Original Article

The indications and safety of rituximab for the treatment of pediatric autoimmune diseases: a single-center retrospective study

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Background: Autoimmune diseases in children pose therapeutic challenges due to their refractory nature and the associated morbidity. Rituximab (RTX), a monoclonal antibody targeting CD20, has emerged as a promising steroid-sparing therapy for various autoimmune disorders by depleting B cells. However, its indications and safety in pediatric populations in our region remain insufficiently studied. This study aims to review the indications and safety of RTX in treating pediatric autoimmune diseases within a single-center setting.

Methods: A retrospective study was conducted on pediatric patients aged 18 years or younger who received RTX for different autoimmune diseases between January 2013 and March 2023 at King Abdulaziz University Hospital, Saudi Arabia. Data on demographics, indications, infusion details, adverse events, and concurrent medications were collected and analyzed.

Results: Twenty-two patients were included, with nephrotic syndrome and systemic lupus erythematosus (SLE) being the most common indications for RTX. The mean age at diagnosis and first RTX infusion was 8 and 9 years, respectively. The most commonly used protocol involved administering 2 infusions of 375 mg/m^2 each, given 2 weeks apart. RTX was commonly used as a second-line treatment following corticosteroids. Infusion-related adverse events occurred in 31.8% of patients, ranging from mild reactions such as chest tightness, fever, and headache to severe reactions such as anaphylaxis. No infectious related adverse events were observed.

Conclusions: This study highlights both the varied indications for which RTX was prescribed and the need for vigilance concerning infusion-related adverse events. It underscores the importance of close monitoring and appropriate management to ensure the safety of RTX therapy in pediatric patients. Further research is warranted to optimize treatment strategies and enhance patient outcomes in this population.

Keywords: Rituximab (RTX); autoimmune diseases; immunity; pediatrics; safety

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Introduction

In the pathogenesis of autoimmune diseases, a critical role is played by B cells, which are involved in antigen presentation, cytokine production, and the generation of autoantibodies (1). Therefore, depleting B cells has been considered a therapeutic approach for disrupting key components of the autoimmune response and treating autoimmune diseases (2).

Rituximab (RTX) is a chimeric monoclonal antibody that targets the CD20 protein, a cell surface antigen specific to B cells (3). Originally developed for treating B-cell lymphomas (4). RTX has since shown significant therapeutic potential in managing various immune-mediated diseases, including rheumatoid arthritis, systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, immune thrombocytopenic purpura (ITP), autoimmune hemolytic anemia, nephrotic syndrome, and humoral rejection in kidney transplant cases (5-9). Even though it is generally well tolerated, RTX can cause various adverse events, including infusion-related reactions, infections, and hypogammaglobulinemia. While an increased risk of infection has been documented, it is typically considered minor to moderate (10). The formation of anti-drug antibodies may compromise both the effectiveness and safety of the treatment (11). Studies indicate that although there may be an initial positive response to RTX, the development of anti-drug antibodies could play a crucial role in the subsequent loss of efficacy during retreatment (12). Additionally, it may also predict the likelihood of infusion reactions with subsequent treatments (13). However, this information could not be involved in our study, as it is not available in our center. The safety of such drug is not well studied in our region. We conducted a single-center retrospective study to review the uses and safety of RTX in autoimmune diseases in the pediatric population. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-233/rc).

Highlight box

Key findings

- We contribute additional insights into the literature on the indications and safety profile of rituximab in pediatric patients.

What is known and what is new?

- Rituximab is prescribed for various autoimmune conditions; the frequent occurrence of infusion-related adverse events underscores the need for careful monitoring and appropriate management of adverse events, including allergic reactions, during treatment.
- While there are studies on the pathophysiology and management of infusion-related reactions, our study aims to contribute additional insights into these adverse events, which can help healthcare providers anticipate and manage potential complications.

What is the implication, and what should change now?

- Close monitoring for infusion-related adverse events is important during rituximab therapy in pediatric patients to ensure safety and effective management.

Methods

Study design and setting

This retrospective study included pediatric patients aged 18 years or younger who received at least one RTX infusion therapy for autoimmune diseases during the period from January 2013 to March 2023 in the Department of Pediatrics at King Abdulaziz University Hospital in Jeddah, Saudi Arabia.

Data collection

Patients' data were extracted from medical records, including demographics (age and sex), RTX indication, date of diagnosis, date of the first dose of RTX administration, dosage, treatment protocol, preinfusion prophylaxis, details of the first-line treatment along with its dosage and administration date, concurrent immunomodulatory agents, tests conducted for potential viral and bacterial reactivation syndromes, and whether the patient received an additional RTX infusion after one treatment cycle. A new cycle was defined as one starting after a 4-week period without any RTX infusion. A manual review was conducted on the notes relating to RTX infusions and associated adverse events along with the corresponding management used. Severity of reactions was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (14).

