immunoglobulin (Ig)G level began to decline significantly after 2 years of treatment, steadily declined at a rate of 2%–8% per year for the following 8 years, and then plateaued after 10 years. The proportion of patients with hypo-IgG (<6 g/L) increased from 1.2% after 1 year of treatment to 41% after 14 years of treatment. While being treated with RTX, 58 (34%) patients had 114 infections, of whom 14 (8%) patients had 15 severe infections. Multivariable logistic regression analyses identified duration of RTX treatment in years (odds ratio [OR] 1.234, 95% confidence interval [CI] 1.015–1.502), mean annual RTX dose (OR 0.063, 95% CI 0.009–0.434), history of mitoxantrone (OR 3.318, 95% CI 1.109–9.93), hypo-IgG at baseline (OR 40.552, 95% CI 3.024–543.786), and body mass index >25 kg/m^2 (OR 4.798, 95% CI 1.468–15.678) as independent predictors of hypo-IgG. The risk of infection during RTX treatment was independently associated with high Expanded Disability Status Scale scores (OR 1.427, 95% CI 1.2–1.697) and relapses during RTX treatment (OR 1.665, 95% CI 1.112–2.492), but not with hypogammaglobulinemia.

Discussion

Over 14 years of long-term RTX treatment, IgG levels gradually decreased, and the frequency of hypo-IgG increased to 41% of the patients. Patients with prolonged memory B-cell depletion after RTX, previous mitoxantrone history, hypo-IgG at baseline, or obesity were at risk of developing RTX-induced hypogammaglobulinemia. Nevertheless, infection rates remained low during treatment, and reduced immunoglobulin levels were not associated with an increased incidence of infections.

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

BMI = body mass index; **CNS-ID** = CNS-inflammatory disease; **CVID** = common variable immune deficiency; **EDSS** = Expanded Disability Status Scale; **HBS** = hepatitis B surface; **Ig** = immunoglobulin; **IQR** = interquartile range; **MS** = multiple sclerosis; **OR** = odds ratio; **PY** = patient-year; **SIE** = severe infection event; **UTI** = urinary tract infection.

Rituximab (RTX), an anti-CD20 monoclonal antibody, is increasingly being used to treat CNS inflammatory diseases (IDs), including neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS). RTX depletes CD20-expressing B cells in the peripheral blood for inter-individually variable periods. Despite the high efficacy and well-tolerated safety profile of RTX, concerns exist about prolonged hypogammaglobulinemia and an increased risk of infection in a subset of patients receiving repeated infusions of RTX.[1,2] Mature plasma cells do not express CD20, but long-term depletion of plasma cell precursors by RTX may diminish the replenishment of plasma cells, leading to secondary hypogammaglobulinemia.[3,4] The etiology of RTX-induced hypogammaglobulinemia is likely multifactorial, and its reported incidence varies between 5% and 73% depending on the underlying disease and its relationship to B-cell function, previous and concurrent immunosuppressive medications, baseline immunoglobulin (Ig) levels, and RTX courses.[1,5-7] The clinical consequence of RTX-induced hypogammaglobulinemia, particularly whether it is directly associated with an increased risk of infection in patients with systemic autoimmune diseases and malignancies, remains controversial.[3,8-12] Furthermore, there are limited long-term data on the variables and infectious risks associated with RTX-induced hypogammaglobulinemia in CNS IDs (CNS-IDs). A previous study of 5 years of RTX treatment included only 15 patients with NMOSD,[1] whereas studies with larger patient numbers reported relatively short-term follow-up results.[2,7,13] Here, we describe the frequency and predictors of RTX-associated hypogammaglobulinemia and its association with infections in a large cohort of patients with NMOSD undergoing long-term RTX treatment.

