A Retrospective Study on Infusion-Related Reactions to Rituximab in a Heterogeneous Pediatric Population

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OBJECTIVES To assess risks and outcomes of infusion-related reactions to rituximab in a heterogeneous pediatric population.

METHODS All patients who received rituximab between July 2010 and July 2012 were retrieved from the pharmacy software and included for analysis. Data were collected according to 4 categories: demographic data, infusion data, infusion-related reactions, and biological data considered as risk factors (i.e., absolute lymphocyte count, lactate dehydrogenase levels).

RESULTS Sixty-seven patients treated for a total of 17 different indications were included. A total of 282 rituximab infusions were administered. Forty-three, mostly grade 1 or 2, infusion-related reactions occurred in 30 patients. Reactions occurred in 39.2% “first-dose” infusions, but this rate dropped drastically to 2.7% in subsequent doses. In multivariate analysis, high absolute lymphocyte count was the only risk factor for infusion-related reaction (OR = 1.03; 95% CI: 1.01–1.06; $p = 0.014$).

CONCLUSIONS Rituximab infusion-related reactions in a heterogeneous pediatric population were frequent on first infusion, but rare in subsequent ones. Overall, these reactions were mild and manageable through pharmacological treatment. Patients with an elevated absolute lymphocyte count before infusion were at greater risk for an infusion-related reaction.

ABBREVIATIONS ALC, absolute lymphocyte count; IRR, infusion-related reaction

KEYWORDS hematology; immunology; infusion reactions; pediatric; rituximab

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Introduction

Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen on the B lymphocyte's surface. This treatment is associated with a high risk of infusion-related reaction (IRR) on first administration (up to 77%). The risk decreases with each subsequent infusion.¹ Most of these reactions are mild and transient, but up to 7% of grade 3 or 4 reactions have been reported at first infusion.¹ Rituximab has been widely used over the last few years in children. In our pediatric institution, the number of doses administered over the last 8 years has increased from 27 doses in 10 patients in 2004 to 153 doses in 46 patients in 2012. The manufacturer recommends a slow rate of administration in order to prevent an IRR.¹ These recommendations put a heavy strain on hospital resources, patient comfort, and quality of life. However, in adult practice, rapid-infusions of rituximab have been implemented in several settings with substantial savings and good tolerance.² Before implementing such a change of practice in pediatrics, rituximab's tolerance in this population should be assessed. A few studies recently assessed rituximab side effects in specific indications, mainly autoimmune diseases, such as autoimmune hemolytic anemia, ne-

phrotic syndrome, and others.^{3–6} Rituximab seems well tolerated in most pediatric indications, with the main side effect being IRRs. Nonetheless, data are missing on rituximab's tolerance in a large heterogeneous pediatric population treated for rare diseases.

We aimed to describe IRRs in a heterogenic pediatric population, through their incidence, severity, and treatment. A secondary objective was to investigate risk factors for IRR with rituximab in our institution.

Materials and Methods

This was a retrospective descriptive study. We included all patients who received rituximab over a 2-year period from July 1, 2010, to July 1, 2012, in a pediatric hospital without limits of age. Patients were identified through pharmacy's software. Data were collected on patient characteristics (i.e., age, weight, height), rituximab indication, premedications, rituximab infusions (i.e., infusion rate, dose, number of doses), IRR (i.e., type of reaction, treatment of reaction, duration of interruption of infusion), and potential biological risk factors for an IRR (i.e., absolute lymphocyte count [ALC] and lactate dehydrogenase blood levels) before treatment.⁷

Table 1. Demographics for Patients Treated With Rituximab (N = 67)

