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ORIGINAL ARTICLE

The association between hypogammaglobulinemia severity and infection risk in rituximab-treated patients with childhood-onset idiopathic nephrotic syndrome

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Abstract

Background Hypogammaglobulinemia is a major adverse effect from rituximab. However, the association between rituximab-induced hypogammaglobulinemia and infection frequency is unknown.

Methods Patients who received rituximab for complicated nephrotic syndrome between February 2006 and October 2020 were enrolled in this retrospective observational study. Infections requiring antibacterial or antiviral agents or hospitalization were identified, and the characteristics of infections were compared according to infection type.

Results One hundred and forty patients were enrolled. Fifty infection events were detected in 36 patients, 45 infection events in 32 patients required hospitalization, and 1 severe infection event required intensive care unit admission. In eight patients who developed severe hypogammaglobulinemia (serum IgG level < 200 mg/dL) for more than 1 year after rituximab treatment, eight infections occurred in six patients; six of these infections did not occur during the period of severe hypogammaglobulinemia. Febrile neutropenia accounted for 54.2% (13/24) of all infections among the patients with hypogammaglobulinemia. The incidence of infections was 0.028 (95% confidence interval = 0.017–0.448), 0.071 (95% [*CI*] = 0.041–0.114), and 0.096 (95% [*CI*] = 0.019–0.282) patient-years in patients with normal serum IgG levels and those with mild and severe hypogammaglobulinemia, respectively. Immunoglobulin replacement therapy was not administered to any patients except for the treatment of infection.

Conclusions Our results showed no statistically significant association between hypogammaglobulinemia severity and infection rate. In addition, the frequency of infection was relatively low even in patients with severe hypogammaglobulinemia, suggesting that immunoglobulin replacement therapy may not be necessary for rituximab-treated patients with severe hypogammaglobulinemia.

Keywords Children · Complicated nephrotic syndrome · Hypogammaglobulinemia · Immunoglobulin replacement therapy · Infection · Rituximab

Introduction

Rituximab is an anti-CD20 monoclonal antibody, which is an effective and relatively safe treatment for patients with complicated steroid-dependent or frequently relapsing nephrotic syndrome (SDNS/FRNS) [1, 2], and also could be an effective treatment for multidrug-resistant steroid-resistant nephrotic syndrome (SRNS) [3]. Rituximab binds to CD20 and leads to B-cell depletion and dysfunction, which can impact T cell immunity and reduce immunoglobulin levels [4]. In addition to B- and T-cell-mediated immunosuppression, rituximab may also induce neutropenia. These effects of rituximab on the immune system may increase the incidence of infection after rituximab treatment [4, 5].

The incidence of infections and hypogammaglobulinemia after rituximab treatment differs among patients with primary diseases [5–8]. Several studies reported that the incidence of hypogammaglobulinemia ranged between 11 and 58% after rituximab treatment in patients with childhood-onset SDNS [9–13]. Most patients develop transient and mild hypogammaglobulinemia, with their serum

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immunoglobulin G (IgG) levels returning to baseline within a year; however, some patients develop severe persistent hypogammaglobulinemia and require immunoglobulin replacement treatment [9, 14–16].

Whether rituximab-induced hypogammaglobulinemia is associated with increased infection risk is unclear. Moreover, it remains unclear whether persistent severe hypogammaglobulinemia after rituximab treatment, which might require immunoglobulin replacement therapy, results in severe and recurrent infection in patients with SDNS/FRNS or SRNS. The threshold for the initiation of immunoglobulin replacement therapy after rituximab treatment varies based on the underlying conditions in the absence of formal guidelines [16]. Therefore, it is crucial to determine the incidence of infection and the association between the degree of immunoglobulin deficiency and infection among patients with SDNS/FRNS or SRNS.

In the present study, we investigated the association between the severity of hypogammaglobulinemia and the risk of infection after rituximab treatment in patients with complicated SDNS/FRNS or SRNS.

Methods

Study design and patient population

In this retrospective observational study, we enrolled patients with childhood-onset complicated SDNS/FRNS or SRNS who were treated with rituximab between February 1, 2006, and October 31, 2020, in the National Center for Child Health and Development in Tokyo. Patients who were followed for less than 6 months after rituximab treatment and those without available data on serum IgG levels were excluded. The last follow-up was October 31, 2021.