Methods

Study Design and Participants

We identified a total of 178 patients with NMOSD who received RTX for at least 1 year at the National Cancer Center, Korea, between February 2006 and July 2021. Nine patients without serial Ig measurements were excluded. Data on demographics, medications, Expanded Disability Status Scale (EDSS) score, infection events, and laboratory parameters were collected retrospectively from medical records. Serum IgG, IgA, and IgM levels measured before and annually during RTX therapy as part of routine clinical monitoring were reviewed. The serostatus of antibodies for varicella and measles and titers of hepatitis B surface (HBS) antibodies, measured every 3 years, were also collected. The FCG3RA-V158F genotype data of 89 patients who were included in our previous study were retrieved.[14]

RTX Treatment

After induction therapy (375 mg/m^2 weekly for 4 consecutive weeks or two 1,000 mg 2 weeks apart), patients received RTX maintenance therapy which was administered IV at a dose of 375 mg/m^2 whenever the proportion of CD27$^+$ memory B cells in peripheral blood mononuclear cells was >0.05% in the initial 2 years and >0.1% thereafter.[14] Some patients were administered a 100-mg methylprednisolone infusion as a premedication to minimize the infusion-related reaction. During RTX treatment, an acute relapse was treated with IV administration of 3–5 g methylprednisolone and/or plasmapheresis. No patient concomitantly received immunosuppressive agents.

Evaluation for Hypogammaglobulinemia

Serum Ig levels were graded based on their lowest levels during the follow-up. Hypo-IgG was categorized as mild (4.0–5.9 g/L) or severe (<4 g/L). Hypo-IgM and hypo-IgA were defined as serum levels of <0.4 and <0.7 g/L, respectively. Infection was defined as suspicion or confirmation of infection based on physical signs suggestive of infection including, but not limited to, fever or positive radiographic or laboratory findings. A severe infection event (SIE) was defined as a suspected or confirmed infection requiring IV antibiotics/antiviral agent administration and/or hospitalization.

Standard Protocol Approvals, Registration, and Patient Consents

The data used in this study were collected between February 2006 and July 2021. The Institutional Review Board of the National Cancer Center approved this study (NCC2014-0146), and all patients provided written informed consent.

Statistical Analyses

The results for categorical variables are expressed as values and proportions, while those for continuous variables are expressed as either medians and interquartile ranges (IQRs) or ranges. Between-group differences in categorical variables were assessed using the Fisher exact test. Longitudinal changes were assessed using the Wilcoxon signed-rank test for paired samples. For missing values, the last value carried forward method was used. The relationships between potentially associated factors and hypo-IgG were evaluated using a logistic regression model.

Unadjusted odds ratios (ORs) were calculated using univariable logistic regression analysis, while adjusted ORs were calculated using multivariable logistic regression analysis. Variables with a p value of less than 0.2 in the univariable regression models were included in the multivariable

regression model. The associations between infection and hypo-IgG, hypo-IgA, and hypo-IgM were also evaluated using a multivariable logistic regression model. All results were analyzed using SAS software (version 9.4; SAS Institute Inc, Cary, NC) and Stata Statistical software, version 14.2 (StataCorp LP, College Station, TX). Two-sided p values of less than 0.05 were considered statistically significant.

Data Availability

The data sets analyzed during this study are available from the corresponding author on reasonable request.

Results

As of July 2021, 169 patients received a median of 10 (range, 1–27) courses of RTX treatment after induction over a median of 8.4 (range, 1.3–15.5) years (1,393 patient-years [PYs]). Of them, 122 patients and 74 patients had been followed for >5 and >10 years, respectively. Demographic data and treatment history are summarized in Table 1. Freedom from relapse was achieved in 119 (68%) patients, and improvement or stabilization of disability was achieved in 162 (96%) patients after RTX treatment. Ten patients discontinued RTX treatment: 3 went abroad at 3, 6, and 7 years after RTX treatment; 4 switched from RTX to satralizumab or tocilizumab because of relapses or poor B-cell depletion at 1, 1, 2, and 11 years; and 3 patients died from aspiration pneumonia (1 year), suicide (2 years), and fungal pneumonia (6 years). Three patients switched from RTX to mitoxantrone therapy because of repeated events of inadequate depletion of memory B cells. After 6 months of mitoxantrone treatment (12 mg/m^2, monthly), these 3 patients resumed RTX treatment. Ninety-nine (59%) patients used at least 1 immunosuppressive agent before RTX.