Anaphylaxis was defined according to the criteria set forth by the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network (15).

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows (IBM Corp. Released 2011. IBM

Table 1 Demographics and clinical characteristics of patients at the time of the first rituximab infusion

Characteristics	Value (n=22)
Gender, n (%)	
Male	11 (50.0)
Female	11 (50.0)
Diagnosis (indication of rituximab), n (%)	
Nephrotic syndrome	8 (36.4)
SLE	6 (27.3)
ITP	2 (9.1)
Myasthenia gravis	2 (9.1)
NMOSD	1 (4.5)
Anti-NMDAR encephalitis	1 (4.5)
Transverse myelitis	1 (4.5)
Autoimmune haemolytic anemia	1 (4.5)
Age at diagnosis, years	
Mean ± SD	7.86±4.85
Range	1–18
Age at fist dose of rituximab, years	
Mean ± SD	9.30±5.20
Range	1–18
Duration between diagnosis and rituximab administration, months	
Median (IQR)	5.50 (28.8)

SLE, systemic lupus erythematosus; ITP, immune thrombocytopenic purpura; NMOSD, neuromyelitis optica spectrum disorder; anti-NMDAR, anti-N-methyl-D-aspartate receptor; SD, standard deviation; IQR, interquartile range.

SPSS Statistics for Windows, version 21.0; IBM Corp., Armonk, NY, USA). Normal distribution was assessed using histograms and the Shapiro-Wilk test. Descriptive statistics were expressed using means and standard deviations for normal distribution quantitative variables and median [interquartile range (IQR)] for non-normal variables. Categorical variables were presented in numbers and percentages. Bivariate analysis was conducted using the Chi-squared test or Fisher's exact test for qualitative variables with expected cell counts below 5. For normally distributed quantitative variables, the independent sample *t*-test was applied, while the Mann-Whitney *U* test was used for non-normally distributed variables. A P value of less than 0.05 was considered statistically significant.

Ethical statement

The study was approved by the Research Ethics Committee of the Faculty of Medicine at King Abdulaziz University in Jeddah, Saudi Arabia (No. 119-23), individual consent for this retrospective analysis was waived. The study was conducted under the guiding principles of the World Medical Association Declaration of Helsinki (as revised in 2013).

Results

Clinical characteristic

We reviewed 22 patients, with an equal distribution between males and females. The mean age at diagnosis was 7.86±4.85 years (range, 1–18 years), and the mean age at the first dose of RTX administration was 9.30±5.20 years (range, 1–18 years). The median duration between diagnosis and RTX administration was 5.5 months (IQR =28.8 years; range, 0–89 years). RTX was prescribed for eight different indications. The most prevalent single indication was nephrotic syndrome with a presumed autoimmune etiology, constituting 36.4% of cases, followed by SLE at 27.3%. Other indications included haematological diseases including autoimmune haemolytic anemia, and ITP, as well as neurological conditions like myasthenia gravis, neuromyelitis optica spectrum disorder (NMOSD), anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, and transverse myelitis (*Table 1*).

RTX infusions details

All patients received the standard premedications: acetaminophen (10 mg/kg/dose, maximum 50 mg/dose), diphenhydramine (1 mg/kg/dose), and corticosteroids (4 mg/kg, maximum 100 mg). The most commonly used protocol involved administering 2 infusions of 375 mg/m^2 each, given 2 weeks apart. Moreover, 59.1% of patients received additional dose of RTX after one cycle of treatment. *Table 2* shows the RTX infusions details.

First line and concurrent medications

RTX was used as the second-line treatment for all patients, with corticosteroids employed as the first-line treatment in 86.4% of cases. Intravenous immunoglobulin (IVIG) was the primary therapy for three patients, including two diagnosed with ITP and one with SLE. Additionally, plasmapheresis was performed concurrently with

Table 2 Rituximab infusions details

Rituximab courses	Number (%)
Rituximab administration protocols	
375 mg/m^2, 2 doses separated by 2 weeks	20 (90.9)
375 mg/m^2, 4 weekly rituximab infusions over 1 month	2 (9.1)
Additional rituximab infusion after one cycle of treatment	
Yes	13 (59.1)
No	9 (40.9)

Table 3 First line and concurrent medications

Medications	Number (%)
First line treatment	
Corticosteroids	19 (79.2)
IVIG	3 (12.5)
Plasmapheresis	2 (8.3)
Concurrent immunosuppressive therapy	
Corticosteroids	9 (42.8)
IVIG	7 (33.3)
Azathioprine	2 (9.5)
Mycophenolate mofetil	1 (4.8)
Cyclophosphamide	1 (4.8)
Cyclosporin	1 (4.8)

IVIG, intravenous immunoglobulin.

corticosteroids for two patients diagnosed with transverse myelitis and NMOSD. Concomitant medications with RTX included corticosteroids (40.9%), IVIG (31.8%), azathioprine (9.1%), mycophenolate mofetil (4.5%), cyclophosphamide (4.5%), and cyclosporin (4.5%) as outlined in *Table 3*.