SDNS was defined as two consecutive relapses during tapering or within 2 weeks of stopping steroid treatment. FRNS was defined as two or more relapses within the first 6 months of remission or four or more relapses within any 12-month period. SRNS was defined as persistent proteinuria after 4 weeks of treatment with 60 mg/m^2/day oral prednisolone. Complicated nephrotic SDNS/FRNS was defined as the development of SDNS or FRNS under immunosuppressive agents. B-cell depletion was defined as a peripheral blood CD19$^+$ or CD20$^+$ B-cell count of $< 1\%$ of the total number of lymphocytes, and B-cell recovery was defined as a peripheral blood CD19$^+$ or CD20$^+$ B-cell count of $\geq 1\%$ of the total number of lymphocytes. Hypogammaglobulinemia was categorized as mild (serum IgG level, 200–500 mg/dL) or severe (serum IgG level, < 200 mg/dL) [6, 14, 17, 18]. Persistent severe hypogammaglobulinemia was defined as a serum IgG level of < 200 mg/dL for more than 1 year after rituximab treatment initiation. In the present study, infections were defined as events requiring antiviral or antibacterial treatment or hospitalization during the follow-up period.

Treatment protocol

Rituximab was administered at a single dose of 375 mg/m^2, two doses of 375 mg/m^2 every 2 weeks, or 4 weekly doses of 375 mg/m^2 as a single course. CD19$^+$ or CD20$^+$ B-cell counts were assessed once every 1–2 months by flow cytometry until B-cell recovery was observed. Oral immunosuppressive treatments were continued after rituximab treatment. Relapses were treated with 60 mg/m^2 prednisolone daily, with a maximum daily dose of 60 mg. Prednisolone was tapered off within 2–3 months after remission. Starting in January 2012, trimethoprim-sulfamethoxazole, with a trimethoprim dose of 5 mg/kg, was administered once every 2 days during B-cell depletion for *Pneumocystis jiroveci* pneumonia prophylaxis. In patients with fever during B-cell depletion, extensive assessments including blood tests, chest X-ray, urinalysis, and blood culture were immediately performed.

Data collection and analysis

The following clinical data were extracted using chart review: sex, age at onset of nephrotic syndrome, age at initiation of rituximab treatment, immunosuppressive agents during and after rituximab treatment, number of rituximab treatments, history of SRNS, use of IgG replacement therapy, and characteristics of infections requiring antibacterial or antiviral agents or hospitalization during the follow-up period. The laboratory data included serum IgG and albumin levels once every 1–2 months after rituximab treatment, complete blood count, C-reactive protein level, and serum IgG level during infection. Serum IgG levels with serum albumin levels < 3.0 g/dL were excluded to minimize the effect of urinary leakage of IgG.

The enrolled patients were divided into two groups. Patients who exhibited severe hypogammaglobulinemia for more than 1 year after rituximab treatment were categorized into the persistent severe hypogammaglobulinemia group; whereas patients who never developed severe hypogammaglobulinemia during the period of at least 1 year after rituximab treatment were categorized into the other group. Patient characteristics were compared between the two groups. The characteristics of infection events were compared according to type of infection to assess the relationship between the infection type and the severity of hypogammaglobulinemia. The association between severe hypogammaglobulinemia and infection was estimated using patient-year analysis. In the present study, person-time was defined as the period between the first rituximab course and

last follow-up date. Person-time with normal serum IgG levels, mild hypogammaglobulinemia (serum IgG level, 200–500 mg/dL), or severe hypogammaglobulinemia (serum IgG level, < 200 mg/dL) was measured for each patient. Infection events during the relapse of nephrotic syndrome were excluded in patient-year analysis.

Statistical analysis

Data were expressed as medians with the interquartile ranges (IQRs) for continuous variables and percentages for categorical variables. The Mann–Whitney *U* test was used to compare continuous variables, and Fisher's exact test was used to compare categorical variables. A *P* value of < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using JMP version 14.0 (SAS Institute Japan, Tokyo, Japan) and Stata/SE 17.0 (StataCorp LLC, College Station, TX).

Results

Patient characteristics

During the study period, 140 of the 207 patients who were administered rituximab for complicated SDNS/FRNS fulfilled the inclusion criteria (Fig. 1). Patient characteristics are shown in Table 1. In the entire study cohort, 41 patients received one course of rituximab whereas the remaining patients received more than one course. None of the patients received IgG replacement therapy. At the time of last follow-up, eight patients (5.7%) had developed persistent severe hypogammaglobulinemia. Age at onset of nephrotic syndrome was significantly lower in the persistent severe hypogammaglobulinemia group than in the other group ($P = 0.03$). Age at first rituximab treatment was also significantly lower in the persistent severe hypogammaglobulinemia group than in the other group ($P = 0.004$).

