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Rituximab Desensitization in Pediatric Patients: Results of a Case Series

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Rituximab is a monoclonal antibody (mAb) primarily used to treat oncologic and autoinflammatory conditions. Although hypersensitivity reactions (HSRs) and desensitization protocols to mAbs have been well described in adults, the experience in the pediatric population is very limited. We sought to determine the safety and efficacy of desensitization to rituximab in the pediatric population at our institution. We retrospectively reviewed the experience with HSRs and desensitization to rituximab during a 5-year period in our tertiary care pediatric center, including reaction evaluation, premedication regimens, and desensitization procedures and protocols. A total of 17 desensitizations to rituximab were performed in three patients. A 14-year-old patient underwent successful desensitization to rituximab using a published adult protocol without incident. Two younger patients (ages 7 years and 23 months) experienced significant reactions during initial desensitization attempts. Therefore, we designed a modified desensitization protocol to rituximab, with particular attention to the rate of infusion as mg/kg/h. This new patient weight-based protocol was successfully used in a total of 13 desensitizations in these two patients. Desensitization to rituximab was a safe and effective procedure in our pediatric population. We present a new patient weight-based desensitization protocol for pediatric patients who develop HSRs to rituximab, with particular usefulness for younger pediatric patients and potential utility in pediatric patients with HSRs to other mAbs.

Introduction

Murine and humanized monoclonal antibodies (mAbs) are increasingly used in the treatment of oncologic and autoimmune conditions, which has led to greater awareness of hypersensitivity reactions (HSRs) to these therapeutic agents. Reported reactions to mAbs include urticarial rash, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, and acute respiratory distress.[1] The exact mechanism of HSRs to mAbs is not fully understood.[1–3] While sensitization typically occurs with repeated exposure, there are reports of reactions after the first infusion of mAbs; hence, at least some of the immediate HSRs may be caused by drug-induced cytokine release.[1,4] When treatment options are limited, rapid desensitization, also referred to as temporary induction of tolerance, should be considered to allow for continued use of these drugs in patients with a history of HSRs. While HSRs and desensitization to mAbs have been well described in adults,[1–3] to our knowledge, the experience in children is limited to only two case reports, including only one to rituximab.[5,6] We discuss HSRs and rapid desensitization to rituximab in a tertiary care pediatric center, including reaction evaluation, pretreatment regimens, a successful desensitization protocol, and outcomes. To our knowledge, this is the first report of a series of mAb desensitizations in a pediatric population. Furthermore, we are describing the new concept of modifying desensitization protocols based on the child's weight.

Case Histories

After obtaining institutional review board approval, we conducted a retrospective chart review of pediatric patients undergoing rapid desensitization to rituximab between 2010 and 2015 at the Boston Children's Hospital.

Case 1

A 14-year-old male with X-linked lymphoproliferative disease developed a systemic reaction while receiving rituximab for treatment of granulomatous lymphocytic interstitial lung disease. He had previously received rituximab without incident with acetaminophen and diphenhydramine premedications. The infusion was stopped due to onset of rigors, throat itching, tachycardia, hypotension (blood pressure

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Table 1. Patient Characteristics

Patient	*Agent*	*Age/sex*	*Indication*	*Reaction*	*Reaction severity*[a]	*No. of desensitizations*	*Outcome*
1	Rituximab	14/M	GLILD	5th exposure	Severe	4	Successful
2	Rituximab	7/M	PTLD	4th exposure	Moderate	3	Successful
3	Rituximab	23 months/F	OM	1st exposure	Moderate	10	Successful

Reexposure, reaction occurred after a previously tolerated course.
[a]Brown classification criteria were used to classify reaction severity as mild, moderate, and severe.[8]
GLILD, granulomatous-lymphocytic interstitial lung disease; OM, opsoclonus myoclonus; PTLD, posttransplant lymphoproliferative disease.

93/22), and tachypnea (respiratory rate 30). There was no fever, hypoxia, or hypoxemia noted. Another infusion was attempted with the addition of steroid pretreatment, but he developed urticaria and tachycardia after15 min. The infusion was aborted and future treatments were given through rapid desensitization.

Case 2

A 7-year-old boy with history of orthotopic liver transplant and subsequent posttransplant lymphoproliferative disease received treatment with rituximab, prednisone, and cyclophosphamide. Rituximab infusions were premedicated with acetaminophen and diphenhydramine. The first infusion was uncomplicated, but during the second infusion, he developed a diffuse erythematous rash, which resolved with diphenhydramine. During subsequent infusion, despite premedications with acetaminophen, diphenhydramine, and hydrocortisone, he developed a diffuse erythematous rash, oral pruritus, and cough. The decision was made to perform rapid desensitization for future infusions.

