Original Article

Rituximab Hypersensitivity: Evaluation, Desensitization, and Potential Mechanisms

Johnson T. Wong, MD, and Aidan Long, MD *Boston, Mass*

What is already known about this topic? Hypersensitivity reactions to rituximab are common and desensitizations may be performed. Cytokine release is thought to be the major mechanism and tumor lysis may also contribute.

What does this article add to our knowledge? Rituximab hypersensitivity has many similarities but also key differences to patients with other chemotherapeutic drug hypersensitivity. The range and severity of hypersensitivity reaction pattern are broad but all can be managed with desensitization.

How does this study impact current management guidelines? Most types of hypersensitivity reactions are markedly reduced in frequency with desensitization. Skin tests, though supportive of the potential role of IgE-mediated mechanism, do not yield prognostic information. Nearly all patients with RITS, including patients with serum sickness and mast cell disorders, can be desensitized successfully.

BACKGROUND: Rituximab (Rituxan) hypersensitivity (RITS) can be severe and limits the ability to further administer the treatment. Understanding its pattern and desensitization may permit administration in difficult cases.
OBJECTIVE: Analyze RITS patient characteristics, hypersensitivity pattern, and desensitization outcomes to optimize management.
METHODS: Twenty-five patients with RITS were referred to the Allergy/Immunology Unit at Massachusetts General Hospital over 5 1/2 years. Their clinical reaction patterns were analyzed. Drug desensitizations were performed using 3 related continuous intravenous protocols that were chosen on the basis of clinical history, skin test reactivity, and the patient's previous desensitization outcomes.
RESULTS: Of the 25 referred patients, 23 had lymphoma of various types. The 25 patients underwent 170 continuous intravenous desensitizations based on 3 related protocols, with most based on the intermediate protocol. All but 2 desensitizations were completed successfully. Overall 24% of the desensitizations were complicated by hypersensitivity reactions. Two patients with serum sickness and a patient with mast cell disorder were also successfully managed. The average hypersensitivity reaction grade was 3.0 (2-4) before desensitization and 0.41 with desensitization. Skin tests were performed in 18 patients, with 5 patients positive initially and 2 more converted from negative to positive. Skin test status was not helpful for risk stratification for hypersensitivity reactions. Tryptase level was elevated during 21% of desensitizations with reactions but rare among asymptomatic desensitizations.
CONCLUSIONS: Nearly all patients with severe sensitivity to rituximab can be successfully desensitized. IgE-mediated mechanism and mast cell degranulation, in addition to cytokine release syndrome and tumor lysis syndrome, may contribute to a significant portion of hypersensitivity reactions among patients with RITS. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1564-71)

Key words: *Rituximab; Hypersensitivity; Desensitization; Reaction grade; Lymphoma; Autoimmune; Multiple sclerosis; Serum sickness; Mast cell disorder*

Rituximab is a chimeric murine/human anti-CD20 mAb that has been widely used to treat B-cell non-Hodgkin lymphoma[1,2] and rheumatoid arthritis.[3,4] Off-label/investigational usage has also included treatment of other lymphomas/leukemia of the B-cell lineage,[5,6] various autoimmune diseases such as multiple sclerosis (MS),[7] systemic lupus erythematosus,[8] autoimmune hemolytic anemia,[9,10] immune thrombocytopenic purpura,[11] anti-neutrophilic cytoplasmic antibodies (ANCA)-associated disease,[12] and various other vasculitis.[8,13,14] Early infusion-associated adverse reactions (EIARs) have been common during the first few infusions and may include a combination of fever, chills, nausea, vomiting, hypotension, bronchospasm, rhinitis, angioedema, urticaria, and/or flushing, often attributed to cytokine release syndrome associated with elevated TNF-α and IL-6.[1,2,4,7] Overlapping the cytokine release syndrome, tumor lysis syndrome has occasionally been associated with renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, hypophophatasemia, and/or acute pulmonary failure within 12 to 24 hours of the first infusion.[15-17] The frequency and severity of these EIARs have varied among the different diseases for which rituximab was used and may also be

Allergy & Immunology Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Mass
Conflicts of interest: A. Long has received consultancy fees from Genentech, Novartis, and AstraZeneca. J. T. Wong declares no relevant conflicts of interest.
Received for publication July 25, 2016; revised August 11, 2017; accepted for publication August 14, 2017.
Corresponding author: Johnson T. Wong, MD, Cox 2, Massachusetts General Hospital, Boston, MA 02114. E-mail: jwong1@partners.org.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2017.08.004

