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Case Report

Successful desensitization to high dose rituximab for a child with nephrotic syndrome – The first report in the literature

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Conflict of Interest
The authors have no financial conflicts of interest.

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ABSTRACT

Rituximab is a chimeric monoclonal antibody, which is mainly used in the treatment of lymphoma and autoimmune disorders, but also has been recently approved for the treatment of nephrotic syndrome. The treatment dose is between 375 mg/m^2 and 750 mg/m^2. Rituximab has been associated with hypersensitivity reactions, which can be classified either into early and late infusion-associated adverse reactions. Different desensitization protocols have been described in adult patients who require rituximab, however, there is a limited experience in children and in patients with nephrotic syndrome. Additionally, all the published protocols for adults and children are based on the low-dose rituximab desensitization. We report the first case in the literature of desensitization to high-dose rituximab in a child with nephrotic syndrome, suggesting a well-tolerated protocol adjusted on the high dose and the clinical reaction to the drug. This protocol can be used for children with nephrotic syndrome and severe reaction that require 750 mg/m^2 of rituximab.

Keywords: Rituximab; High dose; Child; Desensitization; Nephrotic syndrome

INTRODUCTION

Rituximab is a monoclonal antibody used in the treatment of lymphomas and autoimmune disorders [1, 2]. It is also indicated for nephrotic syndrome, although not formally approved [3, 4]. The treatment dose is between 375 mg/m^2 and 750 mg/m^2 [5].

Rituximab is a well-tolerated medication for children with nephrotic syndrome; however, side-effects do present. The commonest side-effect is infusion-associated adverse reaction manifesting with fever, headache, rigor, nausea, vomiting, hypotension, tachycardia, and rash. This reaction is attributed to cytokine release of tumor necrosis factor (TNF)-α and interleukin (IL)-6 [6]. Immediate hypersensitivity IgE-mediated reactions have also been reported [7]. The risk increases with higher doses of rituximab and increased comorbidities, for example azathioprine treatment. Death has been reported in approximately 5% of patients [8-10].

Infusion-associated adverse reactions can be prevented with the use of H1-antihistamines, paracetamol, and previously with ranitidine, before commencing the infusion, along

with a slower infusion rate. Where immediate hypersensitivity reactions (HRs) occur, the recommended advice is avoidance of the medication or desensitization if there is no alternative drug. We report the first case in the literature of successful desensitization to high dose rituximab for a child with nephrotic syndrome.

CASE REPORT

A 10-year-old girl was referred to the pediatric allergy team for rituximab desensitization.

Rituximab therapy at a dose of 375 mg/m^2 had been tried previously. When the patient was given the initial infusion of rituximab, despite full pretreatment, the 3rd increase in the infusion rate (3.5 mg/kg/hr) resulted in her reporting throat tightness. The infusion was paused and symptoms resolved spontaneously. The infusion was then restarted at the previous uneventful slower rate, remaining at that rate for the remainder of the infusion. The following night she complained of severe headache resembling migraine, but this resolved.

The renal team decided to treat the patient with higher 750 mg/m^2 dose. When the patient presented for the second rituximab infusion using the higher dose of 1,110 mg (weight, 52 kg; body surface area [BSA], 1.45 m^2), she was premedicated with oral paracetamol, intravenous chlorphenamine, methylprednisolone, and hydrocortisone. The rituximab infusion was stopped at 34 mL/hr due to symptoms of throat pruritus, tongue swelling, difficulty breathing, and wheeze. The reaction was treated with oral H1-antihistamine medication and intravenous hydrocortisone. Decision was made to discontinue the infusion and desensitize the patient.

The allergy team chose to perform a 15-step desensitization protocol consisting of 3 solutions; dilutions of 1:100, 1:10, 1:1 to administer a total dose of 1,120 mg (weight, 54 kg; BSA, 1.49 m^2) (**Table 1**).

Table 1. Desensitization protocol to rituximab

Stock solution	Dilution	Volume	Fluid volume to be removed	Volume of Rituximab to be added	Final concentration
A	1/100	250 mL	Nil	1 mL (10 mg)	0.04 mg/mL
B	1/10	250 mL	10 mL	10 mL (100 mg)	0.4 mg/mL
C	1/1	250 mL	100 mL	100 mL (1,000 mg)	4 mg/mL