Figure 2 shows the clinical course of patients with persistent severe hypogammaglobulinemia. Briefly, the median age at onset and median duration of persistent severe hypogammaglobulinemia were 8.1 (*IQR* 5.2–12.8) and 2.6 (*IQR* 1.2–5.3) years, respectively. Two patients developed persistent severe hypogammaglobulinemia at age < 4 years and achieved normalized serum IgG levels within 2 years after developing persistent severe hypogammaglobulinemia. The remaining six patients developed persistent severe hypogammaglobulinemia at age ≥ 7 years and did not achieve normalized serum IgG levels at last follow-up.

Infections

Table 2 shows the characteristics of infection events. During the follow-up period, 50 infection events occurred in 36 patients and 45 infection events in 32 patients required hospitalization. Of these, 21, 15, 8, 7, 2, and 1 event included febrile neutropenia, varicella-zoster virus infection, bacterial infection, pneumonia, herpetic gingivostomatitis, and mumps meningitis, respectively (4 events were mixed infections). The median age at the time of infection was 8.4 (*IQR* 5.4–13.3) years. Infection requiring intensive care unit admission occurred in one patient who developed *Pneumocystis jiroveci* pneumonia, and no deaths occurred. A detailed description of this patient was previously reported [19]. The

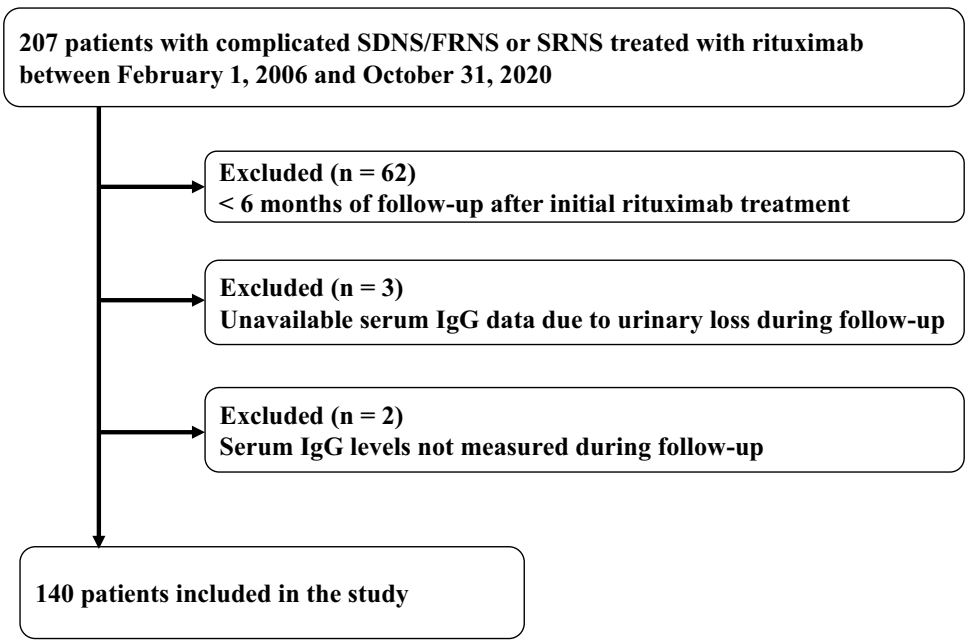

Fig. 1 Flow diagram of the study population. SDNS, steroid-dependent nephrotic syndrome; FRNS, frequently relapsing nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; IgG, immunoglobulin G

Table 1 Patient characteristics

Patient characteristics	Total ($n=140$)	Patients who developed persistent severe hypogammaglobulinemia ($n=8$)	Patients who did not develop persistent severe hypogammaglobulinemia ($n=132$)
Male sex, *n* (%)	93 (66.4)	7 (87.5)	86 (65.2)
Age at onset of nephrotic syndrome (years), median [IQR]	3.8 [2.1–8.5]	2.1 [1.6–2.9]§	4.0 [2.1–8.7]§
Age at first rituximab treatment (years), median [IQR]	10.9 [6.4–15.2]	5.1 [2.7–6.9]†	11.5 [6.8–15.8]†
Past history of SRNS, *n* (%)	69 (49.3)	5 (62.5)	64 (48.5)
Courses of rituximab treatment, patient number (%)			
1	41 (29.3)	1 (12.5)	40 (30.3)
2	40 (28.6)	2 (25.0)	38 (28.8)
3	17 (12.1)	2 (25.0)	15 (11.4)
4	10 (7.1)	1 (12.5)	9 (6.8)
5	8 (5.7)	0 (0.0)	8 (6.1)
6	10 (7.1)	0 (0.0)	10 (7.6)
7	5 (3.6)	1 (12.5)	4 (3.0)
8	1 (0.7)	0 (0.0)	1 (0.8)
9	2 (1.4)	0 (0.0)	2 (1.5)
10	2 (1.4)	1 (12.5)	1 (0.8)
≥11	4 (2.9)	0 (0.0)	4 (3.0)
Total follow-up period (months), median [IQR]	50.0 [21.5–80.5]	110.0 [83.3–165.3]	71.5 [36.5–108.0]
Immunosuppressive agents after rituximab treatment			
CsA, *n* (%)	3 (2.1)	0 (0.0)	3 (2.3)
CsA + MMF, *n* (%)	28 (20.0)	2 (25.0)	26 (19.7)
CsA + MZR, *n* (%)	6 (4.3)	0 (0.0)	6 (4.5)
CsA + MMF + MZR, *n* (%)	92 (65.7)	5 (62.5)	87 (65.9)
Tac + MZR, *n* (%)	1 (0.7)	0 (0.0)	1 (0.8)
Tac + MMF, *n* (%)	1 (0.7)	1 (12.5)	0 (0.0)
Tac + MMF + MZR, *n* (%)	2 (1.4)	0 (0.0)	2 (1.5)
CsA + Tac + MMF, *n* (%)	4 (2.9)	0 (0.0)	4 (3.0)
CsA + Tac + MMF + MZR, *n* (%)	3 (2.1)	0 (0.0)	3 (2.3)
IgG replacement therapy, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Trimethoprim-sulfamethoxazole, *n* (%)	120 (85.7)	8 (100)	112 (84.8)

