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Editorial Board Member of *World Journal of Clinical Cases*, Wilbert Aronow, MD, Professor, Statistical Worker, Department of Medicine, Davar, J (reprint author), Royal Free Hosp, Dept Cardiol, Carcinoid Heart Dis Clin, Pond St, London NW3 2QG, England., Valhalla, NY 10595, United States

AIMS AND SCOPE

World Journal of Clinical Cases (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The primary task of *WJCC* is to rapidly publish high-quality Case Report, Clinical Management, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Meta-Analysis, Minireviews, and Review, in the fields of allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, *etc*.

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The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2018 Edition of Journal Citation Reports cites the 2017 impact factor for *WJCC* as 1.931 (5-year impact factor: N/A), ranking *WJCC* as 60 among 154 journals in Medicine, General and Internal (quartile in category Q2).

RESPONSIBLE EDITORS FOR THIS ISSUE

Retrospective Cohort Study

Rituximab-induced IgG hypogammaglobulinemia in children with nephrotic syndrome and normal pre-treatment IgG values

Pierluigi Marzuillo, Stefano Guarino, Tiziana Esposito, Anna Di Sessa, Sara Immacolata Orsini, Daniela Capalbo, Emanuele Miraglia del Giudice, Angela La Manna

ORCID number: Pierluigi Marzuillo (0000-0003-4682-0170); Stefano Guarino (0000-0002-0551-5236); Tiziana Esposito (0000-0002-8215-3988); Anna Di Sessa (0000-0002-5877-3757); Sara Immacolata Orsini (0000-0003-3279-7643); Daniela Capalbo (0000-0002-3612-7383); Emanuele Miraglia del Giudice (0000-0002-1492-076X); Angela La Manna (0000-0002-5531-2656).

Author contributions: Marzuillo P, La Manna A, and Guarino S contributed to research idea and study design; Esposito T, Di Sessa A, and Orsini SI contributed to data acquisition; Marzuillo P and Miraglia del Giudice E contributed to data analysis/interpretation; Marzuillo P, Di Sessa A, and Capalbo D contributed to statistical analysis; Miraglia del Giudice E, La Manna A , and Marzuillo P contributed to supervision or mentorship; Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Pierluigi Marzuillo, Stefano Guarino, Tiziana Esposito, Anna Di Sessa, Sara Immacolata Orsini, Daniela Capalbo, Emanuele Miraglia del Giudice, Angela La Manna, Department of Woman, Child and of General and Specialized Surgery, Università degli Studi della Campania "Luigi Vanvitelli", Napoli 80138, Italy

Corresponding author: Pierluigi Marzuillo, MD, PhD, Doctor, Department of Woman, Child and of General and Specialized Surgery, Università degli Studi della Campania "Luigi Vanvitelli", Via Luigi De Crecchio 2, Naples 80138, Italy. pierluigi.marzuillo@gmail.com
Telephone: +39-81-5665465
Fax: +39-81-5665427

Abstract

BACKGROUND
In paediatric patients with complicated nephrotic syndrome (NS), rituximab (RTX) administration can induce persistent IgG hypogammaglobulinemia among subjects showing low basal immunoglobulin G (IgG) levels.

AIM
To evaluate the effect of RTX on IgG levels and infections in patients with complicated NS and normal basal IgG levels.

METHODS
We consecutively enrolled all patients with complicated NS and normal basal IgG levels undergoing the first RTX infusion from January 2008 to January 2016. Basal IgG levels were dosed after 6 wk of absent proteinuria and with a maximal interval of 3 mo before RTX infusion. The primary outcome was the onset of IgG hypogammaglobulinemia during the follow-up according to the IgG normal values for age [mean ± standard deviation (SD)].

RESULTS
We enrolled 20 patients with mean age at NS diagnosis of 4.2 ± 3.3 years. The mean age at the first RTX infusion was 10.9 ± 3.5 years. Eleven out of twenty patients (55%) developed IgG hypogammaglobulinemia. None of these patients showed severe or recurrent infections. Only one patient suffered from recurrent acute otitis media and underwent substitutive IgG infusion. Three patients undergoing only the two "starting doses" experienced normalization of IgG levels. Using Kaplan-Meier analysis, the cumulative proportion of patients free of IgG hypogammaglobulinemia was 57.8% after the first RTX dose, 51.5% after the third dose, 44.1% after the fourth dose, and 35.5% after the fifth dose.