Infusion and infectious related adverse events

Table 4 shows the infusion related adverse events and its severity. A total of 21 infusion reactions were observed in seven patients. The most prevalent reactions included chest or throat tightness (n=5), fever (n=4), anaemia (n=3), headache (n=2), and skin rash (n=2). Out of these

Table 4 Infusion related adverse events of rituximab

Adverse event	Number (%)
Grade of infusion related adverse events	
Grade 1	12 (57.1)
Grade 2	7 (33.3)
Grade 3	1 (4.8)
Grade 4	1 (4.8)
Grade 5	0
Symptoms	
Chest or throat tightness	5 (23.8)
Fever	4 (19.0)
Anaemia	3 (14.2)
Headache	2 (9.5)
Skin rash	2 (9.5)
Tachycardia	1 (4.8)
Hypertension	1 (4.8)
Neutropenia	1 (4.8)
Thrombocytopenia	1 (4.8)
Anaphylactic reaction	1 (4.8)

reactions, six required treatment involving acetaminophen, diphenhydramine, and/or corticosteroids. The remaining reactions were resolved by temporarily discontinuing the infusion. One patient experienced a grade 3 reaction with tachycardia and elevated blood pressure, which required discontinuing the infusion for over an hour and administering nifedipine, acetaminophen, diphenhydramine, and corticosteroids. A patient with SLE experienced anaphylactic reactions (grade 4), which were effectively managed by discontinuing the infusion and administering epinephrine, hydrocortisone, and antihistamines. No infectious-related adverse events were observed during a median follow-up of 3 years (range, 0.9 to 9 years) after the initial RTX infusion.

In bivariate analysis, there was no statistically significant difference between patients who experienced adverse events and those who did not regarding gender, diagnosis, age at diagnosis, age at first dose of RTX, duration between diagnosis and RTX administration, first-line treatment, and concurrent immunosuppressive therapy.

Discussion

Recent data updates indicate that RTX treatment for persistent autoimmune diseases has improved in effectiveness and safety. However, research on RTX efficacy in treating autoimmune conditions in pediatric populations remains comparatively limited, with existing studies primarily focusing on hematological conditions (16).

In the present study, the mean age at diagnosis and initial RTX treatment fell within the range of 8–9 years, suggesting that RTX is commonly administered at a relatively young age. This finding in our research aligns with a previous study involving pediatric patients with neurological conditions, where the median age of symptom onset was approximately 7.8 years, and the first RTX therapy occurred around 8.9 years (10). However, other studies reported older ages, with a median age at first dose of 14.3 years (17). Additionally, in another study, the mean age at disease onset was 11 years, with an average treatment age of 16 years (16).

The duration between diagnosis or the onset of the disease to the start of the RTX infusion is considered significantly fundamental, with considerable variation noted across studies. In our study, we found that the median duration from diagnosis to RTX administration was nearly 6 months. This suggests that RTX is often prescribed after other treatment options have been tried or when the disease is more advanced.

In our study, RTX was prescribed for eight different indications, with nephrotic syndrome (36.4%) being the most frequent indication, followed by SLE (27.3%). This distribution closely resembled findings from a retrospective cohort study that involved 468 patients receiving RTX for over 25 indications, where the most common indications for RTX were SLE (26.5%), nephrotic syndrome (13.0%), autoimmune encephalitis (9.0%), and lymphoma (6.4%) (17).

Additionally, 59% of patients received an additional dose of RTX, indicating that multiple doses were often necessary for treatment effectiveness.

Our study underscores the potential for infusion-related adverse events associated with RTX treatment in pediatric patients, revealing occurrences of mild to moderate reactions such as chest tightness, fever, anaemia, headache, and rash, along with one severe reaction resulting in anaphylaxis. Significantly, among the 22 patients who received RTX, 7 encountered infusion-related adverse events, resulting in an incidence rate of 31.8%. The findings align with those of a prior retrospective study involving 282 infusions among 67 pediatric patients, revealing a 40% incidence of infusion-related reactions during the initial infusion of each treatment cycle (18). Our results corroborate this trend emphasizing the need for careful monitoring during the initial treatment stages to ensure both patient safety and comfort. Furthermore, the same retrospective study noted only three cases of grade 3 reactions, with no instances of grade 4 or higher reactions recorded. Notably, the risk of infusion-related reactions markedly decreased to 2.7% in subsequent doses (18), suggesting a potential adaptation or tolerance development to RTX infusion over the course of treatment. These findings collectively indicate a generally manageable profile of infusion-related adverse events associated with RTX treatment in pediatric patients.