Demographic data	Results
Age, yr*	13.2 (0.75–21)
Sex, male†	35 (52.2%)
Weight at first infusion, kg*	41 (7.5–120.0)
Dosage, mg/m ² *	373.0 (213.2–745.9)
Indication for rituximab‡	
Autoimmune†	39 (58.2)
Juvenile idiopathic arthritis	6 (8.7)
Autoimmune hemolytic anemia	6 (8.7)
Immune thrombocytopenic purpura	5 (7.2)
Host versus graft reaction	5 (7.2)
Alloimmunization	3 (4.3)
Graft versus host reaction	2 (2.9)
Myasthenia gravis	2 (2.9)
Chronic inflammatory demyelinating polyneuropathy	2 (2.9)
Systematic lupus erythematosus	2 (2.9)
Inflammatory colitis	1 (1.4)
Churg-Strauss vasculitis	1 (1.4)
Autoimmune deficiency	1 (1.4)
Guillain-Barre disease	1 (1.4)
Pemphigus	1 (1.4)
Undefined (autoimmune strongly suspected)	1 (1.4)
Oncology	24 (35.8)
EBV-induced lymphoproliferation	17 (24.6)
Lymphoma	7 (10.1)
Nephrotic syndrome	6 (8.7)

EBV, Epstein-Barr Virus

* Median (range).

† No. (%).

‡ Two patients received rituximab for 2 different indications at different times: 1 patient for pemphigus and Guillain-Barré disease and another one for EBV-induced lymphoproliferation and autoimmune hemolytic anemia.

Consultation of patients' records was approved by the hospital Ethics Board.

In our institution, during this study, rituximab was diluted in 0.9% sodium chloride at a final concentration of 2 mg/mL and administered according to the manufacturer's (Genentech/Roche, San Francisco, CA) recommendations.¹ First infusion started at a rate of 0.5 mg/kg/hr (maximum 50 mg/hr) for 1 hour. The rate was then increased by 0.5 mg/kg/hr (maximum 50 mg/hr) every 30 minutes up to a maximum of 400 mg/hr. This administration pattern will be referred to as "first dose rate" and was applied for every first infusion of a new cycle. A new cycle was defined as a cycle starting after a 4-week period without rituximab infusion. If an IRR occurred during first infusion, subsequent infusion was administered at the same rate. When an infusion was well tolerated, subsequent infusion was administered

at a rate of 1 mg/kg/hr (maximum 100 mg/hr) for 1 hour. The rate was then increased by 1 mg/kg/hr (maximum 100 mg/hr) every 30 minutes up to a maximum of 400 mg/hr. This administration pattern will be referred to as "subsequent dose rate."

Standard premedications included intravenous diphenhydramine (1 mg/kg/dose, maximum 50 mg/dose) and oral acetaminophen (10 mg/kg/dose, maximum 650 mg/dose). Corticosteroids were not included within that standard regimen. Physicians could prescribe corticosteroids based on previous tolerance to rituximab.

Severity of reactions was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03⁸ through record review by author CL. Any doubts about severity of an IRR were discussed with all authors until consensus was found. A "brief interruption of infusion" was defined as an

Table 2. Rituximab Infusions and Infusion-Related Reactions

	N	No. of reactions (%)
Patients	67	30 (44.8)
Infusions	282	43 (15.2)
First doses of a new cycle	97	38 (39.2)
Subsequent doses	185	5 (2.7)
Grade of infusion-related reaction		
1	17	
2	23	
3	3	
4 or 5	0	
Dosage, mg/m ²		
375	242 (74 first doses)	36 (14.9)
500	18 (11 first doses)	4 (22.2)
< 375	12 (7 first doses)	3 (25.0)
> 500	10 (5 first doses)	0 (0.0)

interruption that would last less than 1 hour. Thus, any reaction causing an interruption beyond 1 hour would be considered grade 3 or higher.

Confidence limits were calculated according to Clopper-Pearson exact test. Univariate and multivariate regression analysis were performed to identify risk factors associated with IRR. All variables with a $p < 0.20$ in univariate analysis were included in the multivariate model. All statistical tests were performed using SPSS 19.0 software (Statistical Package for the Social Sciences, Chicago, IL). A p value < 0.05 was considered significant.

Results

Population Characteristics. We assessed 282 infusions administered to 67 patients (35 males). Demographic data are summarized in Table 1. Ninety-seven infusions were administered in an outpatient ward.

Rituximab was prescribed in 17 different indications. Autoimmune diseases represented 58.2% of indications. The most frequent single indication was Epstein Barr Virus reactivation/Epstein Barr Virus-induced lymphoproliferative disorder (24.6%) followed by lymphoma (10.1%), nephrotic syndrome (8.7%), and juvenile idiopathic arthritis (8.7%).

