Original Article

Reactions to Rituximab in an Outpatient Infusion Center: A 5-Year Review

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What is already known about this topic? Reactions to rituximab occur frequently especially after first exposure and no guidelines exist to manage patients subsequently.

What does this article add to our knowledge? We review current management strategies and discuss an algorithm for managing patients on the basis of the grade of their rituximab infusion reactions.

How does this study impact current management guidelines? This study helps guide management after a rituximab infusion reaction especially for nonallergists and prevents unnecessary avoidance of rituximab.

BACKGROUND: Reactions to rituximab occur frequently, with up to 77% of patients developing a reaction during initial exposure. The safety of rechallenging patients after a reaction is not clear and standard guidelines are lacking.
OBJECTIVE: To better understand clinical decision making surrounding rituximab reactions and subsequent rechallenge.
METHODS: We performed a 5-year retrospective review of all rituximab reactions at a large academic outpatient infusion center. Patients' demographic characteristics, clinical symptoms, and management of reactions were reviewed. Reaction severity was classified using standard criteria.
RESULTS: Between June 2006 and January 2011, 67 patients (mean age, 58 ± 13 years, 54% men) with at least 1 rituximab reaction were identified. Most reactions occurred during the first exposure to rituximab (63%). Most reactions (n = 59 [88%]) were grade 1 or 2. Fifty-one patients (n = 51 [88%]) were rechallenged with rituximab on the same day as the initial reaction. Most patients with a grade 1 reaction tolerated rechallenge. Conversely, all 4 patients with a grade 3 reaction had a reaction during rechallenge. The outcome of same-day rechallenge after an initial grade 2 reaction was varied; most patients (26 of 31 [84%]) tolerated same-day challenge, but 5 patients had a reaction (all grade 1-2 severity).
CONCLUSIONS: Consistent with previous data, our observations suggest that patients who experience grade 1 reactions to rituximab can be safely rechallenged the same day. A grade 3 or 4 reaction should prompt referral to an allergy specialist for risk assessment before additional rituximab administration. Further research is needed to understand the optimal management of patients with grade 2 reactions. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: *Rituximab; Monoclonal antibody; Infusion reaction; Desensitization*

mAbs are a valuable therapeutic option for patients with many distinct malignancies and rheumatologic conditions. Rituximab is a chimeric murine/human mAb. The antibody is an IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable regions and human constant regions. It was initially approved in 1997 for the therapy of relapsed indolent non-Hodgkin lymphoma. It is currently approved by the Food and Drug Administration for the hematologic/oncologic treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia.[1] Rituximab binds the surface antigen CD20 on both normal and malignant B cells and causes cell death via direct cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity. It has become one of the most widely used biological agents in oncology.[2]

Rituximab's protean therapeutic benefits must be balanced with a substantial risk of infusional reactions. This risk is especially high during the first infusion, as up to 77% of patients develop a reaction during this initial exposure.[1] Reactions range from mild symptoms (itching, rash, flu-like symptoms, or nausea) to severe anaphylaxis within several hours.[3] Interestingly, the risk of development of these infusion reactions decreases with subsequent rituximab infusions; however, the etiology for this has not been clearly elucidated.[4,5] There are several mechanisms thought to contribute to rituximab infusion reactions. Cytokine release syndrome and mast cell—mediated reactions are

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication January 15, 2016; revised May 31, 2016; accepted for publication June 23, 2016.
Available online ■■
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2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.06.022

Grade 1A	Grade 1B	Grade 2	Grade 3	Grade 4	Grade 5
Cutaneous rash Flushing Generalized pruritus	Grade 1A symptoms plus: Back pain and/or Hypertension	Urticaria Nausea/vomiting Throat tightness Asymptomatic bronchospasm Chest tightness	Symptomatic bronchospasm Dyspnea Hypoxia Wheezing	Anaphylaxis Hypotension	Death

FIGURE 1. Modified National Cancer Institute Common Terminology Criteria for Adverse Events Scale. From National Cancer Institute.[13]

associated with acute reactions such as those studied in this article, whereas tumor lysis and serum sickness mechanisms tend to produce delayed reactions.[6-10] A classification of adverse effects to biologic agents has been proposed, stratifying reactions by etiology (hypersensitivity due to immune reaction against agent, elevated cytokine levels, or cytokine imbalance syndrome, cross-reactivity, and non—immune-mediated reactions).[11]

