



Challenging Clinical Cases

Rituximab hypersensitivity and desensitization a personalized approach to treat cancer and connective tissue diseases

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Introduction

Rituximab is a chimeric monoclonal anti-CD20 antibody with wide use in cancer (lymphoma) and connective tissue diseases (rheumatoid arthritis and vasculitis).¹ Hypersensitivity reactions to rituximab can range from type I immunoglobulin E (IgE)-mediated reaction (urticaria, shortness of breath, hypotension, or anaphylaxis) to cytokine-mediated reaction (fevers, chills, rigors) or a mix of both, thus limiting the use of rituximab as first-line therapy for

many cases. Desensitization is a new therapeutic approach that can be performed with rituximab to offset these reactions.

We offer 3 clinical scenarios with an approach to evaluation of the initial reaction, risk stratification, and proposed recommendations for desensitization. We review the management of reactions during desensitization, as well as outcomes of desensitizations.

Case 1

A 58-year-old woman with a history of rheumatoid arthritis, Sjögren's syndrome, and uveitis received her first rituximab infusion at an outside hospital, because her condition had failed to respond to various agents (methotrexate and tumor necrosis factor inhibitors) for rheumatoid arthritis and Sjögren's. On her second rituximab infusion there, she developed self-limited palpitations.

The incidence of infusion reaction to rituximab is reported to be anywhere between 25% and 78%—per infusion.² When calculating the probability of reaction, each infusion of rituximab is an independent event. Reactions can occur on a patient's first lifetime exposure to rituximab or on any individual exposure thereafter, making it impossible to predict a reaction.³

Because of her self-limited palpitations during her second infusion, the outside hospital premedicated her with diphenhydramine and prednisone starting on her third infusion. Her third infusion was without incident, but 15 minutes into her fourth infusion, she experienced itchiness and had throat tightness. The throat tightness progressed to difficulty breathing and swallowing, with tongue swelling. She received epinephrine intramuscularly and was sent to their emergency department, where she received famotidine and was subsequently discharged home with an automatic intramuscular epinephrine injector. No changes in vital signs were noted.

Clinically, this patient began to have symptoms consistent with anaphylaxis and angioedema. This would immediately classify this as a severe reaction,⁴ and she should be treated with the prompt administration of intramuscular epinephrine, intravenous crystalloid, and glucocorticoids. Her specific symptoms (dyspnea, dysphagia, angioedema) are concerning for a type I IgE-mediated immediate hypersensitivity reaction.

If the patient developed a delayed-type hypersensitivity reaction, such as desquamation, skin blistering, or serum sickness-type symptoms, desensitization would be too dangerous, and the patient would be advised to avoid the medication altogether.⁵

The patient was referred to the allergy clinic, and skin testing performed 3 weeks later was positive at the intradermal level to rituximab 0.01 mg/mL with a wheal of 6 mm and flare of 18 mm. Risk stratification for potential desensitization was done, and based on her severe reaction and positive skin test, the decision was made that the patient would benefit from a 4-bag, 16-step protocol (Table 1) with the following premedication: cetirizine 10 mg orally, famotidine 20 mg orally, montelukast 10 mg orally, aspirin 325 mg orally, and methylprednisolone 50 mg intravenously.

Because epinephrine was administered during her initial reaction, she was deemed to have increased risk, thus leading to the decision of starting with a 4-bag, 16-step protocol.

Premedication is tailored to prevent the specific symptoms experienced during the initial reaction. All protocols include cetirizine 10 mg and famotidine 20 mg for H1 and H2 blockade. β -Adrenergic blocking medications should be held for 24 hours before desensitization because of adrenergic blockade and difficulty treating anaphylaxis with epinephrine.⁶ Montelukast 10 mg can be included for prevention of bronchospasm induced by leukotrienes. Aspirin 81 to 325 mg prevents flushing induced by

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Table 1

Example of the 4-Bag, 16-Step Desensitization That Was Used in Case #1

Name of medication:					<i>Rituximab</i>	
Target dose (mg)					765.0	
Standard volume per bag (mL)					250	
Final rate of infusion (mL/hr)					80	
Calculated target concentration (mg/mL)					3.06	
Standard time of infusion (minutes)					187.5	
					Total mg per bag	Amount of bag infused (mL)
Solution 1	250	mL of	0.002	mg/mL	0.383	9.38
Solution 2	250	mL of	0.031	mg/mL	7.650	9.38
Solution 3	250	mL of	0.306	mg/mL	76.500	18.75
Solution 4	250	mL of	3.036	mg/mL	758.961	250.00
Step	Solution	Rate (mL/hr)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.5	15	0.625	0.001	0.001
2	1	5	15	1.25	0.002	0.003
3	1	10	15	2.5	0.004	0.007
4	1	20	15	5	0.008	0.014
5	2	2.5	15	0.625	0.019	0.033
6	2	5	15	1.25	0.038	0.072
7	2	10	15	2.5	0.077	0.148
8	2	20	15	5	0.153	0.301
9	3	5	15	1.25	0.383	0.684
10	3	10	15	2.5	0.765	1.449
11	3	20	15	5	1.530	2.979
12	3	40	15	10	3.060	6.039
13	4	10	15	2.5	7.590	13.628
14	4	20	15	5	15.179	28.808
15	4	40	15	10	30.358	59.166
16	4	80	174.375	232.5	705.834	765.000
Total time (min) =			399.375	= 6.66 hrs		

prostaglandins, possibly prostaglandin D2. Aspirin was added to the premedication of this patient in spite of a lack of flushing because of the severity of the reaction. Acetaminophen 650 mg, ibuprofen 200 to 800 mg, or meperidine 25 mg is used prevent pain, fever, and rigors. Steroids, usually methylprednisolone 40 to 50 mg, are occasionally used in premedication for more serious reactions. An important part of the protocol is the administration of prophylactic crystalloid solutions intravenously (normal saline at 150-250 mL/hr). During a reaction, the rate of intravenous fluid administration is increased to 500 or more mL/hr in the effort to decrease the effective concentration of antigens and mast cell

mediators in the blood.⁷ Most reactions during desensitization to rituximab will occur during the last step of the protocol.⁸