Case 3

A 23-month-old female required treatment with a regimen of rituximab, corticosteroids, and intravenous immune globulin for opsoclonus myoclonus syndrome. During the first infusion of rituximab, the patient developed diffuse hives despite pretreatment with diphenhydramine and dexamethasone. During the next infusion, the patient again developed hives despite premedication with dexamethasone, diphenhydramine, and ranitidine. Treatment was deemed necessary, so future infusions were administered through rapid desensitization.

Desensitization: Procedures, Protocols, and Outcome

All desensitizations occurred in an intermediate care or intensive care unit setting with one-to-one nursing after obtaining informed consent. Rescue medications (intravenous diphenhydramine, intramuscular epinephrine, nebulized albuterol, methylprednisolone, and normal saline) were available at the bedside.

Table 2. Rituximab Desensitization Protocol Initially Attempted in Patient 2

Solution	*Total volume (mL)*	*Drug per bag (mg)*	*Concentration (mg/mL)*
1	250	2.85	0.011
2	250	28.5	0.114
3	250	282.757	1.131

Step	*Solution*	*Rate (mL/h)*	*Rate (mg/kg/h)*	*Time (min)*	*Dose per step (mg)*	*Cumulative dose (mg)*
1	1	1.5	0.0008	20	0.0057	0.0057
2	1	3.75	0.002	20	0.0143	0.02
3	1	7.5	0.004	20	0.0285	0.0485
4	1	15	0.008	20	0.0570	0.1055
5	2	3.75	0.02	20	0.1425	0.248
6	2	7.5	0.05	20	0.285	0.533
7	2	15	0.1	20	0.57	1.103
8	2	30	0.2	20	1.14	2.243
9	3	7.5	0.5	20	2.8276	5.0705
10	3	15	0.9	20	5.6551	10.7257
11	3	22.5	1.4	20	8.4827	19.2084
12[a]	3	30	1.8	20	11.3103	30.5187
13[b]	3	40	2.4	20	15.0804	45.599
14	3	50	3	20	18.8505	64.4495
15	3	60	3.6	20	22.6206	87.0701
16[c]	3	75	4.5	140	97.9299	285

Total infusion time: 440 min. Final infusion rate: 4.5 mg/kg/h.
[a]Subsequent desensitizations.
[b]Second desensitization to complete dose.
[c]Initial desensitization.

Table 3. Patient 3 - Rituximab Desensitization Protocol

Solution		*Total volume (mL)*		*Drug per bag (mg)*		*Concentration (mg/mL)*
1		250		2.06		0.008
2		250		20.6		0.082
3		250		205.189		0.821
Step	*Solution*	*Rate (mL/h)*	*Rate (mg/kg/h)*	*Time (min)*	*Dose per step (mg)*	*Cumulative dose (mg)*
1	1	1	0.0006	15	0.0021	0.0021
2	1	2.5	0.002	15	0.0052	0.0072
3	1	5	0.003	15	0.0103	0.0175
4	1	10	0.006	15	0.0206	0.0381
5	2	2.5	0.02	15	0.0515	0.0896
6	2	5	0.03	15	0.103	0.1926
7	2	10	0.07	15	0.206	0.3986
8	2	20	0.1	15	0.412	0.8106
9	3	5	0.3	15	1.0259	1.8366
10	3	10	0.7	15	2.0519	3.8885
11	3	20	1.3	15	4.1038	7.9922
12	3	30	2	482.5	198.0078	206

Total infusion time: 648 min. Final infusion rate: 2.0 mg/kg/h.

Premedications were based on the well-described frequency of reactions during infusion and/or desensitization to mAbs.[4] Pretreatment regimens were administered 1 h before the start of the desensitization and depending on the clinician's preference and/or patient's history, included two or more of the following agents: H1 antagonist (diphenhydramine or cetirizine), H2 antagonist (ranitidine), corticosteroids (prednisone or methylprednisolone), and/or acetaminophen. In some cases, steroids were included as part of the patient's chemotherapy regimen.

A total of 17 desensitizations to rituximab were performed in three patients (Table 1).

At our institution, rituximab infusion is initiated at 0.5 mg/kg/h and increased every 30 min by 0.5 mg/kg/h until the therapeutic dose is achieved. Desensitization protocols were designed with this in mind.

Patient 1 underwent successful rapid desensitization using the 12-step protocol described for the adult population.[1] In Patient 2, we recognized that if the 12-step protocol were followed, then increases for each step would be higher than 0.5 mg/kg/h. Therefore, in Patient 2, we initially developed an extended 16-step protocol (Table 2). The patient developed throat pruritus and hives in step 16, which did not improve with rate decrease or antihistamines, so the desensitization was aborted. A modified 13-step desensitization protocol was then attempted with slower rate in the final step. The patient developed an urticarial rash during step 13, so diphenhydramine was given and the infusion rate was decreased. The subject tolerated this rate and received the remainder of the dose. For subsequent desensitizations, we used a modified 12-step protocol with a final rate not exceeding 2 mg/kg/h, which was calculated based on the typical infusion rate, as well as the rate to which the patient reacted.