Dosage ranged from 200 mg/m² to 750 mg/m² and more than 85% of the infusions were administered as a 375-mg/m² dosage protocol.

Infusion-Related Reactions. We observed 43 reactions in 30 patients. Infusion data, IRR characteristics, and assessment of risk factors for IRRs are summarized in Table 2. Thirty-eight of IRRs (88.3%) occurred during first dose of a cycle. There was a 39.2% (95% CI: 29.4–49.6) chance for a patient to experience an IRR during a first infusion. Five (2.7%) subsequent infusions

resulted in an IRR (grade 1 or 2).

Univariate and multivariate analysis on factors associated with IRR are presented in Table 3. Higher ALC count was associated with IRR risk, but lactate dehydrogenase levels were not. Premedication with corticosteroids was not protective against IRR. Infusion-related reaction symptoms are summarized in Table 4.

Twenty-seven of these reactions required treatment with acetaminophen, diphenhydramine, and/or corticosteroids. The other 16 reactions responded to a short discontinuation of infusion. There were three grade 3 reactions, managed through discontinuation of the infusion, and intravenous corticosteroids. Symptoms resolved within 2 hours maximum and no subjects required transfer to an intensive care unit. Median time of infusion interruption following an IRR was 39 minutes (range: 0–120 minutes). In the event of an IRR, subsequent infusions were well tolerated. One infusion was definitively stopped because of IRR recurrence even after symptomatic treatment. It was the final dose of a cycle in a patient who was not rechallenged. Beside this case, there was no interruption in rituximab treatment after an IRR. The main treatment for those reactions was intravenous corticosteroids.

Discussion

In this study, we found a 40% risk of IRR with the first infusion of any cycle. This rate dropped to 2.7% in subsequent doses. We observed only three grade 3 and no grade 4 or higher reactions after assessing 282 infusions in 67 patients. Reactions responded rapidly with symptomatic treatment with acetaminophen, corticosteroids, and diphenhydramine. We found significantly more IRRs at a “first dose rate” than at a

Table 3. Factors Associated With Infusion-Related Reactions in Univariate and Multivariate Analysis

Variable assessed	IRR	No IRR	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Sex						
Male (n)	21	115	1.0	0.93		
Female	22	124	(0.92–1.09)			
Dosage, mg/m ²						
Median	373.0	373.1	1.00	0.61		
Mean (range)	381.8 (303.1–506.9)	387.5 (213.2–746.0)	(1.00–1.00)			
Age at first infusion, yr						
Median	13.0	13.7	1.00	0.33		
Mean (range)	11.2 (1.8–17.6)	12.3 (0.7–20.7)	(0.99–1.00)			
Cycle						
First dose	38	59	0.68	< 0.001*	0.67	< 0.001*
Second dose	0	76	(0.61–0.74)*		(0.59–0.76)*	
First dose	37	59	0.71	< 0.001†	0.70	< 0.001†
Subsequent dose	5	180	(0.65–0.77)†		(0.61–0.79)†	
Premedication with corticosteroids						
Yes	3	23	0.96	0.58		
No	40	216	(0.83–1.11)			
Absolute lymphocyte count before infusion, G/L						
Median	2.8	1.5	1.05	< 0.001	1.03	0.014
Mean (range)	3 (0.5–8.4)	1.9 (0.1–9.7)	(1.02–1.08)		(1.01–1.06)	
Lactate dehydrogenase level before infusion, units/L						
Median	244	265	1.00	0.81		
Mean (range)	306 (179–557)	293 (92–966)	(1.00–1.00)			

IRR, infusion-related reaction

* Comparison of first dose to second dose.

† Comparison of first dose to subsequent dose.

