DOI: 10.7860/JCDR/2019/38080.12821

Case Report

Paediatrics Section

Successful Rapid Desensitization of Two Teenagers with Rituximab Hypersensitivity

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ABSTRACT

Rituximab is one of the monoclonal antibodies that is used in the management of malignancies and auto-inflammatory disorders. Rituximab causes Hypersensitivity Reactions (HSRs) during infusions. The delay of treatment or loss of a highly efficient drug can be prevented by rapid drug desensitization method in patients who are allergic to rituximab. Although HSRs and desensitization protocols to mAbs have been well described in adults, the experience in the paediatric population is very limited. To best of author's knowledge, this is the first case series describing a novel, rapid desensitization protocol against rituximab hypersensitivity in two teenagers with high-grade B cell non-Hodgkin's lymphoma and steroid-resistant minimal change disease who developed hypersensitivity to rituximab. Here, authors present case reports of two patients who were desensitized successfully by using novel rapid desensitization protocol for rituximab.

Keywords: Anaphylaxis, Minimal change disease rituximab, Non-hodgkin lymphoma

CASE REPORT

Case 1

A 14-year-old boy presented with low back pain and gait disorder which developed following minor cranial trauma two months ago. There was no marked finding in family history and physical examination. The patient underwent MR imaging due to suspected malignancy to obtain whole-body metastasis scanning, which revealed bone lesions and bone marrow lesions at tibia and pathological fracture on T2 vertebral corpus. Thus, due to lesions at tibia on MR imaging, a true-cut bone biopsy was performed from lytic lesions at left tibia, which was reported as diffuse large B cell lymphoma. PET-CT scan was performed to assess disease, which was found to be compatible with Stage 3 lymphoma. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) protocol was initiated for lymphoma therapy. It was planned to give rituximab at a dose of 375 mg/m^2 (total dose: 600 mg) in R-CHOP protocol. It was intended to give 10% of rituximab dose within first 30 minutes, which was followed by infusion of remaining dose within 5.5 hours. However, the patient developed oedema of eyelids and lips, tachycardia and hypotension in five minute after infusion of rituximab test dose. The patient was diagnosed as anaphylaxis with these findings; thus, infusion was stopped immediately and epinephrine (0.01 mg/kg) was given. Pheniramine maleate (1 mg/kg) was added to therapy. Rituximab therapy was withdrawn. Since there is no alternative agent and rituximab is only the option for CD20 positive lymphoma therapy in the patient, authors planned desensitization before second infusion.

A 14-step desensitization protocol was planned to achieve a total therapeutic dose of 600 mg [Table/Fig-1]. For premedication, the patient was given methylprednisolone, hydroxyzine, and ranitidine 13, 7 and 1 hours before desensitization procedure, respectively. Three solutions with different concentrations were used. Initially, 0.012 mg (1: 50,000 of total dose) rituximab was infused over 15 minutes. The dose increments were performed by 15-minutes intervals and infusion rate was reached up to 160 mg/hour at the end of 180 minutes. Then, infusion was maintained with constant infusion rate of 160 mg/hour until end of infusion. The desensitization was performed within 4 hours 45 minutes under supervision of a clinician and nurse. Then onwords, patient was able to receive the therapy planned initially with no problem. No repeated desensitization was performed due to half-life of rituximab.

Total Drug Dose: 600 mg				
Solution	Volume (mL)	Total drug dose per solution	Concentration (mg/mL)	Total infused volume
Solution 1	250	6 mg	0.024	8.5 mL
Solution 2	250	60 mg	0.24	18.5 mL
Solution 3	250	600 mg	2.4	250 mL

Step	Solution	Infusion rate (mL/h)	Time (minute)	Volume (mL)	Dosage administered this step	Cumulative dose
1	1	2	15	0.5	0.012	0.012
2	1	4	15	1	0.024	0.036
3	1	10	15	2.5	0.06	0.086
4	1	20	15	5	0.12	0.206
5	2	4	15	1	0.24	0.446
6	2	10	15	2.5	0.6	1.046
7	2	20	15	5	1.2	2.246
8	2	40	15	10	2.4	4.646
9	3	10	15	2.5	6	10.646
10	3	20	15	5	12	22.646
11	3	40	15	10	24	46.646
12	3	80	15	20	48	94.646
13	3	160	15	40	96	190.646
14	3	160	90	40	409.354	600