Despite the known risks of rituximab, the management of these reactions varies significantly. Common management techniques include avoidance of rituximab, rituximab desensitization, or rechallenge to rituximab using modification of the infusion rate and/or additional premedications. Infusion rate is an especially important variable in this process. Generally, a first infusion of rituximab is started at a rate of 50 mg/h and increased by 50 mg/h every 30 minutes to a maximum of 400 mg/h, whereas subsequent infusions are usually started at 100 mg/h and increased by 100 mg/h every 30 minutes to a maximum of 400 mg/h.[1] If there is a reaction, rituximab should be stopped. However, the safety of rechallenging a patient with rituximab after an infusional reaction is not clear.[12] Complete drug avoidance occurs needlessly in some patients who would benefit from additional rituximab treatment, while other patients are unnecessarily desensitized. *Desensitization* refers to giving a patient increasing doses of a medication at a slow rate until reaching the goal dose. It is important to understand the nature of rituximab reactions and the success (or failure) of current management strategies to propose standardized guidelines that are safe and effective for the management of patients after a rituximab reaction. To better understand these issues, we performed a 5-year review of all patients who developed a rituximab reaction in the outpatient oncology infusion center at a large academic medical center.

METHODS

Adverse events (including drug reactions) are filed as safety reports at our institution, Massachusetts General Hospital, a tertiary care academic medical center. We performed a retrospective chart review of all rituximab-related safety reports at the outpatient oncology infusion center between June 2006 and January 2011. We included only the first documented infusion reaction to rituximab for each patient during this period.

We used clinical notes within the Massachusetts General Hospital electronic health record to gather data including patients' demographic characteristics, history of drug allergies, reason for receiving rituximab treatment, rituximab dose, and cycle number when the reaction occurred. Using problem lists from these notes, we collected data on the following patient comorbidities: eczema, seasonal allergies, asthma, coronary artery disease, hypertension, and diabetes. From both the safety reports and clinical notes, we assessed the nature and frequency of premedication, symptoms of the rituximab reaction, and treatment of the reactions (with H1 blockers, H2 blockers, steroids, epinepherine, beta-agonists, and/or intravenous fluids).

We classified the grade of the reaction using a modified oncologic version of the National Cancer Institute Common Terminology Criteria for Adverse Events Scale, which scores a reaction from 1 (mild reaction) to 4 (severe reaction) similar to our previous work (Figure 1).[14] In the modified grading scale, grade 1A is defined by cutaneous symptoms only (rash, itching, flushing). Grade 1B includes skin manifestations plus either back pain or hypertension. Grade 2 includes urticaria, nausea, vomiting, throat tightness, asymptomatic bronchospasm, and/or chest tightness. Grade 3 is defined by symptomatic bronchospasm, dyspnea, hypoxia, and/or wheezing. Grade 4 includes anaphylaxis or hypotension. Two allergy/immunology physicians (A.B. and T.L.) independently graded the reactions.

At our institution, first-time infusions of rituximab are administered initially at a rate of 50 mg/h for 1 hour, then increased by 50 mg/h every 30 minutes to a maximum of 400 mg/h. For patients who have tolerated previous infusions, subsequent infusions are given at an initial rate of 20% of the total dose over 30 minutes. The remaining 80% of the total dose is then given over 60 minutes. Standard reduction of the infusion rate to 50% occurs after an infusion reaction at our institution. Our allergy clinic uses a standardized rituximab skin test protocol with published nonirritating skin test concentrations, starting with 10 mg/mL percutaneous skin test and then proceeds to 0.02 mL intradermal skin test (0.1 mg/mL, followed by 1 mg/mL).[15,16] We also use a standardized desensitization protocol (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).[16]

Data on rechallenge after initial reaction (either same day or another day), subsequent rituximab infusion rates (slowed/administered at 50% standard rate), and referral to allergy were reviewed. Institutional review board approval was obtained before study initiation, and informed consent was waived for this retrospective chart review.

Statistical analysis

Statistical analysis including means ± SD or percentages was used. Descriptive data are displayed as frequencies or means with SDs.

RESULTS

Among 80 safety reports between June 2006 and January 2011, 67 patients with at least 1 rituximab reaction were identified. To keep our study population consistent and focus on initial rituximab infusion reactions, the 13 additional safety reports (in 9 patients) were excluded from this study because they represented the second or third rituximab reaction within the study period. One patient accounted for 4 of