CONCLUSION

RTX can induce IgG hypogammaglobulinemia in patients with pre-RTX IgG normal values. None of the treated patients showed severe infections.

Key words: Nephrotic syndrome; Rituximab; IgG hypogammaglobulinemia; Immunoglobulin

Core tip: In paediatric patients with complicated nephrotic syndrome (NS), rituximab (RTX) administration can induce persistent immunoglobulin G (IgG) hypogammaglobulinemia among subjects showing low basal IgG levels. Our case series shows that RTX can induce IgG hypogammaglobulinemia also in patients with pre-RTX IgG normal values and that persisting IgG hypogammaglobulinemia could be dose-dependent. When evaluating a patient with complicated NS and post-RTX IgG hypogammaglobulinemia, IgG supplementation may not be needed because, to date, no severe infections have been detected and the possibility of adverse events related to IgG supplementation exists.

INTRODUCTION

Rituximab (RTX) is an effective and safe treatment for childhood-onset, complicated, frequently relapsing, and steroid-dependent nephrotic syndrome (NS)[1]. Data about long-term safety are limited. Recent reports have highlighted the impact of RTX treatment on immunoglobulin (Ig) levels. In studies involving adults with multisystem autoimmune diseases, it had been found that following RTX treatment 34%-56% of patients showed reduced IgG levels, with 13%-26% of them presenting already IgG level reduction before RTX initiation[2-4]. On the other hand, it has been shown in paediatric patients with NS that RTX administration can induce persistent IgG hypogammaglobulinemia among subjects showing low basal IgG levels and in a few cases with normal baseline IgG levels[5-7]. The aim of our study was to evaluate the effect of RTX on IgG levels and infections in patients with complicated, frequently relapsing, and steroid- and cyclosporine-dependent NS who have normal baseline IgG levels.

MATERIALS AND METHODS

We consecutively enrolled patients with complicated NS and normal basal IgG levels undergoing the first RTX infusion from January 2008 to January 2016. The study was approved by our Research Ethical Committee. Informed consent was obtained before any procedure.

Basal IgG levels were dosed after 6 wk of absent proteinuria and with a maximal interval of 3 mo before RTX infusion. Patients with IgG levels under the range of normality for age before the first RTX infusion [mean ± standard deviation (SD)] and with missing data were excluded[8].

Initial RTX course was performed as two infusions of 375 mg/m² with an interval of 7-14 d between the two infusions ("starting doses"). Additional RTX injections were made after every NS relapse just after obtaining remission independently from the levels of CD19-positive cells. IgG levels, white cell blood count, and CD19-positive cells were evaluated at 3 mo and 6 mo after the first RTX infusion and then every 6 mo. After RTX initiation, we slowly tapered cyclosporine dose before stopping completely and then slowly tapered corticosteroid doses stopping their administration.

Primary outcome

The primary outcome was the onset of IgG hypogammaglobulinemia during the follow-up according to normal IgG values for age (mean ± SD) (Figure 1A)[8]. We also documented possible recovery from IgG hypogammaglobulinemia and recorded infections and neutropenia.

Statistical analysis

P values ≤ 0.05 were considered statistically significant. Differences for continuous variables were analysed with the independent-sample *t* test for normally distributed variables and with the Mann-Whitney test in case of non-normality. Qualitative variables were compared using the chi-squared test. The development of primary outcome was determined by survival analysis according to the Kaplan-Meier method. The day of first RTX infusion was considered the starting point, while the end point was the date of the primary outcome onset. Patients arriving at their last available follow-up without showing primary outcome were right censored. The Stat-Graph XVII software for Windows was used for all statistical analyses with the exception of Kaplan-Meir analysis, which was done using Graphpad Prims 7 software for Windows (La Jolla, CA, United States).