Immunologic Evaluation for Hypogammaglobulinemia

Ig levels were available for 164 patients at the initiation of the RTX therapy. Among them, baseline data for 6 patients were excluded because of plasmapheresis history within the preceding month. All 6 patients had Ig levels within the normal range 1 year after RTX treatment. Before RTX therapy, 6 (4%), 6 (4%), and 17 (11%) of the 158 patients had hypo-IgG, hypo-IgA, and hypo-IgM, respectively. The mean serum IgG level began to decline significantly after 2 years of treatment and steadily declined at a rate of 2–8% per year for the next 8 years before plateauing after 10 years (Figure 1A). During the follow-up, 39 (23%) and 16 (9.4%) patients developed hypo-IgG and severe hypo-IgG, respectively. The proportion of patients with hypo-IgG and severe hypo-IgG increased annually from 1.2% and 0%, respectively, after 1 year of treatment, to 41% and 14%, respectively, after 14 years of treatment (Figure 1B). None of the patients with hypo-IgG had normal serum IgG levels at the last follow-up. The median durations of persistent hypo-IgG and severe hypo-IgG were 6 (IQR, 3.5–8.5) years and 4 (IQR, 2.0–6.8) years, respectively. After RTX treatment, 45 (27%) and 82 (49%) patients showed hypo-IgA and hypo-IgM, respectively. The percentage of patients with hypo-IgA and hypo-IgM increased to 50% and 70%, respectively, 14 years after the initiation of RTX therapy (Figure 1D, F). The development of hypo-IgG was significantly associated with the development of hypo-IgA and hypo-IgM (both $p < 0.001$, Fisher exact test). Six (4%) patients received plasmapheresis (once in 5 patients and twice in 1 patient) for treating relapse at a median interval of 16 months (range 1–132 months) from starting RTX treatment. All of them exhibited Ig levels within the normal range within 6–9 months after plasmapheresis. Of 138 patients treated for more than 3 years, 123 and 127 patients exhibited varicella-IgG and measles-IgG positivity at RTX initiation, respectively, of whom only 3 (2%) and 2 (2%) patients had negative seroconversion after RTX treatment, respectively. We also investigated the changes in anti-HBS titers in the 138 patients; anti-HBS antibody positivity (>10 mIU/mL) was noted in 82 (59%) patients at baseline. Median anti-HBS titers after 3 and 6 (213 and 172, respectively) years were not significantly different from those at baseline (180), but they significantly decreased after 9 (138; $p = 0.043$) and 12 (97; $p = 0.001$) years. Among 82 patients, only 2 (2%) showed negative seroconversion of anti-HBS antibodies.

Infections

In our cohort, 58 (34%) patients had 114 infections and 14 (8%) of them had 15 SIEs while being treated with RTX. The overall infection and SIE rates were 8.18/100 and 1.08/100 PY, respectively. Among mild infections, urinary tract infections (UTIs) (59%) were most frequent, followed by upper or lower respiratory tract infections (14%), herpes zoster (8%), and other infections (19%), including 1 tuberculosis reactivation. SIEs included UTIs (n = 5), pneumonia (n = 5), septic shock (n = 1), neutropenic fever (n = 2), gastroenteritis (n = 1), and wound infection (n = 1). All patients with SIEs recovered well and maintained RTX treatment apart from 2 patients: 1 patient with an EDSS score of 8.0 at the initiation of treatment died from aspiration pneumonia with normal Ig levels at 1 year of RTX treatment and 1 patient who received concurrent cyclosporine and steroids from a dermatology clinic because of severe psoriasis died from fungal pneumonia 25 months after the last RTX retreatment. She had undergone RTX treatment for 6 years and did not revisit our clinic after the eighth reinfusion of RTX. Her serum IgG level was <4 g/L at the last follow-up, but the IgG levels at the time of death could not be confirmed because she was at another hospital. During RTX treatment, transient grade ≥3 neutropenia (absolute neutrophil counts <1,000/mm^3) and lymphopenia (absolute lymphocyte count <500 mm^3) were observed in 10 (6%) and 11 (7%) patients, respectively. Among them, 2 patients with grade 4 neutropenia exhibited neutropenic fever and were treated with granulocyte colony-stimulating factors. They recovered well, and subsequent RTX treatment did not reinduce neutropenia. With the exception of 1 patient who experienced pneumonia at the time of lymphopenia, the remaining transient neutropenia and lymphopenia resolved spontaneously without infection. Thirteen (87%) of 15 SIEs occurred in patients with normal IgG levels, and only 1 SIE

