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Rapid Drug Desensitization and Management of Breakthrough Reactions in Pediatric Patients

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ABSTRACT

Objective: Rapid drug desensitization (RDD) is a safe and effective method of inducing temporary tolerance and gradually increasing the dose over a few hours to a few days, thereby preventing severe hypersensitivity reactions. Despite the limited number of pediatric desensitization studies in the literature, it is important to explore this area further to provide better treatment options for patients. This study will determine the safety and efficacy of desensitization and present management strategies for breakthrough reactions in pediatric patients with immediate hypersensitivity reactions (HSR).

Materials and Methods: This retrospective study enrolled 14 pediatric patients with drug HSRs who underwent drug desensitization between January 2020 and January 2024. The desensitization protocols used were developed by Castells and consisted of a 12-step protocol with 3 parenteral preparations with increasing concentrations. The standard protocol included premedication with antihistamine (pheniramine) and methylprednisolone (1 mg/kg) 30 minutes before the infusion.

Results: The study involved 14 patients. A total of 64 desensitizations were carried out for 16 different drugs. Only 13% resulted in mild to severe reactions. Overall, almost 92% of all desensitizations were successful. Additionally, it is important to highlight that all breakthrough reactions (BRs) occurred with monoclonal antibodies. Mild BRs during RDD were associated with more severe reactions during the next RDDs. No BRs were seen during RDD in patients with mild initial reactions.

Conclusion: It is important to note that desensitization is not an extreme method, and that pediatric age is not a contraindication. Desensitization is a safe and successful method for children, with a positive impact on survival and overall prognosis.

Keywords: Rapid drug desensitization, pediatric, drug allergy

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INTRODUCTION

The drug hypersensitivity reaction (DHR) is common in pediatric patients; 9.5% of hospitalized patients and 1-8% of outpatients have been reported to experience suspicious DHRs (1,2). In the United States, studies on pediatric cohorts have revealed that drug-induced anaphylaxis is the most common cause of fatal anaphylaxis (3). It is recommended to discontinue treatment with the culprit drug and consider alternative treatment in cases of confirmed immediate DHR or unevaluated moderate to severe DHR. If an alternative treatment is not available, rapid drug desensitization (RDD) may be considered, even if the alternative drug is less effective than the culprit drug or more toxic (1,4). Chronic diseases necessitate long-term treatment, which can result in sensitization to medication due to recurrent usage (5).

Rapid drug desensitization induces transient tolerance and gradually increases the dosage over a few hours to a few days to prevent severe hypersensitivity reactions. Inhibition of mast cell activation and release of inflammatory mediators may be the mechanism by which RDD induces tolerance. Low doses of antigen may rearrange sensitized mast cell and basophil receptors by preventing internalization of the antigen-receptor complex (6). In addition, the production of IgG-blocking antibodies may neutralize drug epitopes, and mast cell and basophil activation can be inhibited by T-regulatory cells generating inhibitor-regulator cytokines such as IL-10 (7). Also, previous studies have shown altered cellular signaling in mast cells and basophils, such as inhibition of calcium mobilization and decreased syk kinase (8,9).

Limited studies have been presented on pediatric RDD experience in the literature. However, it is important to note that cohorts and guidelines of RDD do not reach a consensus on all details, such as premedication and protocols (1,5,10-17). Despite this, RDD can be used for children with caution, as breakthrough reactions (BRs) can occur and can be severe. Also, the RDD decision for a child should be made carefully due to breakthrough reactions (BRs) that are possibly as severe as anaphylaxis. The World Allergy Organization (WAO) guidelines recommend that very young pediatric patients or patients with developmental disabilities or severe reactions need closer monitoring during RDD, possibly in an intensive care unit, especially during the first RDD (1).

By now, various antibiotics (17,18), monoclonal antibodies (19-21), and chemotherapeutics (11,14,22,23), as well as different drugs, have successfully completed RDD in pediatric patients (1,5,12). Validated pediatric RDD protocols and developing appropriate management strategies are crucial as previous studies have relied on adult protocols for RDD in pediatric patients, leading to various outcomes.

This study aims to identify the safety and effectiveness of RDD and present management strategies for BRs in pediatric patients presenting with immediate HSRs.

