

## Clinical Communications

### Hypersensitivity reactions to rituximab: 53 successful desensitizations in 7 patients with severe, near-fatal reactions

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#### Clinical Implications

- A modified desensitization protocol including pharmacologic prophylaxis before rituximab administration is both reliable and safe. This protocol should be considered in patients whose medical condition mandates rituximab administration despite a previous severe, life-threatening reaction.

#### TO THE EDITOR:

Rituximab is a chimeric antibody instrumental in the treatment of numerous hematological malignancies. A plethora of clinical manifestations are associated with acute hypersensitivity reactions (HSRs) to rituximab.<sup>1</sup> Whether the HSRs are due to immunocytotoxicity or allergic responses, conventional desensitization procedures such as the 12-step protocol are usually effective.<sup>2</sup> Nevertheless, rare, life-threatening immunocytotoxic reactions, as well as delayed reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, and Drug Reaction with Eosinophilia and Systemic Symptoms, are considered absolute contraindications to the desensitization procedure.<sup>1,3,4</sup> Here, we report our experience with hematological patients who had experienced severe, near-fatal, immediate HSRs to rituximab. A “modified desensitization” protocol was used, using intense premedication before the 12-step desensitization procedure.

Following severe HSRs to previous rituximab infusions, 7 patients were admitted to the Hadassah Hematology Department in an attempt to resume rituximab treatment. Patients were included on the basis of the severity of the initial reaction and on their disease status mandating the administration of rituximab. Immediate HSRs were classified according to Brown’s Grading System.<sup>5</sup> This research is a retrospective study (institutional ethical committee approval no. 0230-15-HMO).

The patients’ status and the HSR details before admission to our department are presented in Table I. In 6 of 7 patients, the primary HSR occurred on the first exposure to rituximab. Owing to the severity of the primary disease, repeated rituximab administration was attempted in 5 of 7 patients and failed. Despite slower administration, premedication, and an attempt to desensitize (in patient 3), all patients presented severe HSRs. Five patients experienced cardiovascular collapse; 2 (3 and 6) had anaphylactic shock, necessitating intensive care unit hospitalization, 1 of which (6) suffered a complete cardiac arrest, mandating cardiovascular resuscitation.

The 12-step desensitization protocol, previously described, uses successive increments in the concentration of the drug and

the rate of administration (adapted from Brennan et al<sup>2</sup>). Our “modified desensitization” protocol is illustrated in Table II. It consists of several premedication steps before rituximab administration. The premedication protocol was designed to block various immune pathways that may contribute to the adverse reaction, and is based on the “Algorithm for the Management of Hypersensitivity Reactions Secondary to Biological Agents,”<sup>1</sup> the conventional management for contrast media allergy, and our own experience with chemotherapy.  $\beta$ -Adrenergic blockers were stopped 24 hours before desensitization. Desensitization took place at the hematology day-care unit under cardiac monitoring with constant measurement of blood pressure and oxygen saturation.

Overall, the “modified desensitization” protocol was administered a total of 53 times in our patients. Minor cutaneous reactions occurred in only 3 of 53 (~6%) desensitization procedures. They were treated by stopping the infusion for 30 minutes and administering a single dose of antihistamine. Infusion was resumed at 2 dilution steps lower than the one received when the adverse reaction occurred, with no further adverse events. There was no correlation between initial HSRs to rituximab and subsequent reactions in the “modified desensitization” protocol.

Brennan et al<sup>2</sup> evaluated 23 patients in 105 desensitizations to mAbs (infliximab, rituximab, and trastuzumab) using the 12-step procedure. Of these patients, 14 were given rituximab in 55 desensitization procedures. Among this patient group, 70% had mild or moderate HSRs and approximately 30% experienced severe reactions. One-third of the patients who underwent rituximab desensitization had mild HSRs, generally presenting during the last stage of the administration procedure. As a comparison, all 7 patients admitted to our ward had experienced severe, near-fatal HSRs to rituximab before our “modified desensitization” protocol. Of the 53 desensitization procedures, only 3 elicited minor, cutaneous adverse reactions. Considering the severity of the initial HSRs, the universal success rate of the “modified desensitization” protocol is remarkable.

Mast cells and basophils are considered the primary targets for desensitization in IgE-mediated reactions. Shalit and Levi-Schaffer<sup>6</sup> have demonstrated this concept by increasing the amount of antigens, resulting in mast-cell desensitization. This theory was further validated as its underlying mechanisms were studied: (1) Type I Fc $\epsilon$  receptor internalization and down-regulation<sup>7</sup> and (2) changes in the antigen-specific IgE antibody stoichiometry, which might influence phosphorylation/dephosphorylation signal transduction possibly by inhibition of syk-dependent phosphorylation.<sup>8</sup>

Most HSRs occur during the first dose of rituximab. It has been suggested that 90% to 95% of rituximab-induced HSRs are immunocytotoxic rather than IgE-mediated; therefore, these do not require preceding exposures.<sup>1,2</sup> Rituximab-induced cell lysis may result in massive cytokine spillage through 3 distinct mechanisms of action: (1) antibody-dependent cellular cytotoxicity, (2) complement-dependent cytotoxicity, and (3) induction of apoptosis.<sup>9</sup> Epicutaneous skin tests might distinguish between the 2 types of reactions; however, these tests have not been fully validated and the results have very little impact on patient management.<sup>2</sup>

TABLE I. ■■■■

Patients' demographic characteristics: HSRs to rituximab before and after the modified desensitization protocol