Table 1 Demographic and Clinical Characteristics of the Patients

Characteristic	Patients (n = 169)
Age at disease onset, y, median (IQR)	33 (24–45)
Age at RTX initiation, y, median (IQR)	38 (30–49)
Sex, female, n (%)	144 (85%)
Disease duration before RTX treatment, y, median (IQR)	4.3 (1.7–8.8)
Duration of RTX treatment, y, median (IQR)	8.4 (4.4–12.4)
BMI, kg/m^2, median (IQR)	21.9 (19.8–25.1)
Cumulative RTX dose, g, median (IQR)	8.4 (5.6–11.0)
Patients with comorbidity, n (%)	38 (23%)
Dyslipidemia, n	14
Hypertension, n	11
Diabetes mellitus, n	4
Cancer (thyroid, thymoma, tongue, rectal, breast), n	5
Psychiatric disorder, n	2
Systemic autoimmune disease, n	6
Angina, n	1
Asthma, n	1
Liver cirrhosis, n	1
EDSS score at RTX initiation, median (IQR)	3.5 (2.0–6.0)
EDSS score at the last follow-up, median (IQR)	3.0 (2.0–4.5)
RTX retreatment interval, m, median (IQR)	8.4 (7.0–10.2)
Patients with previous immunosuppressive treatment, n (%)	95 (59%)
Azathioprine, n	47
Mycophenolate mofetil, n	37
Mitoxantrone, n	26
Cyclophosphamide, n	2
Tacrolimus, n	1

Abbreviations: BMI = body mass index; EDSS = Expanded Disability Status Scale; IQR = interquartile range; RTX = rituximab.

(community-acquired pneumonia) occurred in a patients in a mild hypo-IgG state. None of the patients received Ig replacement therapy. The annual incidence rates of infection and SIE did not increase during the follow-up (Figure 2).

Predictors of Hypogammaglobulinemia and Infection

The results of the univariable and multivariable analyses are summarized in Table 2. Hypo-IgG was independently associated with the duration of RTX treatment in years (OR 1.234, 95% confidence interval [CI] 1.015–1.52), mean annual RTX dose (OR 0.063, 95% CI 0.009–0.434), history of mitoxantrone treatment (OR 3.318, 95% CI 1.109–9.93), baseline hypo-IgG (OR 40.552, 95% CI 3.024–543.786), and body mass index (BMI) > 25 kg/m^2 (OR 4.798, 95% CI 1.468–15.678). The mean annual RTX dose (OR 0.006, 95% CI 0–0.123) was the sole independent predictor of severe hypo-IgG. Since the annual RTX dose was higher during the initial 2 years—for the induction dose and more frequent retreatment according to the more stringent memory B-cell threshold for retreatment in our protocol—than the subsequent years, we performed an analysis of risk factors related to the development of hypo-IgG in the subgroup of patients who had received RTX treatment for more than 3 years. Subgroup analysis also showed that the duration of RTX treatment in years (OR 1.246, 95% CI 1.011–1.536), mean annual RTX dose (OR 0.047, 95% CI 0.006–0.36), history of mitoxantrone treatment (OR 3.275, 95% CI 1.077–9.956), and BMI >25 kg/m^2 (OR 5.712, 95% CI 1.656–19.708) were independently associated with hypo-IgG (eTable 1, links.lww.com/NXI/A730). Next, independent variables were identified among patients with infection (eTable 2). The EDSS score at RTX initiation (OR 1.451, 95% CI 1.227–1.715) and relapses on RTX treatment (OR 1.665, 95% CI 1.112–2.494) were independently associated with infection, but severe hypo-IgG, hypo-IgM, and hypo-IgA were not associated with infection. None of the variables, including hypogammaglobulinemia, were independently associated with SIEs in the multivariable analysis.

