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

Görgülü B, Cengiz Seval G, Kendirlihan R, Koçak Toprak S, Özcan M, Bavbek S

1Department of Pulmonary Medicine, Immunology and Allergy Clinic, Ankara University, Cebeci, Ankara, Turkey
2Department of Hematology, Ankara University, Cebeci, Ankara, Turkey

Corresponding Author
Sevim Bavbek
Department of Pulmonary Medicine, Immunology and Allergy Clinic, Ankara University, Cebeci, 06590 Ankara, Turkey
E-mail: bavbek@medicine.ankara.edu.tr

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

The study was a retrospective chart review of patients with immediate HSRs to RTX to which RDDs performed between 2012 and 2017 were evaluated. Reaction severity was classified according to Brown’s classification [8]. Serum tryptase was measured by ELISA radioimmunoassay (ImmunoCAP 100) (>11.5 ng/mL was considered elevated). The local ethics committee approved the study and informed consent was obtained.

Initial phenotypes of HSRs to RTX were defined as infusion-related, cytokine-release, type I (IgE/non-IgE), mixed reactions (cytokine-release + type I), type III, and type IV [9]. Clinical presentations were used for phenotypes and skin testing and tryptase were used for endotypes. Fever/chills, nausea, pain, headache, rigor not responding premedication/slower infusion rate during the first infusion were considered as cytokine release. Flushing, pruritus, urticaria, shortness of breath, wheezing, hypotension, and life-threatening anaphylaxis suggested a massive release of histamine, pointing toward Type I reaction (IgE or non-IgE–mediated mast cell degranulation). Skin test positivity to RTX was considered as an IgE-mediated reaction.
Wheezing, flushing, urticaria, pruritus and/or combination of skin test positivity and/or increased tryptase concentration with fever/chills, nausea, pain, headache, and rigor were considered as mixed reaction.

The study comprised 16 women and 8 men (mean age: 52.8±12.8 years) (Table 1). Fifteen patients experienced Grade 2, and nine experienced Grade 3 reactions. Clinical characteristics are detailed in Table 2 (Supp. File).

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

Twenty (83.3%) patients experienced HSRs during the first exposure, but four (17%) experienced during recurrent cycles. Skin tests with RTX were positive on intradermal test (IDT) in only six subjects (Table 1). There was no significant difference between positive skin tests and initial reaction severity (p=0.76), but the frequency of respiratory symptoms was significantly higher in the skin-test–positive group (p=0.018).

One hundred forty-one 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 had severe pemphigus, the other had lymphoma with a negative skin test to RTX). 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 #1,13,16-18,20,22. The 16-step protocol with the half target dose of RTX was used in
patient #8, whose reaction was associated with severe hypotension. This patient reacted with generalized urticaria in the first desensitization, and premeditations were added at step 8 for subsequent desensitizations. The first desensitization was performed with a half-dose of RTX in a patient with a Grade 3 reaction and a high white blood cell count (#7).

Biologics can cause HSRs during the first or after multiple exposures [11-15]. In a study of 23 patients, 14 patients with no prior exposure developed HSRs to RTX [3]. Similarly, 83.3% of our patients reacted to RTX at the first exposure.

The first step in the evaluation of HSRs includes skin tests with the culprit agent. IgE-mediated HSRs to RXT are estimated to account for 5-10% of immediate reactions [3,11]. Positivity to RXT has mainly been observed in IDTs [3]. Interestingly, in a recent study, seven of 18 skin-test–positive cases to RTX were positive in prick tests [9]. We could perform skin tests in 20 of 24 patients with RTX. None of the patients were positive in prick tests, six were positive in IDTs, only one of whom reacted to RTX at the fifth infusion, the rest reacted at the first exposure.

An association between skin-test positivity and greater severity of initial reaction has been reported [9]; however, we observed no difference between positive skin tests and initial reaction severity. Additionally, a correlation between breakthrough reactions and the positivity of skin tests has been proposed, but 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. RDDs were performed with RTX because it was the most effective option for our patients. During desensitization, breakthrough reactions occurred in which cutaneous symptoms were the predominant (Figure 1, supp file).
However, the overall grade of breakthrough reaction was reduced and nearly all patients received the target dose.

We have some disadvantages and advantages in the study. The lack of tryptase or cytokine measurements during the reactions was a disadvantage. Although cost is a concern, we could perform skin tests with RTX in most patients. The other limitation is the lack of drug provocation (DPT) with RTX in negative skin tests, which could render an overestimation of efficacy and safety of RDD, as indicated in a recent article [13]. However, our department has practical limitations for implementing DPT. Moreover, many large studies recently published about RDD did not include systematic DPT in their methodology.

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

The authors do not have any conflict of interest on this paper.

Patients’ data protection. Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Ethics approval and consent to participate: The local ethics committee of Ankara University, School of Medicine, approved the study and written informed consent was obtained from all subjects.

Consent for publication: The authors declare that they have followed the protocols of their work centre on the publication of patient data and that the patients included in the study received sufficient information and gave their informed consent in writing to participate in that study.

Availability of data and materials: Data are available as printed material and as electronic files in the hospital computer.

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References


Table 1: The clinical characteristics and results of the study group

| Patients (n, %) |  
|---------|---------|  
| **Age (mean± years)** | 52.8±12.8 |  
| **Sex (F/M)** | 16 / 8 |  
| **Atopic / Non atopic (4 / 9)** | Atopic: 4, 31%  
• Pollen: 3, 23%  
• House dust mite: 1, 8% |  
| **Skin test results to RTX** |  
• Prick positive | 20 |  
• IDT positive | 0 |  
• Negative | 6, 30% | 14, 70% |  
| **Serum tryptase** | Basal | 3.98 ng/mL±2.68 ng/mL (min:1, max:10.5 ng/mL) |  
| **Pre-desensitization** | Post-desensitization |  
| **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** | 29% | 13% |  
| **Fever (≥38.3°C)** | 46% | 20% |  
| **During hypersensitivity reactions** | 7.38 ng/mL± 6.29 ng/mL (min:3-max: 24.6 ng/mL) |  
| **Reaction Grade** |  
• Grade 0 | 0 |  
• Grade 1 | 0 |  
• Grade 2 | 15, 63% |  
• Grade 3 | 9, 37% |  
| **Cutaneous symptoms** | 92% | 29% |  
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