MATERIALS and METHODS

Study Design and Population

The study was conducted retrospectively. Between January 2020 and January 2024, children and adolescents (0-21 years old) with physician-diagnosed HSRs during or up to 6 hours after the infusion of monoclonal antibodies, antibiotics, chemotherapeutics, and other various drugs referred to our pediatric allergy and immunology clinic for RDD were enrolled in the study. The study was approved by the Ethics Committee of Istanbul University-Cerrahpasa (E-83045809-604.01-978099).

All patients underwent successful desensitization to at least one drug. Two patients who had been previously reported (20,21). The patients' medical records were thoroughly reviewed to obtain demographic characteristics such as age, gender, chronic and atopic diseases, as well as characteristics of the initial reaction and desensitization protocols, including premedications, BRs during desensitization, and treatment of BRs.

Characteristics and Classification of Initial Reactions and Evaluation of Sensitivity with Skin Tests

The severity of the reactions was classified as mild (grade I), moderate (grade II), or severe (grade III) in accordance with Brown's grading system (24). Signs and symptoms of initial reactions and HSR during desensitizations were defined as cutaneous (urticaria, angioedema, flushing), respiratory (nasal congestion, sneezing, dyspnea, cough, wheezing, chest tightness, oxygen desaturation, tightness of throat), gastrointestinal (nausea/vomiting, diarrhea, abdominal pain), cardiovascular (tachycardia, presyncope, hypotension, loss of consciousness), and neurologic (back pain, headache, seizure, disorientation, numbness/ weakness, persistent crying, restlessness) (25).

Skin tests (Skin prick tests (SPT) and intradermal test (IDT)) were performed with negative control (saline), positive control (10 mg/ml histamine), and recommended concentrations of the culprit drugs at least 4 weeks after the initial reactions if the caregivers/patients gave informed consent (26-28). If the drugs had no validated dilutions for skin prick and intradermal tests, the skin tests were also performed on healthy controls (29).

A mean wheal diameter of 3 mm, or greater than that obtained with the negative control solution, was considered positive (26). In patients with mild to moderate reactions according to Brown's grading system, where drug skin tests were found to be negative, a drug provocation test was performed after obtaining consent from patients and their families.

Desensitization Protocols and Management of Breakthrough Reactions

The desensitization protocols that were developed by Castells as a 12-step protocol with 3 parenteral preparations with incremental concentrations were used. The usual protocol included premedication with antihistamine (pheniramine) and methylprednisolone (1 mg/kg) 30 minutes before the infusion (11). For grade I BRs during desensitization, the infusion was suspended, and the reaction was treated according to symptoms. After the reaction was resolved, the protocol was completed. For patients with grade II and III BRs during desensitizations, the infusion was stopped, and a protocol modification was performed using a 16-step protocol in which a 4th bag was employed. If needed, adaptations of the initial protocol, including the addition of a 20-step protocol with a 5th bag and even of an omalizumab administration, were performed, as well as a pre-medication reinforcement (5,20,30).

Written informed consent was obtained from patients/caregivers before each desensitization procedure.

RESULTS

Patient Characteristics

Fourteen patients were enrolled in the study. The median age of the patients was 14.4 years (IQR: 11.6-17.6), and 57.1% (n=8) of the patients were female. The median age at initial reaction was 13.5 years (IQR: 10.4-15) and the median age at first RDD was similar. Most of the patients were treated for hemato-oncological manifestations (30%, n=1 acute myeloid leukemia, n=1 BCOR/CCN3 sarcoma, n=1 aplastic anemia, n=1 Hodgkin lymphoma, n=1 factor VIII deficiency). The other patients' primary diagnoses were steroid-resistant nephrotic syndrome (20% n=3), cystic fibrosis (6.6% n=1), rheumatologic diseases (6.6% n=1 amyopathic dermatomyositis), primary immunodeficiency (6.6% n=1 IL-10 deficiency), multiple sclerosis (6.6% n=1), congenital anomalies of the kidney and urinary tract (6.6% n=1), and recurrent herpetic keratitis (6.6% n=1) (Table I).

Initial Reactions and Drug Allergy Tests

Two patients had separate HSRs for two drugs; therefore, a total of 16 initial HSRs were investigated. Most of the patients experienced moderate reactions (62.5%); one of four HSRs was urticaria (25%), and two patients experienced severe reactions (12.5%). The most common symptoms of drug-induced reaction were cutaneous (87.5%), followed by respiratory (62.5%), gastrointestinal (31.2%), and cardiovascular (12.5%) (Figure 1A,B). Approximately half of the patients (56.2%) developed HSRs in the first three exposures, and the others experienced it after multiple exposures (Table I).