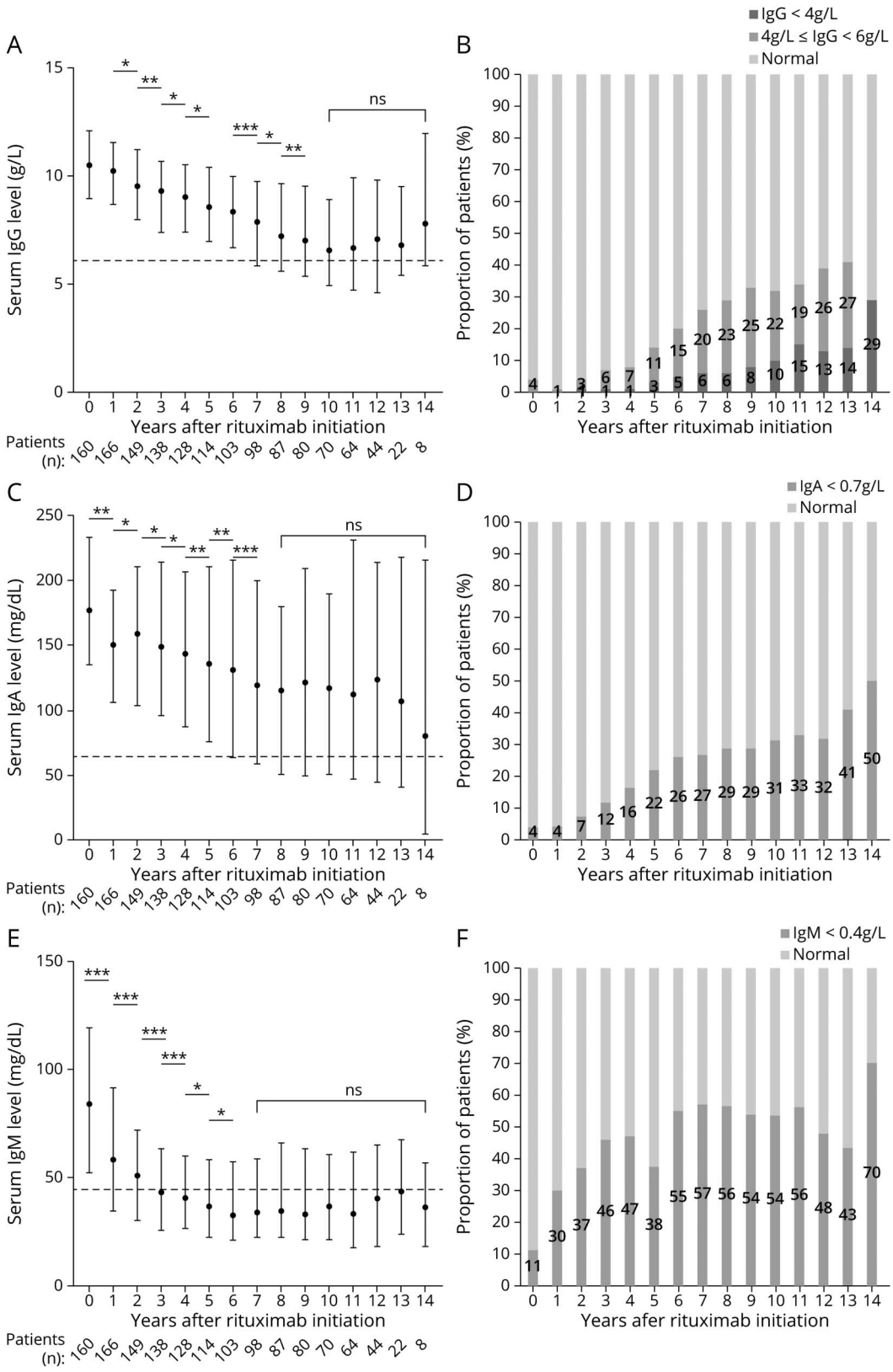
Discussion

We investigated the frequency of hypogammaglobulinemia and its relation to infections in patients with NMOSD receiving long-term RTX treatment. Over 14 years of long-term RTX treatment, IgG levels gradually decreased after the initiation of treatment and remained relatively unchanged after 10 years of treatment. The frequency of RTX-induced hypo-IgG increased from the third year of treatment onward, affecting up to 41% of the patients after 14 years of treatment. Nevertheless, SIE rates remained low during treatment, and reductions in Ig levels were not associated with an increased incidence of infections.

