Rapid Drug Desensitization With Rituximab in 24 Cases: A Single-Center Experience

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Rituximab has become a frequent cause of immediate hypersensitivity reactions (HSRs) [1-3]. Our center has extensive experience [4] with the rapid drug desensitization (RDD) protocols developed at the Brigham and Women's Hospital, Boston, USA [3]. Data on RDD in patients who experience HSRs to rituximab are limited [5-7]. We present our experience regarding the clinical features, outcomes, and characteristics of RDD to rituximab in 24 patients.

We performed a retrospective chart review of patients with immediate HSRs to rituximab to which RDD protocols administered between 2012 and 2017. The severity of the reaction was classified according to Brown [8]. Serum tryptase was measured using ELISA (ImmunoCAP 100) (levels >11.5 ng/mL were considered elevated). The local ethics committee approved the study, and informed consent was obtained.

The phenotypes of HSRs to rituximab were originally defined as infusion-related, cytokine-release, type I (IgE/non-IgE), mixed reactions (cytokine-release + type I), type III, and type IV [9]. Phenotypes were defined based on clinical presentations and endotypes were defined based on skin testing and tryptase levels. The cytokine release phenotype was defined as fever/chills, nausea, pain, headache, and rigor not responding to premedication/slower infusion rate during the first infusion. Type I reaction (IgE or non–IgE-mediated mast cell degranulation) was defined as flushing, pruritus, urticaria, shortness of breath, wheezing, hypotension, and life-threatening anaphylaxis, which indicated massive release of histamine. Skin test positivity to rituximab was considered

Table. Clinical Characteristics and Results

	Patients, No. (%)	
Mean (SD) age, y	52.8 (12.8)	
Sex (F/M)	16/8	
Atopic/Nonatopic (4/9)	Atopic: 4 (31%) • Pollen: 3 (23%) • House dust mite: 1 (8%)	
Skin test results to rituximab • Prick positive • IDT positive • Negative	• 20 • 0 • 6 (30%) • 14 (70%)	
	Baseline	During hypersensitivity reactions
Mean (SD) serum tryptase (minimum-maximum), ng/mL	3.98 (2.68) (1-10.5)	7.38 (6.29) (3- 24.6)
	Predesensitization	Postdesensitization
Reaction grade		
Grade 0	0	10 (42%)
Grade 1	0	4 (17%)
Grade 2	15 (63%)	8 (33%)
Grade 3	9 (37%)	2 (8%)
Cutaneous symptoms	92%	29%
Respiratory symptoms	88%	21%
Cardiovascular symptoms	67%	8%
Gastrointestinal symptoms	55%	4%
Neurologic/muscular symptoms	29%	13%
Fever (≥38.3°C)	46%	20%

an IgE-mediated reaction. A mixed reaction was defined as wheezing, flushing, urticaria, pruritus, and/or a combination of skin test positivity and increased tryptase concentrations with fever/chills, nausea, pain, headache, and rigor.

The study comprised 16 women and 8 men (mean [SD] age, 52.8 [12.8] years) (Table). Fifteen patients experienced grade 2 reactions, and 9 experienced grade 3 reactions. The clinical characteristics are detailed in the Supplementary Table.

Serum tryptase was not tested during the initial reactions but measured at baseline and during breakthrough reactions. Only 1 patient (#3) had elevated tryptase levels (24.6 ng/mL) during the initial reaction. Similar to previous reports [9,10], cutaneous symptoms were the most frequent (Supplementary Figure).

Twenty patients (83.3%) experienced HSRs during the first exposure, but 4 (17%) experienced the reaction during subsequent cycles. Skin tests with rituximab were positive in the intradermal test (IDT) in only 6 patients (Table). There was no significant difference between positive skin test results and the initial severity of the reaction (P=.76), although the frequency of respiratory symptoms was significantly higher in the skin test–positive group (P=.018).

A total of 141 RDDs were performed in 24 patients. Twenty-two desensitizations were complicated by breakthrough reactions in 14 patients (grade 1, n=4 [17%]; grade 2, n=8 [33%]; and grade 3, n=2 [8%] in severity). Only 2 RDDs could not be completed in 2 of 14 patients, because of anaphylactic shock (one patient had severe pemphigus, the other had lymphoma with a negative skin test result to rituximab). Breakthrough reactions were most likely to occur at the twelfth step of the first desensitization.

Except for 2 RDDs, all desensitizations were completed with the full target dose of the drug in patients #1, 13, 16-18, 20, and 22. The 16-step protocol with half the target dose of rituximab was used in patient #8, whose reaction was associated with severe hypotension. This patient reacted with generalized urticaria in the first desensitization, and premedication was added at step 8 for subsequent desensitizations. The first desensitization was performed with half the dose of rituximab in a patient with a grade 3 reaction and a high white blood cell count (#7).

Biologics can cause HSRs during the first exposure or after multiple exposures [11-15]. In a study of 23 patients, 14 patients with no prior exposure developed HSRs to rituximab [3], as did 83.3% of the patients we report.

The first step in the evaluation of HSRs includes skin tests with the culprit agent. IgE-mediated HSRs to rituximab are estimated to account for 5%-10% of immediate reactions [3,11]. Positivity to rituximab has mainly been observed in IDTs [3]. Interestingly, in a recent study, 7 of 18 patients with positive skin test results to rituximab also had positive results in prick tests [9]. We performed skin tests with rituximab in 20 of 24 patients. None of the patients had positive results in prick tests, and 6 were positive in IDTs (only 1 reacted to rituximab at the fifth infusion, the remainder reacted at the first exposure).

An association between positive skin test results and greater severity of the initial reaction has been reported [9]; however, we observed no difference between positive skin test results and initial severity of the reaction. Additionally, a correlation between breakthrough reactions and the positivity of skin tests has been proposed, although neither a recent paper [15] nor our study found any correlation between skin tests and the likelihood of developing an HSR during desensitization.

RDD allows a patient to receive the optimal agent for treatment. RDDs were performed with rituximab because it was the most effective option in the cases we report. Breakthrough reactions in which cutaneous symptoms were the predominant event were observed during desensitization (Supplementary Figure). However, the overall grade of breakthrough reaction was low, and nearly all patients received the target dose.

Our study is subject to a series of limitations. Neither tryptase nor cytokine measurements during the reactions were available. Although cost is a concern, we performed skin tests with rituximab in most patients. The study is also limited by the lack of drug provocation testing with rituximab in negative skin tests, which could lead us to overestimate the efficacy and safety of RDD, as indicated in a recent article [13]. However, our department has practical limitations for implementing drug provocation testing. Moreover, many recently published large-scale studies on RDD did not include systematic drug provocation testing in their methodology.

In conclusion, most immediate HSRs to rituximab occur during the first infusion, and IgE-type HSRs to this agent are not uncommon. Based on skin tests, 30% of patients had IgE-mediated type I reactions, although we should bear in mind that positive results were recorded in IDT but not prick testing, even in patients who reacted during the first exposure. In the event of an HSR to rituximab, RDD is a safe and valid alternative, because 98.5% of our RDDs were completed successfully.

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Conflicts of Interest

The authors declare that they have no conflicts of interests.

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