In Patient 3, additional premedications were administered 13 h before (prednisolone, cetirizine, and montelukast) and 7 h before (prednisolone) desensitization. Similar to Patient 2, the desensitization protocol was designed to minimize the rate increase per step to no more than $\sim$0.5 mg/kg/h. The last step had a slower infusion rate of 2 mg/kg/h given the patient's weight and reaction history (Table 3). Using this protocol, the remaining desensitizations were well tolerated.

Discussion

To our knowledge, this is the first case series of desensitization to mAbs in pediatric patients. In addition, we are reporting a successful protocol specifically for the pediatric population, based on the patient's weight, with particular usefulness in younger children.

In two of the three subjects reviewed in this series, HSRs to rituximab occurred with repeated exposure to the drug. This is in contrast with other studies, in which adult subjects experience HSR upon first exposure,[1,4] and consistent with one of the pediatric case reports.[5] It is possible that reactions upon reexposure may be more common in younger patients.

Skin testing was not performed on patients in this case series due to the acute requirement for rituximab infusions after the initial reactions. Reinstituting treatment with mAbs for malignant or autoimmune conditions is often urgent and time sensitive, so skin testing can be difficult to perform due to time limitations. In addition, if the patient's HSR occurred recently, the probability of false negative reactions on skin testing is increased.[2] Despite these limitations, skin testing should be considered in the setting of HSR to mAbs to aid in understanding the mechanism of HSR. Skin testing may aid in the development of the desensitization protocol with positive testing or alternative treatment plan with negative testing.

Obtaining tryptase and/or histamine level immediately following the reaction may be helpful in diagnosing IgE-mediated allergy.[2] Tryptase and/or histamine levels were not obtained by the physicians taking care of our patients during the acute reaction, possibly due to these physicians not being specialized in allergy. Despite this, an IgE-mediated mechanism was suspected, given the immediate nature and the characteristics of the reactions.

While there are no previous reports of rapid desensitization to monoclonal antibodies in the younger pediatric

population, there are two case reports of such procedures in adolescents, one of them describing rituximab desensitization in a 14-year-old, which involved use of the 12-step rituximab protocol described by Brennan et al. with minor modifications.[1,6] The other case report described desensitization to infliximab in a 14-year-old patient using a 13-step protocol. This protocol started at a lower dose than the protocol we described for rituximab (1/1,000,000 compared with our 1/100,000) and tripled the dose in each step instead of doubling the dose.[5] In general, it is preferable that the dose increase for each step of desensitization is no more than a 2-fold increase.[7] Our protocol not only adheres to this concept but also addresses a new concept of adjusting the rate of infusion during desensitization for the patient's weight, which is particularly helpful in younger patients. This differs from the standard adult 12-step desensitization protocol mostly because the infusion rate of the last step is lower related to the lower weight of pediatric patients. This three-bag protocol is also different from the 16 steps (four bags) or 20 steps (five bags), used in adult subjects who react during a 12-step desensitization,[8] not only based on the number of bags but also because of the final lower/patient weight-based infusion rate. For our rapid desensitization protocol, we aimed for rate increases to be no more than ~ 0.5 mg/kg/h. This protocol with the final infusion rate not exceeding 2 mg/kg/h was well-tolerated without any reactions. In young patients with HSRs to mAbs, we recommend this protocol with premedications to decrease chances of reactions during desensitization.

Approximately, one-third of adults undergoing mAb desensitization are reported to have reactions during desensitization. Although most of these reactions are mild, two out of 105 desensitizations described in Brennan's review had serious reactions during desensitization, particularly during the last step with a more rapid infusion rate.[1] If breakthrough reactions occur during desensitization, the reaction severity should be evaluated by the allergist and appropriate steps be taken, which may include one or more of the following: temporarily stopping the infusion, treating the reaction, proceeding after lowering the infusion rate, and/or adding steps to the protocol.[1–3] In the adult population, the use of 16 steps (four bags) or 20 steps (five bags) has been successfully used in subjects who react during a 12-step desensitization.[8] While we report a smaller number of desensitizations, we did have a 100% success rate with no reactions using our protocol, which is likely due to the slower infusion rate of the final step. Therefore, our protocol may be of potential use in some adult patients with a history of hypersensitivity to mAbs who have failed previously established desensitization protocols.

We report the first case series of rapid desensitization to rituximab in a pediatric population using a successful and well-tolerated protocol, modified based on the patient's weight. This protocol should be considered in pediatric patients who have HSRs to mAbs, particularly in younger children.

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Author Disclosure Statement

No competing financial interests exist.

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