The risk factors for hypo-IgG identified in our study—longer RTX treatment duration, mitoxantrone exposure, and baseline hypo-IgG—are in line with previously identified factors predisposing to the development of RTX-induced hypogammaglobulinemia.[3,6,15,16] In addition, we found that obesity was associated with the development of hypo-IgG. Obesity promotes inflammation and induces metabolic and functional changes in immune cells by altering humoral immunity and reducing the antibody response to vaccine immunization or viral infection.[17,18] Obesity-associated dysregulation of the immune system may negatively affect IgG production in patients treated with RTX.

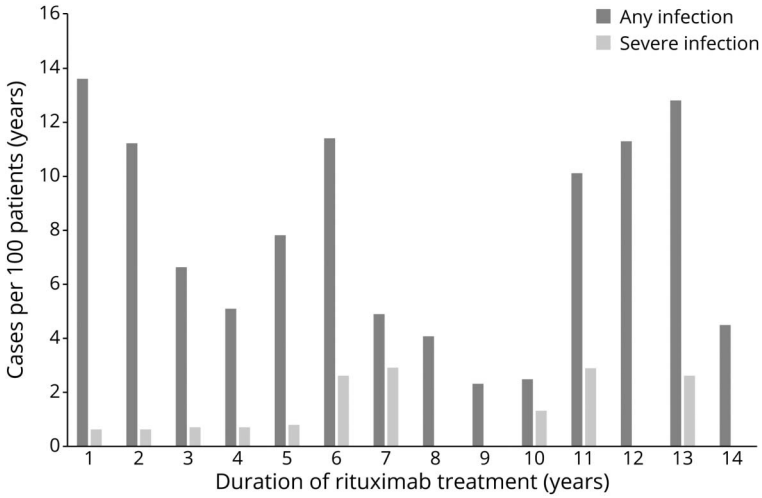
Notably, a low annual RTX dose was associated with an increased risk of hypo-IgG. Particularly, we found that a low

Figure 1 Immunoglobulin Levels (Median and Interquartile Range) (A,C,E) and Patient Proportions of Ranges (B,D,F)



annual dose was the sole risk factor for the development of severe hypo-IgG. In our cohort, retreatment with RTX was administered whenever the memory B-cell count was above the therapeutic threshold because sufficient and persistent depletion of memory B cells correlates with a good clinical response to RTX.[15,19] Thus, a low annual dose indicates

Figure 2 Annual Incidence Rates of Any and Severe Infections During Rituximab Treatment



infrequent retreatment due to delayed memory B-cell reconstitution after RTX administration, indicating that patients with prolonged memory B-cell depletion after RTX treatment are more prone to developing hypogammaglobulinemia while being more likely to maintain disease remission. This has also been described in patients with idiopathic nephrotic syndrome, in whom prolonged and profound depletion of switched memory B cells after RTX treatment can elicit both long-term disease remission and persistent severe hypogammaglobulinemia.[20] Total B-cell reconstitution is not closely correlated with the recovery of hypogammaglobulinemia, which may be in part due to an increased proportion of naïve B cells and decreased proportion of switched memory B cells.[21] Altogether, profound and sustained memory B-cell depletion post-RTX may be an important risk factor for hypogammaglobulinemia.