RESULTS

A total of 20 patients were enrolled. The mean age of the study population at the time of NS diagnosis was 4.2 ± 3.3 years (range 1.6-11.5 years). All patients developed complicated, frequently relapsing, and steroid- and cyclosporine-dependent NS and were treated with the "starting doses" of RTX at mean age of 10.9 ± 3.5 years. RTX doses were repeated in 11 patients because of NS relapses. Therefore, a total of 79 doses of RTX were administered in the study period: Only the two "starting doses" in eight patients, three doses in 2 patients, four doses in five patients, five doses in 1 patient, seven doses in 1 patient, eight doses in 2 patients, nine doses in 1 patient. The mean follow-up available after the last RTX infusion was 29.8 ± 17.5 mo.

IgG hypogammaglobulinemia after RTX therapy was recorded in 11/20 (55%) patients. In 8 out of 11 patients, IgG hypogammaglobulinemia occurred after the RTX "starting doses" and in the remaining three patients after the subsequent doses (Figure 1A). Only 3 out of the 11 patients experienced subsequent normalization of IgG levels. These 3 patients underwent only the two "starting doses" of RTX and did not receive further RTX infusions. None of the patients who developed IgG hypogammaglobulinemia showed severe infections. Only one patient (Figure 1A) suffered from recurrent acute otitis media and underwent substitutive IgG infusion after immunological consultation. The first episode of NS in this patient was at the age of 1.6 years. Before the RTX infusion, he showed 16 NS relapses despite corticosteroids, cyclophosphamide, tacrolimus, and mycophenolate treatments. This patient underwent his first RTX doses at 6.8 years of age and showed persisting IgG hypogammaglobulinemia after the fifth dose of RTX. After the eighth RTX dose, he had six episodes of acute otitis media in 8 mo. Therefore, substitutive IgG infusion was started. He has undergone substitutive IgG infusions for 18 mo, and he has not shown other acute otitis media episodes.

CD19-positive cell depletion was found in all the patients with a mean recovery time of 6.3 ± 17.5 mo from every RTX infusion. None of the patients showed neutropenia. When comparing patients showing and not showing IgG hypogammaglobulinemia, no differences were found in the utilization of corticosteroids, cyclosporine, cyclophosphamide, other immunosuppressive agents, and more than one immunosuppressive agent (Table 1). The months of follow-up after the last RTX infusion, the number of RTX infusions, and the months of CD-19 cells depletion were similar between patients showing and not showing IgG hypogammaglobulinemia. Moreover, a non-significant trend showing a lower number of relapses after RTX infusion and younger age at first RTX infusion for the patients presenting IgG hypogammaglobulinemia compared with the patients not presenting IgG hypogammaglobulinemia was present (Table 1).

Using Kaplan-Meier analysis, the cumulative proportion of patients free of IgG hypogammaglobulinemia was 57.8% after the first dose of RTX, 51.5% after the third dose, 44.1% after the fourth dose, and 35.5% after the fifth dose (Figure 1B).