Only one patient received the drug perorally initially (oxybutynin chloride), and all of the other patients had received the drug intravenously.

Skin tests were performed for 8 out of 16 HSRs, and three (37.5%) of the skin tests were positive (Table I). Two patients with negative SPT were evaluated with positive DPT. Also, one patient was accepted as positive DPT due to recurrent BRs during desensitization. Two patients with negative SPT (one was factor VIII, and the other was rituximab) had experienced severe reactions (tachypnea, dyspnea, tachycardia, hypotension, chills, and vomiting), and DPT was contraindicated. Therefore, a desensitization protocol was performed for both patients (Table I). There was no correlation between the grade of the initial HSR and the result of the skin test (p=0.71).

Desensitization Protocols and Management of Breakthrough Reactions

A total of 64 RDDs were performed on 16 different drugs in 14 patients. Eighty-seven percent (n=56) of desensitizations were performed without any BRs, and 13% (n=8) had mild to severe reactions (respectively mild, moderate, and severe; 4.6, 4.6, and 3.1%) (Figure 1B,C).

Table I: Patients and Reaction Characteristics and Management of the Desensitization Protocols.

P	Age (y), Gender	Culprit Drug	Dose at which HSR occurred	IR Characteristics	IR Grade	Age at IR (y)
1	18 F	Ocrelizumab	1	Anaphylaxis: Urticaria, dyspnea and chest tightness	Moderate	15
2	16.5 M	Infliximab	10	Anaphylaxis: Urticaria, dyspnea and chest tightness	Moderate	14.5
3	5.5 M	Rituximab	1	Anaphylaxis: Generalized urticaria-Ao, dyspnea, chest tightness and vomiting	Moderate	4
4	20.5 F	Rituximab	2	Anaphylaxis: Ocular congestion, cough, dyspnea, hypotension, palpitation and tachycardia	Severe	19
5	18.5 M	Rituximab	3	Anaphylaxis: Flushing, urticaria, dyspnea, chest tightness and tightness of throat	Moderate	17
6	11.5 M	Rituximab	1	Anaphylaxis: Cough, dyspnea and edema of the uvula	Moderate	10.8
7	8.5 F	Acyclovir	Multiple doses	Urticaria	Mild	5.3
8	16.4 M	Colistin	Multiple doses	Anaphylaxis: Urticaria, vomiting and edema of the uvula	Moderate	15
		Meropenem	Multiple doses	Anaphylaxis: Urticaria, vomiting and edema of the uvula	Moderate	15.1
9	15 F	Liposomal Amphotericin-B	Multiple doses	Urticaria	Mild	13.5
		Voriconazole	2	Urticaria	Mild	13.5
10	12.4 F	Etoposide	2	Paresthesia of the arms, cough, urticaria and vomiting	Moderate	12
11	18.5 F	Etoposide	1	Anaphylaxis: Urticaria, dyspnea and chest tightness	Moderate	16
12	13.8 F	Antithymocyte globulin	3	Anaphylaxis: Urticaria, dyspnea and chest tightness	Moderate	13.6
13	10.5 M	Factor VIII	Multiple doses	Anaphylaxis: tachypnea, dyspnea, tachycardia, hypotension, chills and vomiting	Severe	8.2
14	12 F	Oxybutynin Chloride	Multiple doses	Urticaria	Mild	9.3

P	Skin Tests or Drug Provocation Tests	Protocol	No of RDDs	BR	Management of BR
1	SPT and IDT: negative, BRs were accepted as positive DPT that were developed during RDD	12-step Castell protocol	7	5th RDD: after the 12th step throat and facial itch; 6th RDD: anaphylaxis, low blood pressure and throat tightness, was developed finishing RDD	The protocol was modified with 16-step protocol at 7th RDD (21)
2	SPT and IDT: negative, DPT: positive	12-step Castell protocol	7	3rd RDD: after the 12th step an urticarial plaque; 7th RDD: anaphylaxis, low blood pressure and urticaria, was developed finishing RDD	The drug was changed another moAB by the specialists
3	SPT: positive	12-step Castell protocol	8	3rd step in 1st RDD with 12-step, 16-step, 20-step protocols: generalized urticaria-Ao	Omalizumab and montelukast were added for premedication (20)
4	SPT: negative	12-step Castell protocol	6	None	None
5	Drug skin testing could not be performed, the patient refused to tests	12-step Castell protocol	6	3rd RDD: after the 12th step an urticarial plaque	None, BR did not repeated next RDD protocols
6	Drug allergy testing could not be performed, given the immediate need to treat the patient's lung disease, unfortunately the patient was deceased due to this acute exacerbation of the disease.	12-step Castell protocol	1	None	None