Despite a median of over 8 years of RTX treatment, the frequency of hypo-IgG in our cohort was lower than the corresponding values in other reports, in which 23–30% of the patients developed hypo-IgG (<6 g/L) after a mean of 3 years of treatment[2,22] and 73% of the patients exhibited hypo-IgG (<7 g/L) after a mean of 70 months of treatment.[1] Although the heterogeneity in age, baseline IgG levels, and differences in concomitant therapy or pretreatment does not allow us to draw definite conclusions, our RTX protocol, in which retreatment with RTX was administered when reemergence of memory B cells occurred and the threshold for retreatment was increased after the initial 2 years of treatment, may have resulted in a lower frequency of hypo-IgG in our cohort than other studies where retreatment with RTX was administered either every 6 months or based on the reconstitution of $CD19^+$ B cells.[1,7] In 1 study, retreatment with RTX was administered according to the frequency of reconstitution of memory B cells, but patients who did not show reconstitution of memory B cells even at 6 months were retreated, regardless of the memory B-cell count.[2] This treatment strategy may increase the frequency of hypo-IgG.[2] Moreover, the reduction rate of serum IgG levels in our cohort plateaued after 10 years of treatment. Previously, we reported that retreatment with RTX based on memory B-cell reconstitution resulted in long retreatment intervals (mean, 41 weeks) after 6 years because the time to memory B-cell reconstitution increased.[23] Thus, after long-term treatment, the reduction rate of serum Ig levels may have decreased as the retreatment interval prolonged because retreatment was not provided until memory B cells reconstituted. These results suggest that the personalized RTX retreatment protocol through monitoring memory B cells may lower the risk of hypo-IgG.

We also analyzed the associations between serum Ig levels and risk of infections. High EDSS scores at RTX initiation were associated with an increased risk of infection. Previous studies on CNS-IDs have consistently shown that increased disability is commonly associated with infections in RTX-treated patients.[2,7,13] Relapses during RTX treatment also seem to increase the risk of infection, given the associated increase in neurologic disability and administration of high-dose steroids. The high incidence of infection during the initial 2 years of RTX treatment (Figure 2) may reflect the high disability level and frequent steroid use of these patients, who often experience many relapses before starting RTX treatment. However, hypogammaglobulinemia was not associated with the risk of developing infection, including SIEs, although none of the patients with hypogammaglobulinemia in this study received Ig replacement. Similarly, previous large-scale studies did not report an increased risk of infection in patients with rheumatoid arthritis who had RTX-induced hypogammaglobulinemia.[11,24,25] Two large studies on CNS-IDs reported conflicting results for the association between hypogammaglobulinemia and the risk of infection. Based on 831 PY of follow-up in the Danish MS Registry, serum IgG and IgM levels decreased as the duration of therapy increased, but they were not associated with an increased risk of severe infection.[7] Conversely, a study of 1,000 patients treated with anti-CD20 therapy, with a median follow-up of 25 months,

Table 2 Univariable and Multivariable Regression Analyses to Identify Variables Associated With Hypogammaglobulinemia and Severe Hypogammaglobulinemia

	Hypogammaglobulinemia (n = 39)				Severe hypogammaglobulinemia (n = 16)			
	Univariable		Multivariable		Univariable		Multivariable	
Variable	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age at RTX initiation, y	0.987	0.959–1.016			0.986	0.946–1.028		
Sex								
Female	1.069	0.283–4.048			0.596	0.121–2.935		
Male	Ref.							
Duration before RTX treatment, y	1.002	0.932–1.077			0.967	0.865–1.08		
Duration of RTX treatment, y	1.346	1.189–1.524	1.323	1.110–1.576	1.362	1.119–1.659		
Mean annual rituximab dose (g/y)	0.042	0.011–0.166	0.063	0.009–0.434	0.195	0.064–0.594	0.006	0–0.123
Mitoxantrone treatment								
Yes	7.598	3.19–18.099	3.318	1.109–9.93	3.391	1.123–10.239		
No	Ref.		Ref.					
Comorbidity								
Yes	2.473	1.122–5.451			1.653	0.537–5.092		
No	Ref.							
IgG level at RTX initiation								
<6 g/L	5.419	1.153–25.473	40.552	3.024–543.786	5.88	1.011–34.194		
≥6 g/L	Ref.		Ref.		Ref.			
EDSS score at RTX initiation	1.139	0.967–1.324			1.144	0.908–1.443		
BMI								
>25 kg/m^2	2.473	1.122–5.451	4.798	1.468–15.678	2.269	0.767–6.711		
≤25 kg/m^2	Ref.		Ref.		Ref.			
FCGR3A variation (n = 89)								
FF genotype (n = 50)	0.972	0.169–5.607			1.405	0.271–4.95		
VV or VF genotypes (n = 39)	Ref.				Ref.			