DISCUSSION

Evidence on the impact of RTX treatment on IgG levels in children with complicated
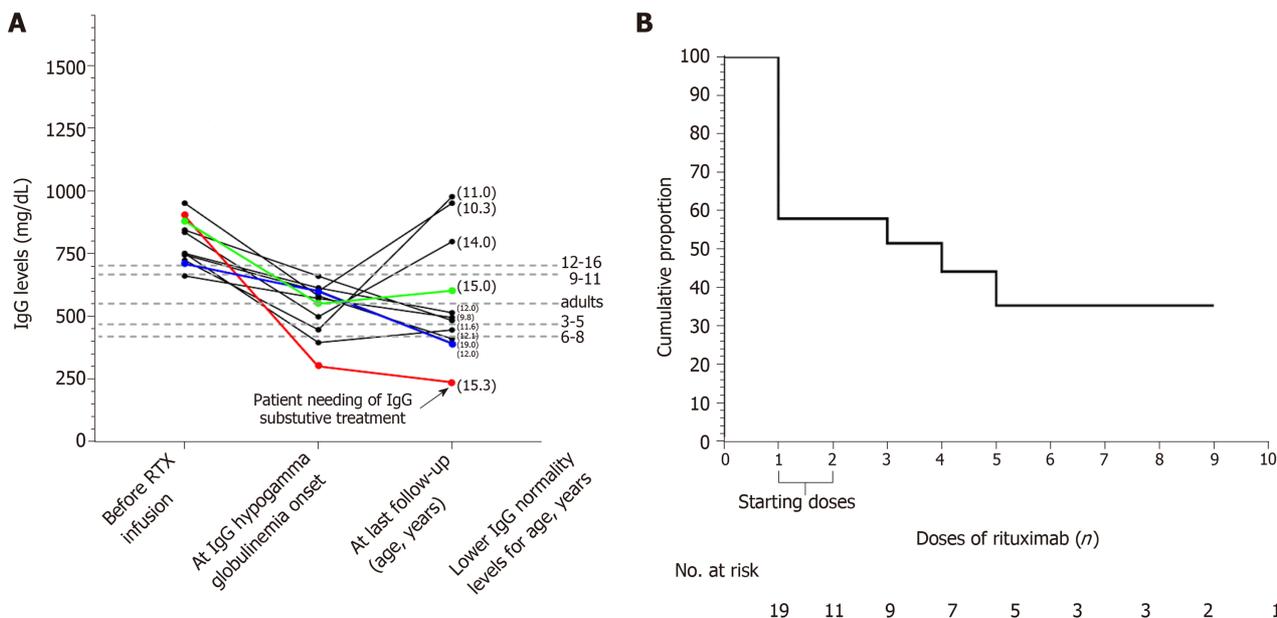
Figure 1 Trend of the IgG values among patients presenting IgG hypogammaglobulinemia and survival from IgG hypogammaglobulinemia. A: Trend of the IgG values among patients presenting with IgG hypogammaglobulinemia. Eight patients (dark coloured) developed IgG hypogammaglobulinemia after the "starting doses" (7 out of 8 patients showed IgG hypogammaglobulinemia at the scheduled follow-up 3 mo after the RTX "starting doses", and one patients developed IgG hypogammaglobulinemia 24 mo after the RTX infusion), one (green coloured) patient after the third dose (this patient showed IgG hypogammaglobulinemia 3 mo after the third dose), one (blue coloured) after the fourth (this patient showed IgG hypogammaglobulinemia 3 mo after the fourth dose), and one (red coloured) after the fifth dose (this patient showed IgG hypogammaglobulinemia 13 mo after the fifth dose); B: Survival from IgG hypogammaglobulinemia. The cumulative proportion of patients free of IgG hypogammaglobulinemia was 57.8% after the first dose of RTX, 51.5% after the third dose, 44.1% after the fourth dose, and 35.5% after the fifth dose. The time between the RTX infusion and IgG hypogammaglobulinemia onset is specified in the legend of Figure 1A. RTX: Rituximab; IgG: Immunoglobulin G.

NS having normal baseline IgG levels are limited to few cases for each available study[5-7]. Delbe-Bertin *et al*[5] reported that persisting post-RTX IgG hypogammaglobulinemia was observed in 7 patients with IgG hypogammaglobulinemia before RTX infusion, while none of the 4 patients with normal pre-RTX IgG levels presented IgG hypogammaglobulinemia after RTX initiation. In addition, Fujinaga *et al*[6] found that nine out of 60 patients with complicated steroid-dependent NS showed hypogammaglobulinemia (defined as IgG levels < 500 mg/dL) after RTX infusion. Among these 9 patients, only 3 patients had normal IgG levels before the RTX infusion. In another multi-centre case series, Guigonis *et al*[7] found that 4 out of 22 patients with severe steroid- and cyclosporine-dependent NS developed RTX-related hypogammaglobulinemia. In that case series, no further follow-up of IgG levels was reported.