7	SPT and DPT: positive	12-step Castell protocol	1	None	None
8	Drug skin testing could not be performed, given the immediate need to treat the patient's infectious conditions	12-step Castell protocol	1	None	None
	Drug skin testing could not be performed, given the immediate need to treat the patient's infectious conditions	12-step Castell protocol	2	None	None
9	Drug skin testing could not be performed, given the immediate need to treat the patient's infectious conditions, however graded challenge with the culprit drug was positive.	12-step Castell protocol	1	None	None
	Drug skin testing could not be performed, given the immediate need to treat the patient's infectious conditions, however graded challenge with the culprit drug was positive.	12-step Castell protocol	1	None	None
10	Drug skin testing to etoposide could not be performed, given the immediate need to treat each patient's oncologic condition.	12-step Castell protocol	10	None	None
11	SPT: Negative IDT: positive	12-step Castell protocol	6	None	None
12	Drug skin testing could not be performed, given the immediate need to treat the patient's oncologic conditions, however graded challenge with the culprit drug was positive.	12-step Castell protocol	1	None	None
13	SPT: negative	12-step Castell protocol	2	None	None
14	SPT and IDT: negative, DPT: positive	13-step Castell protocol	1	None	None

SPT: Skin prick test, **IDT:** Intradermal test, **DPT:** Drug provocation test, **RDD:** Rapid drug desensitization, **BR:** Breakthrough reaction, **IR:** Initial reaction.

All RDDs were performed intravenously except for one patient with oxybutynin chloride HSR, for whom the 13th step peroral RDD was performed (Table II) (25).

One patient who experienced HSRs with ocrelizumab experienced a mild reaction (throat and facial itch) after the 5th RDD protocol and a severe reaction (low blood pressure and throat tightness) after the 6th RDD protocol. The protocol was modified from the 12-steps RDD to the 16-steps RDD (Table III), and performed successfully (21).

The patient who had HSRs with infliximab experienced a mild reaction (an urticarial plaque) after the 3rd RDD protocol and a severe reaction (low blood pressure, dyspnea, and urticaria) after the 7th RDD protocol. The treatment was changed by the patient's specialist.

One patient with HSRs with rituximab experienced moderate reactions (generalized urticaria and angioedema) at the first 12, 16, and 20-steps RDD. After the protocol modification was performed with omalizumab, the 20-steps RDD was completed succesfully (20).

One mild BR (an urticarial plaque) was experienced after 3rd rituximab RDD in a patient and was not repeated in the next RDD protocols.

Table II: Oxybutynin chloride peroral desensitization: 13-step protocol.

Step	Solution	Volume per step (ml)	Dose/Step (mg)	Cumulative Dose (mg)
1	2	0.05	0.0005	0.0005
2	2	0.1	0.001	0.0015
3	2	0.2	0.002	0.0035
4	2	0.4	0.004	0.0075
5	2	1	0.01	0.0175
6	2	2	0.02	0.0375
7	2	4	0.04	0.0775
8	2	8	0.078	0.155
9	1	0.15	0.156	0.0311
10	1	0.3	0.3125	0.624
11	1	0.6	0.625	1.249
12	1	1.25	1.25	2.49
13	1	2.5	2.5	4.99

Solution 1: 1 ml = 1 mg perioral suspension. Solution 2: 0.001 mg /ml dilution. Each step was applied every 15 minutes.