SRNS, steroid-resistant nephrotic syndrome; *IQR*, interquartile range; *MMF*, mycophenolate mofetil; *CsA*, cyclosporin A; *MZR*, mizoribine; *Tac*, tacrolimus; *IgG*, immunoglobulin G. *P* value: §, 0.03; †, 0.004

median duration of hospitalization was 8.5 (*IQR* 7.0–10.0) days.

The characteristics of the patients with infection were compared with those of the patients without infection during follow-up period. The number of patients with less than one oral immunosuppressive agent was not significantly higher in patients with infection (0%, $P=0.57$) than patients without infection (2.9%).

Association between the degree of hypogammaglobulinemia and infection

Table 3 shows the characteristics of infections categorized according to the infection type. Of the four patients with mixed infections, one patient with viral pneumonia and febrile neutropenia was categorized in the pneumonia group, one patient with bacterial pneumonia and pneumococcal

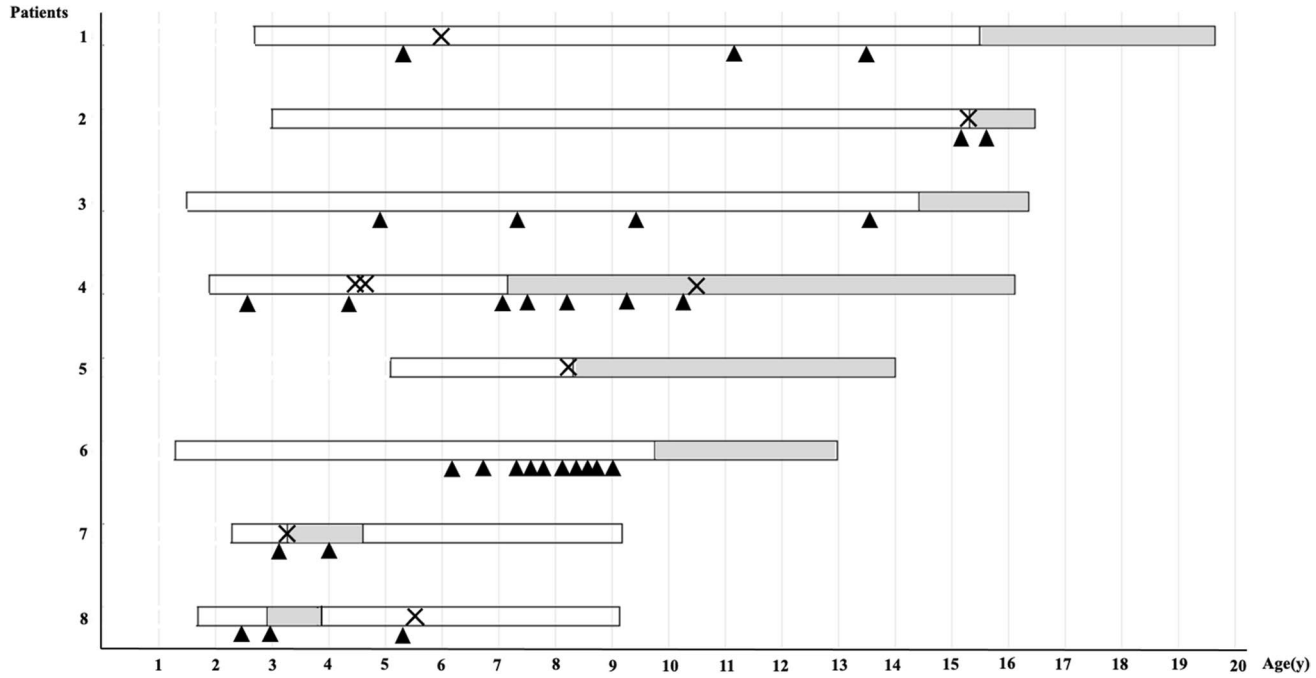

Fig. 2 Clinical course of patients who developed persistent severe hypogammaglobulinemia after rituximab treatment. Boxes indicate the period between the age at onset and the age at last follow-up, crosses indicate infections, triangles indicate rituximab treatment, and gray lines indicate the duration of severe hypogammaglobulinemia

bacteremia was categorized in the bacterial infection group, and two patients with febrile neutropenia and herpetic gingivostomatitis were categorized in the febrile neutropenia group. Infections with hypogammaglobulinemia accounted for 57.1% (24/42) of all infections and febrile neutropenia accounted for 54.2% (13/24) of all infections with hypogammaglobulinemia. During the follow-up period including the relapse of nephrotic syndrome, seven infections with severe hypogammaglobulinemia were recorded: varicella-zoster virus infection ($n=2$), febrile neutropenia ($n=1$), bacterial pneumonia with pneumococcal bacteremia ($n=1$), bacteremia with peritonitis ($n=1$), bacteremia ($n=1$), and *Pneumocystis jiroveci* pneumonia ($n=1$). All except one patient who suffered from bacterial pneumonia with pneumococcal bacteremia were treated with intravenous immunoglobulin, and all except one patient who suffered from *Pneumocystis jiroveci* pneumonia improved immediately after treatment.