The present single-centre study was specifically designed to enrol only patients with complicated, frequently relapsing, and steroid- and cyclosporine-dependent NS with normal basal IgG levels. We found that 11 out of 20 patients (55%) developed IgG hypogammaglobulinemia after RTX therapy, with eight of them having developed IgG hypogammaglobulinemia after the "starting doses" and three after the following RTX doses. Noteworthy, we found recovery from IgG hypogammaglobulinemia only in the 3 who underwent "starting doses" of RTX without receiving further RTX infusions. None of the patients who developed IgG hypogammaglobulinemia showed severe infections. Only one patient (Figure 1A) suffered from recurrent acute otitis media, and he underwent substitutive IgG infusion

We failed to demonstrate potential risk factors of developing IgG hypogammaglobulinemia after RTX treatment in patients with NS probably because of the limited population number. However, we did identify a trend showing that the patients developing IgG hypogammaglobulinemia were younger both at NS onset and first RTX infusion than patients who did not develop IgG hypogammaglobulinemia. In the literature, data about risk factors of developing post-RTX hypogammaglobulinemia in children with NS are not yet available. However, more than one course of RTX, previous exposure to purine analogues, more than eight doses of RTX, RTX maintenance regimens, age at the administration of RTX, and post-RTX mycophenolate administration have been identified as risk factors in adults undergoing RTX administration because of non-Hodgkin lymphoma, rheumatoid arthritis, and systemic Lupus Erythematous[9].

Table 1 Characteristics of the patients presenting and not presenting post-rituximab IgG hypogammaglobulinemia

	Presenting IgG hypogammaglobulinemia, *n* = 11	Not presenting IgG hypogammaglobulinemia, *n* = 9	*P*-value
Age at NS onset, yr	2.8 (1.1)	5.2 (4.7)	0.07
Female sex *n* (%)	0 (0)	3 (33.3)	0.1
Corticosteroids *n* (%)	11 (100)	9 (100)	> 0.99
Corticosteroids (mean ± SD, mo)	76.5 ± 54.2	73.2 ± 30.9	0.87
Cyclosporine *n* (%)	11 (100)	9 (100)	> 0.99
Cyclosporine (mean ± SD, mo)	56.1 ± 23.1	66.4 ± 40.0	0.48
Cyclophosphamide *n* (%)	8 (72.3)	6 (66.7)	0.9
Cyclophosphamide (mean ± SD, mo)	3 ± 0.27	3 ± 0.33	0.9
Other immunosuppressive agents *n* (%)	2 (0.2)	3 (0.33)	0.43
> 1 immunosuppressive agents *n* (%)	8 (72.3)	7 (77.8)	0.43
Relapses (mean ± SD)	11.5 ± 4.6	16.5 ± 9.7	0.15
Relapses after first RTX infusion (mean ± SD)	1.6 ± 1.5	3.9 ± 4.6	0.15
RTX infusions (mean ± SD)	3.3 ± 1.8	5.0 ± 2.7	0.11
Age at first RTX infusion, (mean ± SD, yr)	9.2 ± 1.8	11.8 ± 4.5	0.09
Months of CD19-positive cells depletion (mean ± SD)	6.4 ± 3	6.2 ± 2.6	0.9
Months of follow-up after the last RTX infusion (mean ± SD)	31.1 ± 14.9	27.4 ± 20.7	0.59

RTX: Rituximab; IgG: Immunoglobulin G; NS: Nephrotic syndrome; SD: Standard deviation.

Regarding the risk of severe infections following RTX infusion in paediatric patients affected by NS, among the 27 patients showing post-RTX IgG hypogammaglobulinemia (including our patients and other in the literature with available follow-up)[5,6], no life-threatening infections were detected. Among non-life-threatening infections, one patient presented bronchitis[6], one enteritis[6], and one recurrent episodes of acute otitis media. Moreover, evaluating the need of substitutive IgG infusion, 4 out of the 27 patients underwent IgG supplementation. Among these 4 patients, 3 received IgG supplementation only for low IgG levels[5,6], and one for recurrent acute otitis media. It is important to emphasize that one of these patients in IgG supplementation presented aseptic meningitis as an adverse effect of IgG supplementation[5].