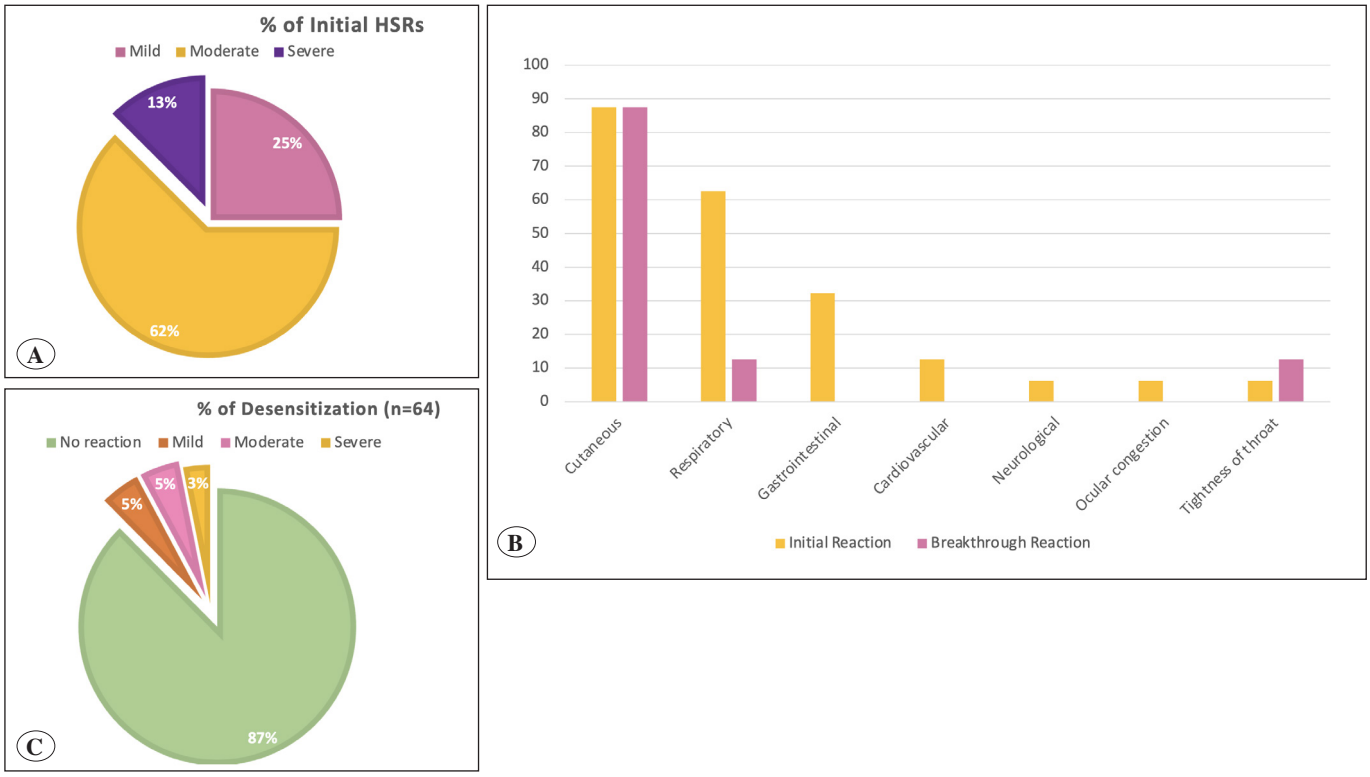

Figure 1. A) Most of the patients experienced moderate reactions (62.5%); one of the four HSRs was urticaria (25%), and two patients experienced severe reactions (12.5%). **B)** The most common symptoms of drug-induced reaction were cutaneous (87.5%), followed by respiratory (62.5%), gastrointestinal (31.2%), and cardiovascular (12.5%) **C)** Eighty-seven percent (n=56) of desensitizations were performed without any BRs, and 13% (n=8) had mild to severe reactions (respectively mild, moderate, and severe; 4.6, 4.6, and 3.1%).

Table III. Ocrelizumab desensitization: 16-step protocol.

Stock Solution	Dilution	Volume	Final Concentration
A	1/1000	250 mL	0.0024 mg/mL
B	1/100	250 mL	0.024 mg/mL
C	1/10	250 mL	0.24 mg/mL
D	1/1	250 mL	2.4 mg/mL

Step	Solution	Rate (ml/hour)	Time per step(min)	Volume per step (ml)	Dose/Step (mg)	Cumulatice Dose (mg)
1	A	0.5	15	0.125	0.0003	0.0003
2	A	1	15	0.25	0.0006	0.0009
3	A	2	15	0.5	0.0012	0.0021
4	A	4	15	1	0.0024	0.0045
5	B	1	15	0.25	0.006	0.0105
6	B	2	15	0.5	0.012	0.0225
7	B	4	15	1	0.024	0.0465
8	B	8	15	2	0.048	0.0945
9	C	2	15	0.5	0.12	0.2145
10	C	4	15	1	0.24	0.4545
11	C	8	15	2	0.48	0.9345
12	C	16	15	4	0.96	1.8945
13	D	4	15	1	2.4	4.2945
14	D	10	15	2.5	6	10.2945
15	D	20	15	5	12	22.2945
16	D	40	325	216.5	519.6	541.8925

In this protocol, after the 12th step, we repeated the premedication (with antihistamine -pheniramine- and methylprednisolone) except for the initial premedication.