[Table/Fig-1]: Desensitization solutions and protocol of the Patient 1.
Solution 1: 250 mL, 0.9% saline, (0.024 mg/mL: 1: 100 of total dose, 250 mL/6 mg); Solution 2: 250 mL, 0.9 % saline, (0.24 mg/mL: 1: 10 of total dose, 250 mL/60 mg); Solution 3: 250 mL, 0.9 % saline, (2.4 mg/mL: 1: 1 of total dose, 250 mL/600 mg); Premedication: 13 hour, 7 hour and 1 hour before pheniramine 60 mg IV, prednisolone 60 mg IV, and famotidine 60 mg IV

Case 2

A 15-year-old boy had been diagnosed as nephrotic syndrome with symptoms of pretibial oedema, hypoalbuminemia and proteinuria at two years of age. Renal biopsy was found to be compatible with minimal change disease. Since the patient achieved remission by steroid therapy with frequent recurrences, the patient was considered as steroid-dependent nephrotic syndrome. No remission could be achieved despite cyclosporine, mycophenolate mofetil and tacrolimus; thus, 375 mg/m^2 rituximab was added. First 4 sessions of rituximab

were successfully completed; however, the patient experienced urticaria, angioedema and respiratory distress 15 minutes after test dose in session 5. The patient was diagnosed as anaphylaxis. Infusion was stopped immediately and epinephrine (0.01 mg/kg) was given. Pheniramine maleate (1 mg/kg) was added to therapy. Rituximab therapy was withdrawn. Desensitization was planned before session 5 as there was no alternative agent.

A 14-step desensitization protocol was planned to achieve a total therapeutic dose of 500 mg [Table/Fig-2]. For premedication, the patient was given methylprednisolone, hydroxyzine, and ranitidine 13, 7 and 1 hour before desensitization procedure, respectively. Three solutions with different concentrations were used. Initially, 0.012 mg (1: 50,000 of total dose) rituximab was infused over 15 minutes. The dose increments were performed by 15-minutes intervals and overall 0.34 mg rituximab was given within first hour of desensitization. Infusion rate was reached up to 160 mg/hr at the end of 180 minutes. Then, infusion was maintained with constant infusion rate of 160 mg/hour until end of infusion. The desensitization was performed within 4 hours 40 minutes under supervision of a clinician and nurse. Then onwords, patient was able to receive the therapy planned initially with no problem. No repeated desensitization was performed due to half-life of rituximab.

Total Drug Dose: 500 mg				
Solution	Volume (mL)	Total drug dose per solution	Concentration (mg/mL)	Total infused volume
Solution 1	250	5 mg	0.020	9 mL
Solution 2	250	50 mg	0.20	18.5 mL
Solution 3	250	500 mg	2.0	250 mL

Step	Solution	Infusion rate (mL/h)	Time (minute)	Volume (mL)	Dosage administered this step	Cumulative dose
1	1	2	15	0.5	0.01	0.01
2	1	4	15	1	0.02	0.03
3	1	10	15	2.5	0.05	0.08
4	1	20	15	5	0.1	0.18
5	2	4	15	1	0.2	0.38
6	2	10	15	2.5	0.5	0.88
7	2	20	15	5	1	1.88
8	2	40	15	10	2	3.88
9	3	10	15	2.5	5	8.88
10	3	20	15	5	10	18.88
11	3	40	15	10	20	38.88
12	3	80	15	20	40	78.88
13	3	160	15	40	80	158.88
14	3	160	85	40	341.88	500

[Table/Fig-2]: Desensitization solutions and protocol of the Patient 2.
Solution 1: 250 mL, 0.9% saline, (0.020 mg/mL: 1: 100 of total dose, 250 mL/5 mg); Solution 2: 250 mL, 0.9 % saline, (0.20 mg/mL: 1: 10 of total dose, 250 mL/50 mg); Solution 3: 250 mL, 0.9 % saline, (2.0 mg/mL: 1: 1 of total dose, 250 mL/500 mg); Premedication: 13 hour, 7 hour and 1 hour before pheniramine 46 mg IV, prednisolone 46 mg IV, and famotidine 46 mg IV

