Hypogammaglobulinaemia following rituximab therapy in childhood nephrotic syndrome

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Introduction

In this issue of *Pediatric Nephrology*, Kamei et al. describe the incidence and risk factors for developing hypogammaglobulinaemia following rituximab therapy in 103 children with complicated idiopathic nephrotic syndrome (NS) [1]. The group from Tokyo have published numerous articles on the use of rituximab in NS, and in this paper, they have extended our knowledge on the safety profiles of this medication.

While the majority of children with NS respond to corticosteroids, half of these patients develop frequent relapses (FR) and/or steroid dependency (SD) and require multiple immunosuppressive agents, either in sequence or combination, to prevent relapse [2]. These children are at high risk of significant medication side effects such as short stature, Cushing syndrome, infection, and calcineurin inhibitor-associated nephrotoxicity. Rituximab, a chimeric anti-CD monoclonal antibody, has emerged as an effective therapy in children with FRSDNS to induce long-term disease remission and avoid steroid toxicities [3, 4].

The safety profiles of rituximab appear to be safe in children, but unusual significant complications can occur [3–5]. Most infusion reactions are self-limiting, but there are worrying side effects such as agranulocytosis, lung injury, fatal hepatitis reactivation, and multifocal leukoencephalopathy [6–9]. Hypogammaglobulinaemia is commonly observed following rituximab therapy for FRSDNS [10, 11]. There are growing concerns of this complication since it can be severe, protracted, and occasionally associated with infections [10, 11]. Many children do also have hypogammaglobulinaemia

that is pre-existing to the rituximab treatment [10, 11], possibly caused by the nephrotic state itself or other immunosuppressing agents. The true incidence and clinical significance of rituximab-induced hypogammaglobulinaemia is still unclear. Of note, the drug effect of rituximab is not permanent, be it the clinical effects or its side effects. Most children (80%) would eventually develop a relapse and might require additional courses of rituximab [5]. Therefore, it is important to understand the long-term safety of rituximab in this context to justify its repeated usage in children.

Results of the latest study by Kamei et al.

In the current paper, Kamei et al. present a single-centre, retrospective cohort study in 103 children who received rituximab therapy for complicated FRSDNS. The patient population was well-defined and representative, with appropriate inclusion/exclusion criteria. The treatment exposure was standardized, and only patients who received a single dose (375 mg/m²) of rituximab were included. The primary outcome measure was the incidence of hypogammaglobulinaemia, which was defined by serum IgG levels according to the age-specific reference range. Normal IgG values depend on the ethnicity and the assay method [12, 13]. The authors did, however, utilize the normal reference range of children from the USA, although they did not specify the method employed for IgG assay. The definition for severe hypogammaglobulinaemia (<250 mg/dL) was also arbitrary as there is no universal consensus on that. The monitoring of IgG levels was not standardized due to the retrospective study design. On the other hand, IgM level, which might be reduced after rituximab, was not measured in this study [14, 15]. Its reduction would potentially contribute to infections as well [14, 15]. Last but not least, an appropriate control group without rituximab treatment would have been very interesting, since hypogammaglobulinaemia is prevalent

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among children with NS under intense oral immunosuppression without exposure to rituximab and also before treatment in this study [10, 16].

The authors presented that 58% of the patients had at least one episode of hypogammaglobulinaemia and 22% had persistent hypogammaglobulinaemia for more than 1 year. Patients with low serum IgG levels prior to rituximab, as well as the history of steroid-resistant nephrotic syndrome (SRNS), were at particular risk of this complication. The authors concluded that hypogammaglobulinaemia is a frequent adverse event associated with the use of rituximab. Rather surprisingly, IgG levels actually increased during B-cell depletion, which complicated the conclusion. While the authors did not offer a convincing reason, one possible explanation for this finding is that the memory B cells within the secondary lymphoid organs, such as lymph node and spleen, were not depleted by rituximab and continued to produce immunoglobulins [17, 18]. Another possible explanation is that other factors including the NS per se, or other treatments, could have accounted for the low IgG levels.