The most common BR was cutaneous (87.5% n=7) symptoms. All of the BRs developed in RDDs of biological agents. No reaction was recorded in desensitization for acyclovir, colistin, meropenem, liposomal amphotericin B, voriconazole, etoposide, anti-thymocyte globulin, factor VIII, and oxybutynin chloride (Table IV, V). Importantly, mild BRs during RDD were associated with more severe reactions during the next RDDs. Among the 4 patients who experienced RDD, mild BR occurred initially during desensitization protocols in 3 patients; subsequent protocols resulted in moderate or severe reactions regardless of protocol revision based on reaction severity (single urticarial plaque or more extensive plaque) (75%). In one patient, subsequent protocols were successfully administered without issues following a mild BR.

No BRs were seen during RDD in patients with mild initial reactions. The univariate and multivariate analyses were suboptimal due to limited participant numbers, and there was no statistical association between BRs and gender, age at the initial reaction, skin test positivity, severity of the initial reaction, the time since the initial reaction, the number of desensitizations, and the number of exposures to the culprit drug in the initial reaction (p>0.05).

DISCUSSION

The study clearly demonstrates the high efficacy and safety of RDDs as a continuation treatment in pediatric patients (5). Three of 64 RDDs were not completed due to generalized urticaria at the 3rd step, and anaphylaxis developed after completing two RDD protocols.

Confirmation of a drug allergy diagnosis involves IgE-mediated in vivo or in vitro tests. Skin prick or intradermal tests are recommended to be performed at least 4 weeks after the initial reaction to ensure optimal timing; however,

Table IV: Acyclovir intravenous desensitization protocol and continuation with oral formulation.

Stock Solution	Dilution	Volume	Final Concentration
A	1/100	250 mL	0.016 mg/mL
B	1/10	250 mL	0.14 mg/mL
C	1/1	250 mL	1.46 mg/mL

Step	Solution	Rate (ml/hour)	Time per step (min)	Volume per step (ml)	Dose/Step (mg)	Cumulatice Dose (mg)
1	1	2	15	0.5	0.008	0.008
2	1	5	15	1.25	0.02	0.028
3	1	10	15	2.5	0.04	0.068
4	1	20	15	5	0.08	0.148
5	2	5	15	1.25	0.175	0.323
6	2	10	15	2.5	0.35	0.673
7	2	20	15	5	0.7	1.373
8	2	40	15	10	1.4	2.773
9	3	10	15	2.5	3.65	6.423
10	3	20	15	5	7.3	13.723
11	3	40	15	10	14.6	28.323
12	3	80	172.95	230.60	336.677	365

After the RDD application, for two days, acyclovir was given intravenously, the third day the patients received peroral acyclovir in the hospital and continued in house for seven days without any reactions.

Table V: Antithymocyte globulin desensitization: 12-step protocol.

Stock Solution	Dilution	Volume	Final Concentration
A	1/100	250 mL	0.04 mg/mL
B	1/10	250 mL	0.4 mg/mL
C	1/1	250 mL	4 mg/mL

Step	Solution	Rate (ml/hour)	Time per step (min)	Volume per step (ml)	Dose/Step (mg)	Cumulatice Dose (mg)
1	A	4	15	1	0.04	0.04
2	A	10	15	2.5	0.1	0.14
3	A	20	15	5	0.2	0.34
4	A	40	15	10	0.4	0.74
5	B	10	15	2.5	1	1.74
6	B	20	15	5	2	3.74
7	B	40	15	10	4	7.74
8	B	80	15	20	8	15.74
9	C	20	15	5	20	35.74
10	C	40	15	10	40	75.74
11	C	80	15	20	80	155.74
12	C	160	172.9	415	1844.26	2000