Our study is subject to certain limitations. Firstly, the small sample size, comprising only 22 pediatric patients, may restrict the generalizability of the findings to a larger population. This small number might be reflected by the unavailability of the medication at certain time as well as the lack of eligibility for some patients. Secondly, the retrospective records review design of the study introduces the possibility of incomplete or inaccurate documentation.

Conclusions

Overall, the findings of the study provide important information on the indications and safety of RTX in pediatric patients. The results suggest that RTX is being prescribed for various autoimmune conditions. However, the occurrence of infusion-related adverse events highlights the need for careful monitoring and appropriate management during RTX treatment. Understanding and identifying these adverse events can help healthcare providers anticipate and address potential complications during RTX administration. Further research is warranted to optimize treatment strategies, identify potential risk factors for adverse events, and enhance the safety of RTX in pediatric patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-233/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-233/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-233/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Research Ethics Committee of the Faculty of Medicine at King Abdulaziz University in Jeddah, Saudi Arabia (No. 119-23), individual consent for this retrospective analysis was waived. The study was conducted under the guiding principles of the World Medical Association Declaration of Helsinki (as revised in 2013).

References

1. Schett G, Nagy G, Krönke G, et al. B-cell depletion in autoimmune diseases. Ann Rheum Dis 2024;83:1409-20.
2. Furman MJ, Meuth SG, Albrecht P, et al. B cell targeted therapies in inflammatory autoimmune disease of the central nervous system. Front Immunol 2023;14:1129906.
3. Mostkowska A, Rousseau G, Raynal NJ. Repurposing of rituximab biosimilars to treat B cell mediated autoimmune diseases. FASEB J 2024;38:e23536.
4. Techa-Angkoon P, Siritho S, Tisavipat N, et al. Current evidence of rituximab in the treatment of multiple sclerosis. Mult Scler Relat Disord 2023;75:104729.
5. Thiel J, Rizzi M, Engesser M, et al. B cell repopulation kinetics after rituximab treatment in ANCA-associated vasculitides compared to rheumatoid arthritis, and connective tissue diseases: a longitudinal observational study on 120 patients. Arthritis Res Ther 2017;19:101.
6. Gkogkolou P, Ehrchen J, Goerge T. Severe antiphospholipid antibody syndrome - response to plasmapheresis and rituximab. J Dermatolog Treat 2017;28:564-6.
7. Sanz I. Systemic lupus erythematosus: Extent and patterns of off-label use of rituximab for SLE. Nat Rev Rheumatol 2016;12:700-2.
8. Jellouli M, Charfi R, Maalej B, et al. Rituximab in The Management of Pediatric Steroid-Resistant Nephrotic Syndrome: A Systematic Review. J Pediatr 2018;197:191-197.e1.
9. Ruggenenti P, Ruggiero B, Cravedi P, et al. Rituximab in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. J Am Soc Nephrol 2014;25:850-63.
10. Nguyen AT, Cotteret C, Durrleman C, et al. Indications and Safety of Rituximab in Pediatric Neurology: A 10-Year Retrospective Study. Pediatr Neurol 2022;137:41-8.
11. Strand V, Goncalves J, Isaacs JD. Immunogenicity of biologic agents in rheumatology. Nat Rev Rheumatol 2021;17:81-97.
12. Md Yusof MY, Shaw D, El-Sherbiny YM, et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. Ann Rheum Dis 2017;76:1829-36.
13. Wincup C, Menon M, Smith E, et al. Presence of anti-rituximab antibodies predicts infusion-related reactions in patients with systemic lupus erythematosus. Ann Rheum Dis 2019;78:1140-2.
14. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Published November 27, 2017. Accessed August 14, 2024. Available online: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
15. Anagnostou K. Anaphylaxis in Children: Epidemiology, Risk Factors and Management. Curr Pediatr Rev 2018;14:180-6.
16. El-Hallak M, Binstadt BA, Leichtner AM, et al. Clinical effects and safety of rituximab for treatment of refractory pediatric autoimmune diseases. J Pediatr 2007;150:376-82.
17. McAtee CL, Lubega J, Underbrink K, et al. Association

of Rituximab Use With Adverse Events in Children, Adolescents, and Young Adults. JAMA Netw Open 2021;4:e2036321.
18. Legeay C, Bittencourt H, Haddad E, et al. A Retrospective Study on Infusion-Related Reactions to Rituximab in a Heterogeneous Pediatric Population. J Pediatr Pharmacol Ther 2017;22:369-74.

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