Abbreviations used
EIAR- Early infusion-associated adverse reaction
HRP- High-risk desensitization protocol
HSR- Hypersensitivity reaction
IP- Intermediate protocol
IST−- Initial skin test negative
IST+- Initial skin test positive
LIAR- Late infusion-associated adverse reaction
MS- Multiple sclerosis
RITS- Rituximab hypersensitivity
RP- Rapid protocol

dependent on whether high-dose corticosteroid was included as part of the pretreatment. Incidence rates as high as 70% to 78% during the first infusion have been reported for earlier patients with lymphoma and patients with MS who have not received high-dose corticosteroid pretreatment.[1,2,18,19] The high incidence rates of EIARs in these patients with lymphoma have also been attributed to the high tumor burden. In contrast, lower incidence rates between 25% and 30% have been reported for patients with autoimmune diseases and for patients with MS who had received high-dose corticosteroid as pretreatment.[7,20-22] The EIAR frequencies usually decrease by approximately 50% for the second infusion, with additional decline upon subsequent infusions.[2,7] Although many of the EIARs have been mild to moderate, severe cases and fatalities have also been reported. In addition to the EIARs, late occurring infusion-associated adverse reactions (LIARs) have occurred in a subgroup of patients receiving rituximab. These reactions may be similar to the EIARs but may include additional adverse reactions such as serum sickness, Stevens-Johnson syndrome, toxic epidermal necrolysis, pneumonitis, bronchiolitis obliterans organizing pneumonia, arrhythmias, congestive heart failure, pancytopenia, vasculitis, arthritis, bullous skin eruptions, optic neuritis, uveitis, and/or renal toxicity.[17,23-30] In this report, we examine the desensitization outcome of patients with rituximab hypersensitivity (RITS) with severe EIARs or persistent LIARs referred to the Allergy/Immunology service for management over a 5 1/2-year period.

METHODS

Patients

The data of patients with RITS referred to the Allergy/Immunology Unit at Massachusetts General Hospital from December 2007 to June 2013 were retrospectively reviewed in regard to demographic characteristics, hypersensitivity pattern, time of onset of the hypersensitivity, skin test result, tryptase level, and desensitization outcome. Institutional review board approval was obtained for this study.

Desensitization protocols

All patients with RITS underwent desensitization with 1 of 3 closely related continuous intravenous desensitization protocols that varied in starting concentration, the number of steps (8-13), and the total time taken (4.7-16 hours) (Table I). These protocols were adopted standardized protocols for Partners Institutions (Massachusetts General Hospital, Brigham & Women's Hospital, and Dana Farber Cancer Institute). They were similar to our published protocols used for carboplatin, cisplatin, and oxaliplatin,[31,32] which were modifications of our previously published vancomycin desensitization protocol.[33] The starting protocol for

TABLE I. Desensitization protocols*† for the 500-mg dose

		RP		IP		HRP	
Step no.	Time (h:min)	Concentration (mg/cc)	Infusion rate (cc/h)	Concentration (mg/cc)	Infusion rate (cc/h)	Concentration (mg/cc)	Infusion rate (cc/h)
1	0:00	0.2	5	0.02	2.5	0:0005	20
2	0:15	0.2	10	0.02	5	0:0005	40
3	0:30	0.2	20	0.02	10	0:0005	80
4	0:45	0.2	40	0.02	20	0.005	20
5	1:00	2.0	10	0.2	5	0.005	40
6	1:15	2.0	20	0.2	10	0.005	80
7	1:30	2.0	40	0.2	20	0.05	20
8 RP‡	1:45-4:40	2.0	80				
8 IP and HRP§	1:45			0.2	40	0.05	40
9	2:00			2.0	10	0.05	80
10	2:15			2.0	20	0.5	20
11	2:30			2.0	40	0.5	40
12	2:45			2.0	60	0.5	60
13 IP‖	3:00-5:45			2.0	80		
13 HRP¶	3:00-15:08					0.5	80

*Adopted standardized protocol for Partners Institutions (Massachusetts General Hospital, Brigham & Women's Hospital, Dana Farber Cancer Institute). Total amount of drug was diluted into 250 cc of normal saline for the RP and the IP, and 1000 cc of normal saline for the HRP as final concentration. Serial 10-fold dilutions were made for the RP (1 dilution), the IP (2 dilutions), and the HRP (3 dilutions). Hence, the concentration of each drug varies for the total dose of the drug.
†Previous Massachusetts General Hospital protocols used a fixed final drug concentration for each protocol with serial 10-fold[20,23] dilutions used for starting concentrations.
‡Duration of step 8 for the RP.
§Duration of step 8 for the IP and the HRP.
‖Duration of step 13 for the IP.
¶Duration of step 13 for the HRP.