treatment urgency may require earlier testing. It is important to note that the sensitivity and specificity of earlier skin tests have not been validated with large series. Skin tests were not performed in 8 out of 16 cases of hypersensitivity reactions (HSRs) due to the lack of family consent or the unavailability of an appropriate drug formulation or the immediate need to treat the patients' conditions. However, three of them had received the culprit drug with graded challenge after the initial reaction, and the reaction repeated. In this study, skin tests were performed on eight patients, and three tested positive (37.5%). The three patients with mild and moderate reactions with negative skin tests had a drug provocation test that was positive. We decided to perform desensitization on two patients due to the severity of the initial HSR despite a negative skin test or without a skin test. Skin test positivity varies in pediatric cohorts (5,11,14). This variability may be caused by drug differences between cohorts and immunosuppression of the patients.

Premedication for RDD is still a matter of debate. However, it is important to note that according to the European Network of Drug Allergy (ENDA), the European Academy for Allergy and Clinical Immunology (EAACI) Drug Hypersensitivity Interest Group, and the World Allergy Organization (WAO), there are no evidence-based guidelines for the use of antihistamines, steroids or other pre-treatments in adults. Therefore, it may be best to follow the manufacturer's instructions (1,20,31,32). The World Allergy Organization (WAO) guideline recommends premedication in pediatric patients to prevent or minimize the severity of breakthrough reactions (BRs) (1). The premedication regimens may vary between the different cohorts. In our cohort, we preferred to follow the WAO guideline and administered pheniramine maleate (1 mg/kg up to 40 mg), 30 minutes prior to the procedure. Additionally, we used concurrent methylprednisolone (1 mg/kg up to 60 mg). Esenboga et al. have administered additional methylprednisolone doses (at 1, 7, and 13 hours before RDD) for index reactions considered severe (5). However, our two patients with severe reactions completed RDD without any BR and no need for additional pretreatment except our preference for routine premedication.

Breakthrough reactions (BRs) during RDD can range from mild to severe. In this study, BRs were observed in 13% of desensitizations, but no risk factors were identified. However, in our cohort, mild BRs such as urticaria and itching occurred before moderate or severe BRs during previous RDDs. It is important to consider that mild BRs may be a warning sign before more severe reactions occur.

Pediatric cohorts, including the present study, have demonstrated that BR can occur at any stage of RDD in children, whereas adult patients tend to develop it during the final step. While Cernadas et al. (14) have revealed that BR during RDD is more severe than the initial reaction, other studies did not confirm this (5). Also, our cohort showed that only one patient developed more severe BR than the initial reaction. Interestingly, all of the BRs developed with monoclonal antibodies in this study. Contrary to previous studies (5,10,14), BR was not observed in any of the 17 RDDs performed with chemotherapeutics.

Discontinuing the infusion can alleviate mild reactions but antihistamines and steroids may be required in some cases. However, immediate treatment is necessary for severe reactions (33), and the protocol must then be revised (10). Cernadas et al. recommended that an additional step before the one at which symptoms arise can be introduced, as well as considering another more diluted bag (10,25). Therefore, we needed to revise protocols for two patients, and one tolerated the treatment successfully in the 16-step protocol. However, one patient was not tolerated well in the 12, 16, and 20-steps protocols. Although montelukast was added for pretreatment, the patient barely tolerated RDD after the omalizumab regimen (20).

The limitations of the study stem from the limited number of patients and the diversity of diseases across different patient groups. However, the study's strength lies in its inclusion of a diverse range of RDD cases, offering valuable insights into the management approach for BRs.

In conclusion, drug hypersensitivity is a very important problem in the management of pediatric diseases. Although life-threatening HSRs are especially handicaps for treatment continuation, RDD allows to receive the culprit drug. Recently, new treatment options for pediatric chronic diseases, such as monoclonal antibodies and chemotherapeutics, have increased HSRs and led to more RDD in the management of therapy. The literature review and present study have shown that RDD is not an extreme method, and that pediatric age is not a contraindication. RDD in children is generally safe and has successful results, and also has a positive impact on survival and overall prognosis. The BRs can be reduced by identifying overall risk factors. Our study demonstrates that mild reactions

during RDD are a red flag. A management algorithm for BR must be created. Further studies should focus on RDD and the management of BR in children for RDD to become a standard alternative for HSRs.

Conflict of Interest

The authors declare that they have no conflict of interest.

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