In the persistent severe hypogammaglobulinemia group, eight infections occurred in six patients (75.0%), six infections (75.0%) were in the absence of severe hypogammaglobulinemia, and recurrent infection occurred in one patient during a follow-up period of 13 years (Fig. 2). The patient with *Pneumocystis jiroveci* pneumonia developed persistent severe hypogammaglobulinemia for more than 1 year after the infection event, but did not develop recurrent infection. Table 4 shows the incidence density of infections stratified by the period of each severity of hypogammaglobulinemia. The overall incidence of infections was 0.055 patient-years. The incidence density of infections was similar in patients with normal serum IgG levels and those with mild and severe hypogammaglobulinemia: 0.028 (95% confidence interval [*CI*] = 0.017–0.448), 0.071 (95% [*CI*] = 0.041–0.114), and 0.096 (95% [*CI*] = 0.019–0.282), respectively.

Pneumocystis jiroveci pneumonia prophylaxis after rituximab treatment

Of the 140 patients who fulfilled the inclusion criteria, 120 patients (85.7%) received *Pneumocystis jiroveci* pneumonia prophylaxis after rituximab treatment more than once whereas three patients did not receive prophylaxis due to drug allergy. None of the patients developed *Pneumocystis jiroveci* pneumonia after the initiation of *Pneumocystis jiroveci* pneumonia prophylaxis (Table 2).

Discussion

The present single-center retrospective study investigated the association between the severity of hypogammaglobulinemia and the risk of infection in patients with childhood-onset complicated SDNS/FRNS or SRNS treated with rituximab. Our analyses revealed that the incidence of infections was similar between patients

Table 2 Infection events

Characteristics	
Number of patients	36
Male sex, *n* (%)	28 (77.8)
Number of infection events	50
Infection during B-cell depletion, *n* (%)	28 (56.0)
Age at infection (years), median [IQR]	8.4 [5.4–13.3]
Number of infection events requiring hospitalization	45
Duration of hospitalization (days), median [IQR]	8.5 [7.0–10.0]
Requiring ICU, *n* (%)	1 (2.0)
Infection type	
Febrile neutropenia, *n* (%)	21 (42.0)
With herpetic gingivostomatitis, *n* (%)	2 (4.0)[a]
With viral pneumonia, *n* (%)	1 (2.0)[b]
Varicella-zoster virus infection, *n* (%)	15 (30.0)
Bacterial infection, *n* (%)	8 (16.0)
Bacteremia, *n* (%)	4 (8.0)
With bacterial pneumonia, *n* (%)	1 (2.0)[c]
With peritonitis, *n* (%)	1 (2.0)
Otitis media, *n* (%)	1 (2.0)
Bacterial enterocolitis, *n* (%)	1 (2.0)
Diverticulitis, *n* (%)	2 (4.0)
Pneumonia, *n* (%)	7 (14.0)
Viral pneumonia, *n* (%)	3 (6.0)[b]
Bacterial pneumonia, *n* (%)	2 (4.0)[c]
Mycoplasma pneumonia, *n* (%)	1 (2.0)
Pneumocystis jiroveci pneumonia, *n* (%)	1 (2.0)
Herpetic gingivostomatitis, *n* (%)	2 (4.0)[a]
Mumps meningitis, *n* (%)	1 (2.0)
Immunosuppressive agents at time of infection	
CsA, *n* (%)	5 (10.0)
MMF, *n* (%)	18 (36.0)
CsA + MMF, *n* (%)	23 (46.0)
CsA + MZR, *n* (%)	1 (2.0)
Tac + MMF, *n* (%)	1 (2.0)
No drug, *n* (%)	2 (4.0)
Other drugs at time of infection	
Trimethoprim-sulfamethoxazole, *n* (%)	29 (58.0)