Are children with nephrotic syndrome more susceptible to rituximab-associated hypogammaglobulinaemia?

The true incidence of post-rituximab hypogammaglobulinaemia remains uncertain due to the lack of prospective data in various patient populations. In the landmark trial on rituximab in NS, Iljima et al. evaluated the effect of rituximab in 24 children compared to placebo [3]. Impact on immunoglobulin levels was not reported in the original

paper. However, the authors, in the correspondence, stated that IgG concentrations were monitored throughout the study and no patient in the rituximab group had substantially decreased IgG levels [19]. To our knowledge, no other prospective studies on rituximab in childhood NS adequately and specifically addressed this important complication. Kamei et al. reported overall 58% children had hypogammaglobulinaemia after rituximab. About half of the patients showed reduced IgG values prior to rituximab, and the incidence of hypogammaglobulinaemia was substantially higher (85% vs. 23%) in this group, compared to those with normal baseline values.

The incidences of hypogammaglobulinaemia following rituximab therapy in various patient populations ranged from 35 to 65% and are summarized in Table 1 [10, 11, 15, 16, 20]. Hypogammaglobulinaemia persisted in a large proportion of patients (50–80%) with low baseline IgG levels. In contrast, consistently, 20–30% of patients with normal IgG values prior to rituximab developed hypogammaglobulinaemia. Thus, the difference in prevalence may be related to the variation in patients having a normal baseline IgG concentration. The difference may be due to relapse severity, timing between relapse and rituximab administration, as well as re-dose indication, i.e. prophylactic administration due to B-cell repletion rather than actual disease relapse. Of note, 14–50% of these patients had persistently reduced IgG concentrations beyond 1 year after rituximab therapy [11, 15]. Reduction in IgM values was also observed in up to 46% of patients [15].

Based on these data, it appears that the risk of hypogammaglobulinaemia is similar among different patient populations who have normal immunoglobulin levels upon

Table 1 Rates of hypogammaglobulinaemia following rituximab therapy in different patient populations

Authors	Patient no	Population	Rituximab indications	Rates of hypogammaglobulinaemia		
				Overall	Baseline IgG levels	
					Normal	Reduced
Kamei et al. [1]	103	Children	FRSDNS	58.4%	23.0%	84.3%
Parmentier et al. [11]	107	Children	SDNS	34.6%	29.0%	57.1%
Colucci et al. [10]	27	Children	FRSDNS	40.7% ^d	38.5%	46.2%
McAtee et al. [15]	468	Children	Various ^b	-	23.2%	-
Barmettler et al. [20]	558 ^a	Adult	Various ^c	65.1%	19.3%	22.4%
Marco et al. [16]	177	Adult	Multi-systemic autoimmune disorder	34.4%	22.9%	72.2%

FR, frequently relapsing; NS, nephrotic syndrome; SD, steroid-dependent

^aFive hundred fifty-eight of the 4479 patients had immunoglobulin monitored after rituximab

^bIndications included systemic lupus erythematosus, nephrotic syndrome, autoimmune encephalitis, multiple sclerosis, immune thrombocytopenic purpura, lymphoma, and others

^cIndications included cancer, primary immunodeficiency, and rheumatological and haematological conditions

^dThe rates of hypogammaglobulinaemia at last follow-up, which were at least 2 years from last rituximab

initiation of rituximab. The issue is that pre-existing hypogammaglobulinaemia tends to persist and even worsen after rituximab, and this situation is prevalent among children with NS. It has been reported that IgG levels markedly decrease during NS and may take up to 12 months to recover following remission [21, 22], likely due to urinary loss during active nephrotic state. Besides, the use of immunosuppression such as corticosteroids and possible immune dysfunction may also predispose patients to develop pre-existing hypogammaglobulinaemia [23]. Finally, most patients receive rituximab soon after remission in order to reduce medication side effects and they often have low IgG levels at that time.

In summary, hypogammaglobulinaemia is frequently observed in children with NS requiring rituximab. It is reasonable to monitor immunoglobulin levels regularly, especially prior to elective administration of rituximab to identify susceptible patient groups.