Finally, evaluating the percentage of recovery of serum levels of IgG in patients developing IgG hypogammaglobulinemia, Fujinaga *et al*[6] showed IgG levels recovery in 6 out of 9 patients, Delbe-Bertin *et al*[5] showed IgG recovery in 1 out of 8 patients, and in the present case series we found IgG recovery in 3 out of 11 patients.

In conclusion, our case series shows that RTX can induce IgG hypogammaglobulinemia in patients with pre-RTX IgG normal values and that persisting IgG hypogammaglobulinemia could be dose-dependent.

When evaluating a patient with complicated NS and post-RTX IgG hypogammaglobulinemia, IgG supplementation may not be needed because, to date, no severe infections have been detected and the possibility of adverse events related to IgG supplementation exists.

ACKNOWLEDGMENTS

ARTICLE HIGHLIGHTS

Research background

It has been shown in paediatric patients with complicated nephrotic syndrome (NS) that

rituximab (RTX) administration can induce persistent IgG hypogammaglobulinemia among subjects showing low basal IgG levels.

Research motivation

RTX is an effective and safe treatment for childhood-onset, complicated, frequently relapsing, and steroid-dependent NS. Data about long-term safety are limited. Evidence on the impact of RTX treatment on IgG levels in children with complicated NS having normal baseline IgG levels are limited to a few cases for each available study. Here, we aimed to provide further evidence about RTX safety in childhood and provide a way for possible future perspective multi-centre studies about this topic.

Research objectives

The aim of our study was to evaluate the effect of RTX on IgG levels and infections in patients with complicated, frequently relapsing, and steroid- and cyclosporine-dependent NS with normal baseline IgG levels.

Research methods

We consecutively enrolled all patients with complicated NS and normal basal IgG levels undergoing the first RTX infusion from January 2008 to January 2016. Basal IgG levels were dosed after 6 wk of absent proteinuria and with a maximal interval of 3 mo before RTX infusion. The primary outcome was the onset of IgG hypogammaglobulinemia during the follow-up according to IgG normal values for age (mean ± SD).

Research results

We enrolled 20 patients with a mean age at NS diagnosis of 4.2 ± 3.3 years. The mean age at the first RTX infusion was 10.9 ± 3.5 years. Eleven out of twenty patients (55%) developed IgG hypogammaglobulinemia. None of these patients showed severe or recurrent infections. Only one patient suffered from recurrent acute otitis media and underwent substitutive IgG infusion. Three patients undergoing only the two "starting doses" experienced normalization of IgG levels. When comparing patients showing and not showing IgG hypogammaglobulinemia, no differences were found in the utilization of corticosteroids, cyclosporine, cyclophosphamide, other immunosuppressive agents, and more than one immunosuppressive agent. A non-significant trend showing a lower number of relapses after RTX infusion and younger age at first RTX infusion for the patients presenting IgG hypogammaglobulinemia compared with the patients not presenting IgG hypogammaglobulinemia was present. Using Kaplan-Meier analysis, the cumulative proportion of patients free of IgG hypogammaglobulinemia was 57.8% after the first RTX dose, 51.5% after the third, 44.1% after the fourth, and 35.5% after the fifth dose.

Research conclusions

Our study is the first study specifically designed to enrol only children with complicated, frequently relapsing, and steroid- and cyclosporine-dependent NS with normal basal IgG levels. Our case series shows that RTX can induce IgG hypogammaglobulinemia in patients with pre-RTX IgG normal values and that persisting post-RTX IgG hypogammaglobulinemia could be dose-dependent. None of the patients developing IgG hypogammaglobulinemia showed severe infections. Only one patient suffered from recurrent acute otitis media and underwent substitutive IgG infusion.

Research perspectives

This article adds to our knowledge about the safety of RTX in children with complicated NS. Future studies should prospectively collect multicentre data on the effects of RTX on IgG levels and risk of severe infections. This will improve management of post-RTX IgG hypogammaglobulinemia and help define patients who could benefit from substitutive IgG infusion.

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