“subsequent dose rate.” Reactions to rituximab on a first dose were not predictive of further reactions with subsequent doses. As previously reported in adults,⁹ rituximab toxicity did not correlate with dosage administered. However, IRRs were associated with a higher ALC as reported in adults.⁷

IRRs are the main adverse effect of rituximab, they can be severe in rare cases and should not be ignored.¹⁰ Rituximab binding to CD20 triggers a direct apoptosis pathway, complement-mediated toxicity, and antibody-dependent cytotoxicity through the recruitment of various effector cells (natural killer cells, granulocytes, macrophages).¹¹ These reactions, combined with lymphocyte lysis, provoke a cytokine release likely responsible for the symptoms observed in IRRs to rituximab.¹² A slow rate of administration with a progressive increase in infusion flow can prevent this adverse event.¹ However, these lengths of infusion combined with the increased use of rituximab put a burden on both patients and hospital resources. In adult practice, many centers now apply a “rapid-infusion” protocol for rituximab.

One of these protocols was recently approved by the US Food and Drug Administration in adults.¹³ Numerous studies in adult populations have recently assessed the safety of a “rapid-infusion” of rituximab over 90 minutes both in oncology practice and in treating autoimmune diseases.^{2,14–16} Considering the lack of literature on IRR in

Table 4. Infusion-Related Reaction Symptoms

Symptom	No. (%)
Thoracic oppression	13 (22)
Skin rash	12 (20)
Hyperthermia	8 (13)
Pain	8 (13)
Vomiting	6 (10)
Respiratory problems	6 (10)
Nausea	3 (5)
Hypotension	2 (3)
Chills	2 (3)

Table 5. Comparative Durations of a Rituximab Cycle Between a Rapid-Infusion Protocol and Original Protocol

	Original protocol		Rapid-infusion protocol	
	Patient presenting an IRR	Patients not presenting an IRR	Patient presenting an IRR	Patients not presenting an IRR
IRR at first dose, %	40	60	40	60
Dose, hr				
First	6	6	6	6
Second	6	3.5	6	1.5
Third	3.5	3.5	1.5	1.5
Fourth	3.5	3.5	1.5	1.5
Total infusion duration for a cycle	19	16.5	15	10.5

IRR, infusion-related reaction

pediatric populations, we assessed the risk and severity of IRR in a pediatric population. To our knowledge, this is the first study assessing IRRs in a large set of diseases treated with rituximab in a heterogeneous pediatric population. IRRs to rituximab in the present study were frequent at first infusion but not severe, even in rare diseases. They became rare on subsequent infusions. These findings are consistent with IRRs described in adult populations in studies comparing “slow” and “rapid” infusions of rituximab.² A rapid-infusion of rituximab protocol would allow substantial beneficial services to patients and pediatric oncology institutes and should be assessed. A recent study assessed such a protocol in a pediatric population treated for autoimmune conditions with success and safety.¹⁷ Twenty-two children, who previously received at least 1 infusion of rituximab using a standard titration protocol, were subsequently treated with rituximab administered over 1 hour. Only 1 mild adverse event (transient rash that resolved spontaneously) occurred in 80 rapid infusions. If a rapid infusion of rituximab protocol² (20% of the dose over 30 minutes and the remaining 80% over 1 hour in absence of an IRR) was applied to the cohort described in our study, substantial savings (4–6 hours per cycle) could be made (Table 5).

The population described mostly suffered from autoimmune diseases for which there were fewer data about rituximab use, especially for some rare diseases (e.g., Guillain-Barré disease, chronic inflammatory demyelinating neuropathy, myasthenia gravis). Overall, rituximab was a safe treatment in these patients and appears to be an option in various rare autoimmune disorders that do not respond to conventional therapies in children.^{18–20}

The present study has various limitations. First, the heterogeneity of the assessed population did not allow for subgroup analysis by underlying disease. We also did not have enough power to establish a threshold of

ALC associated with IRR. Some of our patients could be considered young adults instead of children since we did not put restrictions on age in our inclusion criteria. This was a single center study and practices described here might not apply to other centers.

In the present study, IRRs to rituximab were mild and became rare after first infusion. Higher ALC is associated with higher risk for IRR. A larger study could determine these risk factors for IRR, and especially for severe IRR. This could help in designing a safe rapid infusion of rituximab protocol for children. As recommended by the US Food and Drug Administration for adults, this protocol should not be applied to patients with a high ALC ($> 5.0 \times 10^9/L$)¹² and never on a first infusion.

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