IQR, interquartile range; *MMF*, mycophenolate mofetil; *CsA*, cyclosporin A; *MZR*, mizoribine; *Tac*, tacrolimus; *ICU*, intensive care unit. [a]Two patients suffered from mixed infection of febrile neutropenia with herpetic gingivostomatitis. [b]One patient suffered from mixed infection of febrile neutropenia with viral pneumonia. [c]One patient suffered from mixed infection of bacteremia with bacterial pneumonia

with severe hypogammaglobulinemia and those with normal serum IgG levels. Moreover, the incidence of infections in patients with severe hypogammaglobulinemia was low (0.096 patient-years) and all except one patient had a favorable clinical course. Febrile neutropenia, which is rarely attributable to serum IgG levels, was the most common infection in patients with hypogammaglobulinemia.

Clinical trials have reported conflicting results regarding the association of rituximab-induced hypogammaglobulinemia with infection. In adult patients with rheumatoid arthritis and autoimmune diseases, a serum IgG level below 600 mg/dL was an independent risk factor for the development of post-rituximab infection [20]. In adult patients with anti-neutrophil cytoplasmic antibody-associated vasculitis, severe hypogammaglobulinemia, which was defined as a serum IgG level below 375 mg/dL, was reported to be associated with increased odds of severe infection [21]. In contrast, other studies failed to observe an association between rituximab-induced hypogammaglobulinemia and infection [17, 22, 23]. These contradictory findings might be related to the differences in immunosuppressive regimens and the underlying conditions among the studies. In a study of patients with childhood-onset SDNS who were treated with rituximab, Cyrielle et al. reported that 13 infections occurred in 46 patients who developed hypogammaglobulinemia [10]. Fujinaga et al. also reported that seven infections occurred in seven patients with persistent hypogammaglobulinemia who received mycophenolate mofetil after rituximab treatment and that infection events did not occur in two patients with persistent hypogammaglobulinemia who received cyclosporin A after rituximab treatment [11]. However, the association between rituximab-induced hypogammaglobulinemia and infection in childhood-onset idiopathic nephrotic syndrome remains unclear.

To our knowledge, this is the first study demonstrating the relationship between the severity of rituximab-induced hypogammaglobulinemia and infection in childhood-onset idiopathic nephrotic syndrome. In the present study, the incidence density of infections in patients with severe hypogammaglobulinemia was still low (0.096 per person-years) although the incidence density of infections was slightly higher in patients with severe hypogammaglobulinemia than in those with normal serum IgG levels or mild hypogammaglobulinemia. Two previous studies on patients with childhood-onset autoimmune diseases who were treated with rituximab reported that the incidence densities were 0.078 and 0.087 for hospitalized infections after rituximab treatment [24, 25]. Interestingly, these incidence densities were higher than the overall incidence density (0.055 per person-years) observed in the present study, suggesting that the rate of infection might be low in patients with childhood-onset idiopathic nephrotic syndrome.

Whether rituximab treatment in patients with nephrotic syndrome increases the risk of infection remains unclear. A previous study on patients with nephrotic syndrome reported that 57% (4/7) of patients with rituximab treatment developed a bacterial infection, and 43% (25/58) of patients with other immunosuppressive agents developed bacterial