Risk factors for developing hypogammaglobulinaemia

In accordance with other studies [10, 11], findings from the current study confirm that pre-existing low IgG levels prior to rituximab is a significant risk factor for hypogammaglobulinaemia, with an odds ratio of 7.6. Its severity at baseline also correlates well with the nadir IgG levels following rituximab, but was not evaluated in this study [20]. The history of SRNS also increased the risk of hypogammaglobulinaemia by tenfold and was associated with its persistence at 1 year. This is not surprising as these patients are typically the most difficult to treat and have repeated or prolonged nephrotic state as well as exposure to intensive immunosuppression. It would be logical to deduce that patients with history of rituximab-associated hypogammaglobulinaemia are at higher risk of recurrence in subsequent treatment courses, but unfortunately, these have not been addressed in the current study.

In this study, no association was observed between the development of hypogammaglobulinaemia with gender, age at rituximab, duration between remission and rituximab administration, disease relapse, and immunosuppressive agents prior to and during rituximab. In contrast, Colucci et al. and Parmentier et al. both reported that patients of younger age at first rituximab were at a higher risk of developing hypogammaglobulinaemia [10, 11]. The risk also appeared to be more significant in children less than 6 years of age [11]. This association was also observed among those with prior cyclophosphamide exposure and use of corticosteroids [16]. From our unpublished data among 511 FRS-DNS children treated with different rituximab regimens [5], the prevalence of persistent hypogammaglobulinaemia did

not increase with higher dose regimen. Higher cumulative dose or increasing number of rituximab treatment courses do not appear to result in more complications, but these are all retrospective data [5, 11, 24]. No relationship between the B-cell subset populations and hypogammaglobulinaemia has been found [10, 11].

Hypogammaglobulinaemia—what is the infection risk?

The clinical significance of hypogammaglobulinaemia remains uncertain. While there are patients who develop severe or recurrent infections, many children are asymptomatic. Kamei et al. reported that 12 patients on rituximab experienced infections, and in 6 patients, the IgG levels were concurrently low. The infection rates were similar among children with or without hypogammaglobulinaemia, at 0.11 and 0.12 per patient-year at risk, respectively. Most children were hospitalized for less than 10 days, and none of the patients suffered from sepsis or bacteraemia. Only one patient without co-trimoxazole prophylaxis developed pneumocystis pneumonia. This child was also the only patient who received immunoglobulin replacement. With these results, the authors concluded that serious infections are rare with hypogammaglobulinaemia and prophylactic administration of immunoglobulin may not be necessary. However, it was also reported that 8 of the 12 total infectious episodes were due to febrile neutropenia. From these observations, it is likely that children who developed infections despite normal IgG concentrations in the present study suffered from agranulocytosis, which is another rituximab-associated complication and also a major risk factor of infection. Therefore, although the infection rates were reported to be similar among children with or without hypogammaglobulinaemia, children with low IgG concentrations could still be at risk of infection. Of note, only 2 patients had severe hypogammaglobulinaemia <200 mg/dL, suggesting the numerical value does not always correlate with the infection risk and this has also been reported previously [10, 16]. This demonstrates that the adaptive immune system is much more complex than the innate immune system (e.g. neutrophils), as the IgG can be functional with good avidity and neutralization of pathogens despite being low in quantity. Finally, a potential confounder is the use of concurrent immunosuppression in almost all patients with infections.

Parmentier et al. described that 13/46 patients (28%) developed concomitant infection with hypogammaglobulinaemia and 7 children required hospitalizations with intravenous antibiotics [11]. One patient developed enterovirus-associated fulminant viral myocarditis leading to heart transplantation [11, 25]. All these infected children were supplemented by intravenous immunoglobulin infusions

as treatment for their infections. Younger patients also appear to have a higher risk of infection in the presence of hypogammaglobulinaemia [11]. In the adult population, the risk is more definite and severe infections are associated with rituximab use [20]. Patients who receive IVIG replacement following rituximab, especially with a higher cumulative immunoglobulin dose, are less likely to experience serious infections (HR 0.98, per gramme IVIG received) [20].