Step	Solution	Rate	Time per step	Volume per step	Dose/step	Cumulative dose
1	A	2 mL/hr	15 min	0.5 mL	0.02 mg	0.02 mg
2	A	4 mL/hr	15 min	1 mL	0.04 mg	0.06 mg
3	A	10 mL/hr	15 min	2.5 mL	0.1 mg	0.16 mg
4	A	20 mL/hr	15 min	5 mL	0.2 mg	0.36 mg
5	B	4 mL/hr	15 min	1 mL	0.4 mg	0.76 mg
6	B	10 mL/hr	15 min	2.5 mL	1 mg	1.76 mg
7	B	20 mL/hr	15 min	5 mL	2 mg	3.76 mg
8	B	40 mL/hr	15 min	10 mL	4 mg	7.76 mg
9	C	10 mL/hr	15 min	2.5 mL	10 mg	17.76 mg
10	C	20 mL/hr	15 min	5 mL	20 mg	37.76 mg
11	C	40 mL/hr	15 min	10 mL	40 mg	77.76 mg
12	C	60 mL/hr	15 min	15 mL	60 mg	137.76 mg
13	C	80 mL/hr	15 min	20 mL	80 mg	217.76 mg
14	C	160 mL/hr	15 min	40 mL	160 mg	377.76 mg
15	C	160 mL/hr	70 min	185.5 mL	742 mg	1,120 mg

Total drug dose: 1,120 mg (Truxima 10 mg/mL).
Premedication: oral cetirizine 10 mg, oral paracetamol 500 mg, and intravenous methylprednisolone 90 mg approximately 30 minutes prior to commencing the desensitization infusion. In addition, she received 2 doses of montelukast, 5 mg the night before and 5 mg on the morning of the procedure.

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The patient was premedicated with oral cetirizine, paracetamol, and intravenous methylprednisolone. Additionally, she received 2 doses of montelukast, 5 mg the night before and on the morning of the procedure.

The patient did not report any symptoms and was discharged following 2 hours observation after the end of the infusion.

DISCUSSION

To our knowledge, this is the first successful desensitization of a pediatric patient to the high 750 mg/m^2 dose of rituximab required for the management of nephrotic syndrome.

From previous studies, the incidence of HRs to rituximab is 25%–78% [11]. Early infusion-associated adverse reactions (EIAR) such as fever, rigors, nausea, vomiting, hypotension, rhinitis, bronchoconstriction, angioedema, urticaria, and flushing can be caused by an IgE-mediated mechanism or cytokine release syndrome and production of TNF-α and IL-6 [12]. The late infusion-associated adverse reactions may be similar to the EIAR, but also include serum sickness, Stevens-Johnson syndrome, toxic epidermal necrolysis [13]. Our patient has developed symptoms consistent with EIAR. Symptoms from the respiratory system have been reported by up to 60% of patients who receive rituximab infusion [11].

Our team did not perform skin-prick testing (SPT) or intradermal testing (IDT) as there was urgency for patient to receive the infusion and symptoms were consistent with IgE-mediated reaction. The relevance of SPT/IDT in the management of rituximab hypersensitivity is still under investigation [14]. A recent study demonstrated that the status of the SPT and/or IDT did not correlate with desensitization outcome [11].

Previous studies have published desensitization protocols for children with lymphoproliferative syndrome, opsoclonus myoclonus, and B-cell lymphomas [15, 16]. The cumulative dose in these studies varied from 285–600 mg. One study has included an adolescent with steroid-sensitive nephrotic syndrome, who needed the standard 375-mg/m^2 dose [16].

We have created a protocol using 15 steps based on the history of a previous severe reaction to rituximab, in accordance with a recently published guideline [17]. The presence of bronchospasm and wheeze is considered as severe reaction. The protocol started at a dilution of 1:50,000 and, comparable with other protocols, the concentration was doubled at each step, with small adjustments for cost-effective medication use. Previous published protocols have suggested that in pediatric rituximab desensitization, the rate steps should not exceed 0.5 mg/kg/hr and the final infusion rate not be greater than 2 mg/kg/hr [16]. Due to practical reasons and size of the overall dose, the final rate was 6.92 mg/kg/hr and the rate increases were more than 0.5 mg/kg/hr but only during the third solution of our protocol, maintaining doubling of doses at each increment. Despite these modifications, the patient tolerated the desensitization. This highlights the application of using standard desensitization recommendations of doubling the dose at each stage should be used for children. It is a practical approach for desensitization to rituximab high dose. Our protocol is in accordance with published pediatric protocols for rituximab using only 3 dilutions irrespective of the number of steps. This is in contrast to the 16-step (4 dilutions) and 20-step (5 dilutions) protocols utilised in adults [15, 16, 18].

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In comparison to other pediatric protocols, the allergy team used montelukast. The use of montelukast may have been beneficial since the patient's reaction had resulted in bronchoconstriction; montelukast can prevent this as seen in studies of asthma [19]. Our team recommends the regular use of montelukast in the desensitization protocol.

We report the first case of desensitization to high dose rituximab in a child with nephrotic syndrome, suggesting a well-tolerated protocol adjusted on the high dose and the clinical reaction to the drug.

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