Table 3 Comparison of infection characteristics stratified by type of infection

Infection type	Febrile neutropenia	Herpes virus or mumps virus infection	Pneumonia	Bacterial infection
Number of infection events	20	16	6	8
Number of patients	16	14	5	8
Number of infections during relapse of nephrotic syndrome, *n* (%)	1 (5.0)	2 (12.5)	0 (0.0)	2 (25.0)
Number of infections during B-cell depletion, *n* (%)	16 (80.0)	5 (31.2)	3 (50.0)	4 (50.0)
Male sex, *n* (%)	15 (75.0)	11 (68.8)	5 (83.3)	8 (100)
Age at infection (years), median [IQR]	6.6 [4.8–9.8]	13.6 [7.4–15.8]	8.9 [3.5–11.8]	12.1 [5.3–25.7]
Number of infections requiring hospitalization, *n* (%)	20 (100)	12 (75.0)	5 (83.3)	8 (100)
Infection classified according to IgG				
Infection with IgG ≥ 500 mg/dL	6 (30.0)	7 (43.8)	2 (33.3)	3 (37.5)
Infection with 200 mg/dL ≤ IgG < 500 mg/dL	12 (60.0)	2 (12.5)	1 (16.7)	2 (25.0)
Infection with IgG < 200 mg/dL	1 (5.0)	2 (12.5)	2 (33.3)	2 (25.0)
Infection with no data of serum IgG levels	1 (5.0)	5 (31.2)	1 (16.7)	1 (12.5)
Laboratory data				
WBC ($\times 10^9$ /L), median [IQR]	2.89 [1.83–4.29]	7.90 [5.55–9.30]	8.59 [5.29–1.86]	15.20 [8.85–31.43]
Net (%), median [IQR]	5.0 [1.5–8.9]	60.9 [53.9–86.5]	80.8 [38.9–86.0]	82.0 [78.8–88.6]
Neutrophil count ($\times 10^2$ cells/mm^3), median [IQR]	1.38 [0.54–2.25]	39.45 [31.82–66.98]	69.41 [26.26–162.47]	122.40 [69.74–278.47]
IgG (mg/dL), median [IQR]	437 [298–660]	683 [203–1106]	326 [110–867]	427 [110–631]
Alb (g/dL), median [IQR]	3.9 [3.7–4.4]	3.8 [3.4–4.3]	3.6 [2.9–4.3]	3.8 [1.9–3.9]
CRP (mg/dL), median [IQR]	1.8 [1.0–6.6]	0.2 [0.0–0.6]	2.2 [1.3–13.2]	4.2 [0.3–8.8]
Immunosuppressive agents at infection				
Prednisolone, *n* (%)	4 (20.0)	8 (50.0)	1 (16.7)	4 (50.0)
CsA, *n* (%)	1 (5.0)	2 (12.5)	0 (0.0)	2 (25.0)
MMF, *n* (%)	4 (20.0)	7 (43.8)	3 (50.0)	4 (50.0)
CsA + MMF, *n* (%)	12 (60.0)	7 (43.8)	2 (33.3)	2 (25.0)
CsA + MZR, *n* (%)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tac + MMF, *n* (%)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
No drug, *n* (%)	1 (5.0)	0 (0.0)	1 (16.7)	0 (0.0)
Treatment for infections				
Antimicrobial agent, *n* (%)	20 (100)	0 (0.0)	5 (83.3)	8 (100)
Antiviral agent, *n* (%)	2 (10)	15 (93.8)	1 (16.7)	0 (0.0)
G-CSF, *n* (%)	18 (90.0)	0 (0.0)	1 (16.7)	0 (0.0)
Intravenous immunoglobulin, *n* (%)	2 (10)	2 (12.5)	1 (16.7)	2 (25.0)

IQR, interquartile range; *MMF*, mycophenolate mofetil; *CsA*, cyclosporin A; *MZR*, mizoribine; *Tac*, Tacrolimus; *IgG*, immunoglobulin G; *G-CSF*, granulocyte-colony stimulating factor; *Alb*, albumin; *CRP*, C-reactive protein; *WBC*, white blood cell; *Net*, neutrophil

Table 4 Incidence of infection stratified by the severity of hypogammaglobulinemia

	Total	IgG ≥ 500 mg/dL	200 mg/dL ≤ IgG < 500 mg/dL	IgG < 200 mg/dL
Number of patients who experienced each category of IgG	140	127	90	22
Exposure (patient-years)	905.8	635.2	239.5	31.1
Number of infection events	50	18	17	3
Infections (patient-years) (95% *CI*)	0.055	0.028 (0.017–0.448)	0.071 (0.041–0.114)	0.096 (0.020–0.282)

IgG, immunoglobulin G; 95% *CI*, 95% confidence interval

infections [26]. Our study reported that 5.7% (8/140) of patients developed bacterial infection. Moreover, the incidence of pneumonia, which was one of the most common infections in patients with nephrotic syndrome [27], was 1.57–17.37 per 1000 person-years in previous studies on healthy children [28, 29] and 7.73 per 1000 person-years (7/905.8) in our study. This shows that the risk of pneumonia in our patients was almost similar to healthy children.