It is important to note that the risk of infection following rituximab is due to a complex interplay between various factors. These include underlying primary disease (e.g. lupus, oncological conditions), concurrent immunosuppression (e.g. mycophenolate mofetil, calcineurin inhibitors), and chemotherapy, as well as other complications such as neutropenia [10, 15, 20, 26]. Increased mortalities are also observed in male sex, older patients, and those with serious infections 6 months before and after rituximab [20].

Judging from the above data, infection risk seems to increase with hypogammaglobulinaemia. The overall severity of infective episodes appears acceptable, although serious complications do occur. Importantly, most data on the safety of rituximab come from older children and more data are needed for young children. Young patients are likely to require multiple rituximab treatments and are at a higher risk of developing neutropenia and hypogammaglobulinaemia [9, 11]. To date, there is no randomized control trial on whether prophylactic immunoglobulin replacement could prevent infection. It is worth noting that intravenous immunoglobulin contains only minimal IgM content, which limits its ability to prevent infections as patients with IgM deficiency remain at risk for recurrent infections [27]. The product also has a short half-life of 32–36 days [28], so regular monthly replacement may be required.

Hypogammaglobulinaemia—to treat or not to treat

Many centres, as in our practices, do not routinely replace immunoglobulin solely based on the numbers if the child is asymptomatic, and will only treat on the rare occasion when the patients suffer from infections. In contrast, some centres opt for empirical immunoglobulin replacement if the IgG levels fall below certain levels (e.g. 400 mg/dL) to prevent infection, since these patients may be considered as having secondary immunodeficiency. Current guidelines do not recommend a cut-off of IgG levels below which immunoglobulin replacement therapy should be commenced [29]. The decision to substitute immunoglobulin should be individualized, taking into account various factors that may predispose the patients to serious infections, including patient's age, the degree of hypogammaglobulinaemia, previous exposure to intensive immunosuppression, and the

use of concurrent immunosuppressive agents. All details of the clinical context should be considered, including the history of past infection and the nature of current infection, whether they are severe, persistent, unusual, or recurrent [29]. Of note, reduced immunoglobulin levels against HBV and tetanus were also reported following anti-CD20 therapy [10]. This suggests that vaccine competency is also impaired and re-immunization may be indicated. Future prospective, randomized controlled trials are required to evaluate the best management approach to asymptomatic, numerical hypogammaglobulinaemia.

Our recommendation and conclusion

Hypogammaglobulinaemia is common in children with FRSDNS following rituximab therapy. Although most children remain asymptomatic, the risk of infection is not negligible and severe infections may occur. Nonetheless, the use of immunoglobulin replacement to prevent infection remains controversial and requires further investigations for its efficacy and cost-effectiveness. With these in mind, it may be sensible to offer regular immunoglobulin monitoring before and after rituximab and to adopt an individualized approach to immunoglobulin replacement as highlighted above.

Our preferred practice is to use rituximab in children with complicated FRSDNS after all other treatment options have been tried. Using rituximab as the first-line steroid-sparing agent has, however, been associated with encouraging results. Until the long-term safety profile of this approach is better delineated, we still have concerns in recommending a liberal use of rituximab due to infection complications and impact on vaccine competency. Some centres prescribe rituximab with rapid drug tapering, while others use long-term co-medication such as MMF to prolong remission and reduce cost [30]. However, concurrent immunosuppression may pose additional infection risk in patients with hypogammaglobulinaemia and should therefore be taken into consideration when deciding on treatment approach.

There are still many unanswered questions regarding the optimal rituximab regimen in steroid-sensitive nephrotic syndrome. Long-term data regarding the efficacy and safety of repeated dosing of rituximab in these children are urgently needed to guide the optimal approach. We are now in the process of analyzing data in children with repeated doses from 16 paediatric nephrology centres around the world, and hopefully, the results will shed light on the future direction soon.

Declarations

Conflict of interest The authors declare no competing interests.

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