Modified desensitization and outcome of resumed rituximab treatment

| Patient | Age (y)/sex | Indication                            | Timing of reaction               | Type of reaction      | No. of modified desensitizations | Reaction after desensitization*            | Follow-up primary disease                              |
|---------|-------------|---------------------------------------|----------------------------------|-----------------------|----------------------------------|--------------------------------------------|--------------------------------------------------------|
| 1       | 56/M        | CLL                                   | First, reexposure†               | CUT, CV               | 6                                | Very mild, at second desensitization only‡ | Maintenance therapy, minimal symptoms                  |
| 2       | 51/M        | ITP                                   | Third, reexposure                | CUT, RESP, GI, CV     | 4                                | —                                          | Remission                                              |
| 3       | 43/M        | MZL                                   | First                            | CUT, UPA, RESP, CV    | 8                                | Very mild, at first desensitization only   | Remission                                              |
| 4       | 59/M        | FL                                    | First, second, third             | CUT, UPA, RESP, CV    | 8                                | At first desensitization only              | Mildly active disease, no symptoms, marked improvement |
| 5       | 55/M        | FL                                    | First, second, third, reexposure | F/C, CUT, RESP, GI    | 3                                | —                                          | Remission                                              |
| 6       | 44/M        | Splenic MZL + transformation to DLBCL | First, second                    | F/C, UPA, RESP, CV, N | 16                               | —                                          | Remission                                              |
| 7       | 68/F        | DLCBL                                 | First                            | F/C, RESP             | 8                                | —                                          | Died from refractory disease                           |

CLL, Chronic lymphocytic leukemia; CUT, cutaneous (5 of 7 [71%]); CV, cardiovascular (5 of 7 [71%]); DLCBL, diffuse large B-cell lymphoma; F, female; F/C, fever/chills (3 of 7 patients [43%]); FL, follicular lymphoma; GI, gastrointestinal (2 of 7 [29%]); ITP, immune thrombocytopenic purpura; M, male; MZL, marginal zone lymphoma; N, neurological (1 of 7 [14%]); RESP, respiratory (6 of 7 [86%]); UPA, upper airway (3 of 7 [43%]).

Stress/anxiety reactions not included.

\*Only mild cutaneous reactions were observed.

†Reexposure is defined as reaction on reexposure after a prolonged well-tolerated course.

‡Bendamustine was coadministered on the second rituximab infusion.

TABLE II. The modified desensitization protocol

## Step I: Premedication

- Prednisone: 60 mg  $\times$  3 (PO, 13 h, 7 h, 1 h before desensitization)
- Montelukast: 10 mg (PO, 8 h before desensitization)\*
- Promethazine: 25 mg (IV, 1 h before desensitization)
- Desloratadine: 10 mg (PO, 1 h before desensitization)†
- Ranitidine: 150 mg (PO, 1 h before desensitization)
- Acetaminophen: 1000 mg (PO, 1 h before desensitization)

## Step II: Desensitization; accepted 12-step protocol

| Step no. | Solution no.‡ | Rate (mL/h) | Time per step (min) | Volume per step (mL) | Dose/step (mg) |
|----------|---------------|-------------|---------------------|----------------------|----------------|
| 1        | 1             | 2           | 15                  | 0.5                  | 0.02           |
| 2        | 1             | 5           | 15                  | 1.25                 | 0.05           |
| 3        | 1             | 10          | 15                  | 2.5                  | 0.1            |
| 4        | 1             | 20          | 15                  | 5                    | 0.2            |
| 5        | 2             | 5           | 15                  | 1.25                 | 0.5            |
| 6        | 2             | 10          | 15                  | 2.5                  | 1              |
| 7        | 2             | 20          | 15                  | 5                    | 2              |
| 8        | 2             | 40          | 15                  | 10                   | 4              |
| 9        | 3             | 10          | 15                  | 2.5                  | 10             |
| 10       | 3             | 20          | 15                  | 5                    | 20             |
| 11       | 3             | 40          | 15                  | 10                   | 40             |
| 12       | 3             | 80          | 172.8               | 230.5                | 922            |

IV, Intravenous; PO, per os (by mouth).

\*Montelukast was given only to patients 3 and 6, with the most severe HSR.

†Could be replaced by other selective H1 blockers at double dose.

‡As defined by Brennan et al.<sup>2</sup>

Despite our limited understanding of the mechanisms at work, desensitization protocols are firmly established as invaluable procedures in both IgE- and non-IgE-mediated HSRs.

It can be argued that 12- to 16-step desensitization procedures, without premedication, might be sufficient. However, the severity of the primary HSRs made it perilous to attempt rituximab administration without proper preparation. During the months preceding our study, as the patients were off rituximab, tumor burden significantly increased, which could, in turn, potentially aggravate the immunocytotoxic reaction to rituximab. Having said that, the patients might not require premedication in repeated administrations because their tumor burden decreases as they respond to chemotherapy. The fragility of our patients did not allow us to take the risk of omitting premedication.

All the patients in our study had refractory hematological diseases that mandated rituximab administration, despite previous severe, life-threatening HSRs to this drug. They underwent 53 successful desensitization procedures following extensive premedication, which resulted in a 100% success rate with negligible adverse reactions. Six of the 7 patients in our study are currently in remission of their hematological disease. The low number of adverse events in our study supports the use of prophylaxis before desensitization in selected patients. In addition, the “modified protocol” enables rituximab administration within a day-care facility, saving hospitalization costs and easing patient anxiety. We conclude that the “modified protocol” is both safe and cost-effective. Nevertheless, we feel that it should be used only when no viable alternatives exist.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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