The type of infection is another important aspect regarding the relationship between hypogammaglobulinemia and infection. Bacterial and respiratory infections are the two most common infection types in patients with hypogammaglobulinemia [30, 31]. In the present study, febrile neutropenia accounted for 54.2% (13/24) of all infections with hypogammaglobulinemia, suggesting that some infections in the presence of hypogammaglobulinemia might be the result of a mechanism other than low serum IgG levels.

To date, no specific guidelines exist for managing drug-induced hypogammaglobulinemia and the threshold for the initiation of immunoglobulin replacement therapy after rituximab treatment depends on specific underlying conditions [16, 32]. The UK Department of Health clinical guidelines on all causes of secondary antibody deficiency recommend the initiation of immunoglobulin replacement therapy in the following patients: (i) those whose underlying cause of hypogammaglobulinemia cannot be reversed and (ii) those who develop hypogammaglobulinemia (serum IgG level < 500 mg/dL), with a history of severe or recurrent bacterial infection despite the use of prophylactic oral antibiotics for 3 months, and with functional antibody deficiency [33]. A study on autoimmune diseases suggested severe hypogammaglobulinemia, defined as a serum IgG level below 200 mg/dL, as a criterion for immunoglobulin replacement therapy initiation after rituximab treatment in patients with recurrent severe infections, especially respiratory system and bacterial infections, and functional antibody deficiency [31]. In the present study, only one of the eight patients who developed persistent severe hypogammaglobulinemia developed recurrent infections during the long follow-up period and only one patient had a severe infection requiring intensive care unit admission. Considering the abovementioned threshold, the current study patients may not meet the indications for immunoglobulin replacement therapy.

The drawbacks of immunoglobulin replacement therapy, including the need for frequent hospital visits to receive immunoglobulin replacement because of the short medication half-life, insufficiency to prevent major causes of infection such as febrile neutropenia, and high cost, should be considered [3, 34]. In the present study, we could not assess the efficacy of immunoglobulin replacement therapy as none of the study patients received the treatment. However, our study showed the following results, which raised the possibility that immunoglobulin replacement therapy might not be necessary in patients with childhood-onset complicated SDNS/FRNS or SRNS who develop persistent severe hypogammaglobulinemia after rituximab treatment: (i) infections in the persistent severe hypogammaglobulinemia group mainly occurred when the patients did not develop severe hypogammaglobulinemia; (ii) infection rates in patient-year analysis were low; and (iii) more than half of the infections were rarely attributable to serum IgG levels.

The present study has several limitations that should be acknowledged. First, serum IgG levels were not strictly monitored due to the retrospective study design and serum IgG levels during infection were missing in some cases. Second, although the data of serum IgG levels with serum albumin levels of < 3.0 g/dL was excluded to minimize the possibility of urinary loss, the serum IgG levels still could be affected by urinary loss. However, persistent severe hypogammaglobulinemia was not caused by the urinary loss of IgG, as proteinuria did not persist for long time periods in the enrolled patients. Third, potential confounders of susceptibility to infection should be considered. This study included patients with childhood-onset complicated SDNS/FRNS or SRNS treated with rituximab, who had one or two oral immunosuppressive therapies and might have several recurrent relapses during the follow-up period. During the relapse period, several factors other than rituximab-induced immunosuppression, such as steroid treatment, hypoalbuminemia and urinary loss of complement factor, and immunoglobulin, could cause infection. However, almost all patients in the present study had oral immunosuppressive treatments after rituximab treatment, and infection events during the relapse period were excluded in patient-year analysis, which helped to reduce the confounding factor to estimate the relationship between rituximab-induced hypogammaglobulinemia and infection rate.

In conclusion, our findings suggest a weak association between the severity of hypogammaglobulinemia and infection in patients with complicated SDNS/FRNS or SRNS. Our patients, including the persistent severe hypogammaglobulinemia group, may not have had recurrent or severe infections enough to meet the indications for immunoglobulin replacement therapy. Additional studies are warranted to further interrogate the association between hypogammaglobulinemia and infection and to determine the threshold for the initiation of immunoglobulin replacement therapy after rituximab treatment.

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Author contribution All authors are physicians who treated the patients in this study. Yuta Inoki conducted the study, collected the clinical and laboratory data, and wrote the manuscript; Kentaro Nishi, Mai Sato, and Masao Ogura reviewed and edited the manuscript; Koichi Kamei, the corresponding author, supervised the work and revised the manuscript. All authors read and approved the final manuscript.

Data availability The data from this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Declarations

Ethics approval The study was approved by the Ethics Committee of the National Center for Child Health and Development (approval number: 2021–169).

Consent to participate Informed consent regarding participation was exempted in accordance with the principles of the Declaration of Helsinki and the ethical guidelines issued by the Ministry of Health, Labor, and Welfare, Japan.

Consent for publication Informed consent for publication was exempted in accordance with the guidelines.

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