DISCUSSION

The research on monoclonal antibody has now evolved through a new breakthrough in targeting specific proteins involved in disease pathogenesis [1]. However, the use of monoclonal antibodies in practice is limited due to Hypersensitivity Reactions (HSRs) which are reported after first or repeated exposures [1,2]. In majority of HSRs, non-immune cytokine release plays role, which develops during intravenous administration. The release of histamine, leukotrienes, prostaglandins, proteases, and proteoglycans are promoted by IgE-related mast cell activation, mediating immediate type HSRs that may result in urticaria, shock or death [2]. Rituximab is a chimeric mouse-human anti-CD20 monoclonal antibody which has been found to be effective in Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Lymphoma (CLL) and inflammatory disorders including Rheumatoid Arthritis (RA), Wegener's granulomatosis and microscopic polyangiitis [3]. Desensitization process is defined as administration of very small doses of a suspected agent to an individual known to be allergic and escalating doses up to the therapeutic level [4]. This enables to manage patients suffering HSRs with few or no adverse effect. In recent years, rapid desensitization has been introduced as care of standard in order to administer first-line treatment modalities to patients with allergy to drugs in some facilities [5]. In case of limited therapeutic options, rapid desensitization, also known as temporary induction of tolerance, should be considered to allow continuation of treatment in patients with HSRs. Among subjects in this series, HSR against rituximab occurred with repeated rituximab exposure. This is not consistent with adult studies where HSRs occur after first exposure but is in agreement with paediatric case reports [6,7].

In this study, no skin testing was performed as a result of urgent need for continuing rituximab infusions following initial reactions. In malignant disease and autoimmune conditions, it is often urgent and time-sensitive to reinstitute treatment with mAbs, resulting in challenges in performing skin testing. Moreover, there is an increased likelihood of false-negative reaction on skin testing immediately after HSR occurrence [8]. However, skin testing must be considered in case of HSR in order to improve understanding mechanism in HSRs. In addition, skin testing may be helpful to develop a desensitization protocol in case of positive test results or conversion to an alternative treatment in case of negative test results.

In the literature, there is no report regarding rapid desensitization to monoclonal antibodies in younger children but there are reports of two cases in adolescent population including a report about desensitization to rituximab in a 14-year-old patient using 12-step rituximab protocol [9,10]. In the second report, a 14-year-old patient underwent desensitization against infliximab using a 13-step protocol. In this case, desensitization protocol used an initial dose lower than those described for rituximab (1: 1,000,000 vs. 1/100,000) and doses were escalated by 3-folds in each step vs. 2-fold increase in the present study [7]. In general, it is preferred to limit dose increase by 2-folds in each step of desensitization [11]. The novel desensitization protocol presented here is not only in accordance with this recommendation but also addresses a new concept which includes adjusting infusion rate based on body weight during desensitization procedure. This is particularly helpful in younger patient. This novel protocol differs from 12-step desensitization protocol used in adult patients mostly by slower infusion rate based on lower body weight in younger 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 12-step desensitization, not only based on the number of bags but also because of the final lower/patient weight-based infusion rate [12]. In the present rapid desensitization protocol, it was aimed to limit increment in infusion rate by approximately 0.5 mg/kg/hour. This protocol with the final infusion rate not exceeding 2 mg/kg/hour was well-tolerated without any reactions. In young patients with HSRs to mAbs, authors recommend this protocol with premedication to decrease likelihood of reactions during desensitization. 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 [8]. In the indexed cases, desensitization was achieved uneventfully by using the protocol described above. This is presumably due to lower infusion rate in final step. Therefore, the present protocol may be of potential use in some adult patients with a history of hypersensitivity to mAbs who have failed previously established desensitization protocols.

CONCLUSION

Desensitization can be successfully achieved in almost all patients with severe sensitivity to rituximab. Now, the patient is able to continue therapy without HSRs by this protocol. In conclusion, the desensitization protocol described here can be used in patients experiencing anaphylaxis against rituximab.

Patient consent: All patients gave written informed consent.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jul 31, 2018**
Date of Peer Review: **Sep 12, 2018**
Date of Acceptance: **Jan 21, 2019**
Date of Publishing: **May 01, 2019**