Abbreviations: BMI = body mass index; CI = confidence interval; EDSS = Expanded Disability Status Scale; Ig = immunoglobulin; OR = odds ratio; RTX = rituximab.

identified hypogammaglobulinemia (IgG titer <5 g/L) as a predictor of SIE in a multivariable analysis, although most patients with low IgG levels did not present with SIEs.[13]

Ig plays a major role in adaptive immunity, and reduced levels of serum Ig—as observed in primary immunodeficiency syndromes such as common variable immune deficiency (CVID)—increases the risk of recurrent infections.[26] However, the relationship between RTX-induced hypogammaglobulinemia and the risk of infection is not so straightforward. In CVID, B cells do not become fully activated or terminally differentiate into plasma cells and decreased numbers of memory B cells—but not reduced serum Ig levels—might be associated with an increased risk of infection.[27,28] However, RTX results in only a partial depletion of B cells in the bone marrow and synovium, and switched memory B cells persist in lymphoid tissues, in contrast to a rapid, almost complete depletion of CD20$^+$ B cells in the peripheral blood.[13,29] Furthermore, long-lived plasma cells resistant to RTX are able to maintain the IgG pool.[30] Despite repeated memory B-cell depletion, seropositivity to virus and vaccine antigens was maintained in our patients—even those with hypogammaglobulinemia. RTX-induced long-term depletion of mature B cells in the peripheral blood may cause a gradual decrease in Ig levels with maintained B-cell counts in other tissues, such as lymphoid organs and the bone marrow including long-lived plasma cells, and their protective role in humoral immunity may thus be retained.

This study has some limitations, including its retrospective design based on data from a single center. Recall bias might

have occurred for minor infections for which primary care was performed at centers other than ours. However, as we carefully checked the patients' health status and medical events together with laboratory tests every 6–10 weeks, almost all relevant infections were likely identified and included in this study. In addition, our finding that the annual RTX dose is a risk factor for hypogammaglobulinemia cannot be generalized where RTX retreatment is not tailored to the memory B-cell counts.

Nonetheless, our study represents real-life event rates of hypogammaglobulinemia and infections in a large number of patients with NMOSD treated long-term with a unified RTX treatment protocol. The proportion of patients with hypogammaglobulinemia tended to increase over time, but more than half of the patients maintained normal serum IgG levels even after 14 years of RTX treatment. Most cases of hypogammaglobulinemia were asymptomatic, and SIE rates remained low over the 14 years. Further studies are necessary to evaluate the clinical effect of more severe and prolonged hypogammaglobulinemia in patients with NMOSD and to identify high-risk patients for developing symptomatic hypogammaglobulinemia.

Study Funding

This research was funded by the National Research Foundation of Korea (2018R1A5A2023127).

Disclosure

S.-H. Kim, N.Y. Park, K.H. Kim, and J.-W. Hyun report no financial disclosures. H.J. Kim received a grant from the National Research Foundation of Korea and research support from Aprilbio and Eisai; received consultancy/speaker fees from Alexion, Aprilbio, Biogen, Celltrion, Daewoong, Eisai, GC Pharma, HanAll BioPharma, MDimune, Merck Serono, Novartis, Roche, Sanofi Genzyme, Teva-Handok, UCB, and Viela Bio; is a co-editor for the *Multiple Sclerosis Journal* and an associated editor for the *Journal of Clinical Neurology*. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* January 28, 2022. Accepted in final form March 28, 2022. Submitted and externally peer reviewed. The handling editor was Josep O. Dalmau, MD, PhD, FAAN.

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Name	Location	Contribution
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Na Young Park, RN	Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Ki Hoon Kim, MD	Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, Korea	Drafting/revision of the manuscript for content, including medical writing for content
Jae-Won Hyun, MD, PhD	Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, Korea	Drafting/revision of the manuscript for content, including medical writing for content
Ho Jin Kim, MD, PhD	Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, Korea	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; additional contributions: obtained funding

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Neurol Neuroimmunol Neuroinflamm 2022;9;
DOI 10.1212/NXI.0000000000001179