Three minutes into the third step of the desensitization, she experienced a rapid-onset parietal headache and bilateral hand pruritus, for which oral diphenhydramine 25 mg was administered along with normal saline at 500 mL/hr for 30 minutes. Her symptoms resolved within 30 minutes, and the normal saline infusion rate was decreased to 150 mL/hr for the duration of the infusion. She completed the remainder of the infusion without further incident. She went on to complete 5 more infusions using a 3-bag, 12-step protocol with the addition of normal saline running at 150 mL/hr for the entirety of the infusion without reaction.

Case 2

A 53-year-old woman with a history of marginal zone lymphoma received her first lifetime dose of rituximab at an outside hospital, which included premedication with acetaminophen, hydrocortisone, and diphenhydramine (medication doses were not documented by the outside hospital). Within 10 minutes of the start of the infusion, she developed a cough, subjective sensation of her throat closing, chest tightness, and difficulty breathing. The infusion was stopped, and she was treated with nebulized albuterol, supplemental oxygen, and famotidine. Her symptoms resolved within minutes, and she was given additional premedication with a dose of acetaminophen and methylprednisolone. Thirty minutes after this second round of premedication, the rituximab infusion was restarted at half the rate, but within 7 minutes, she developed a sensation of a scratchy throat, so the infusion was stopped entirely. Vital signs were noted to be normal throughout. She was referred to the allergy clinic for potential desensitization to rituximab therapy.

On her initial evaluation, rituximab skin testing was negative, but based on risk stratification for potential desensitization for her moderate reaction, a 3-bag, 12-step protocol was recommended.

Epicutaneous skin testing with the offending medication should be performed a minimum of 2 weeks after the initial reaction to minimize the likelihood of false-negative results. A positive skin test would reinforce the notion of the reaction being IgE-mediated, which puts one at risk for anaphylaxis and also makes a patient more amenable to having successful desensitization.² If skin testing is negative and the initial reaction is mild, a regular infusion of the agent would be recommended with premedication targeted toward specific symptoms. If skin testing is positive or if skin testing is negative and the initial reaction was moderate to severe, rapid desensitization would be recommended.⁵ The decision to proceed with desensitization was based on the strength of her clinical history (Fig 1).

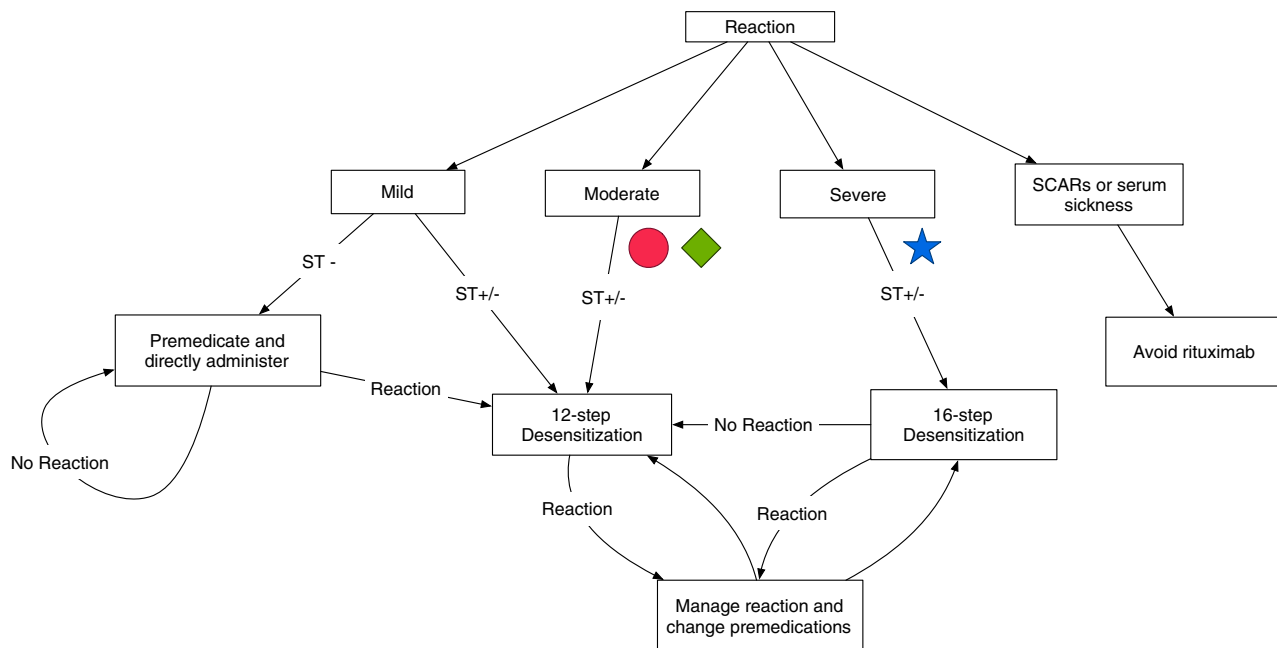


Figure 1. General guideline for indication of rituximab desensitization. If a reaction is mild, one can potentially proceed directly to management of the reaction with pre-medications. The symbols indicate the path taken by each case. Red circle: case #1; green diamond: case #2; blue star: case #3. SCARs are severe cutaneous adverse reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis. Maculopapular reactions are amenable to desensitization, but not SCARs.

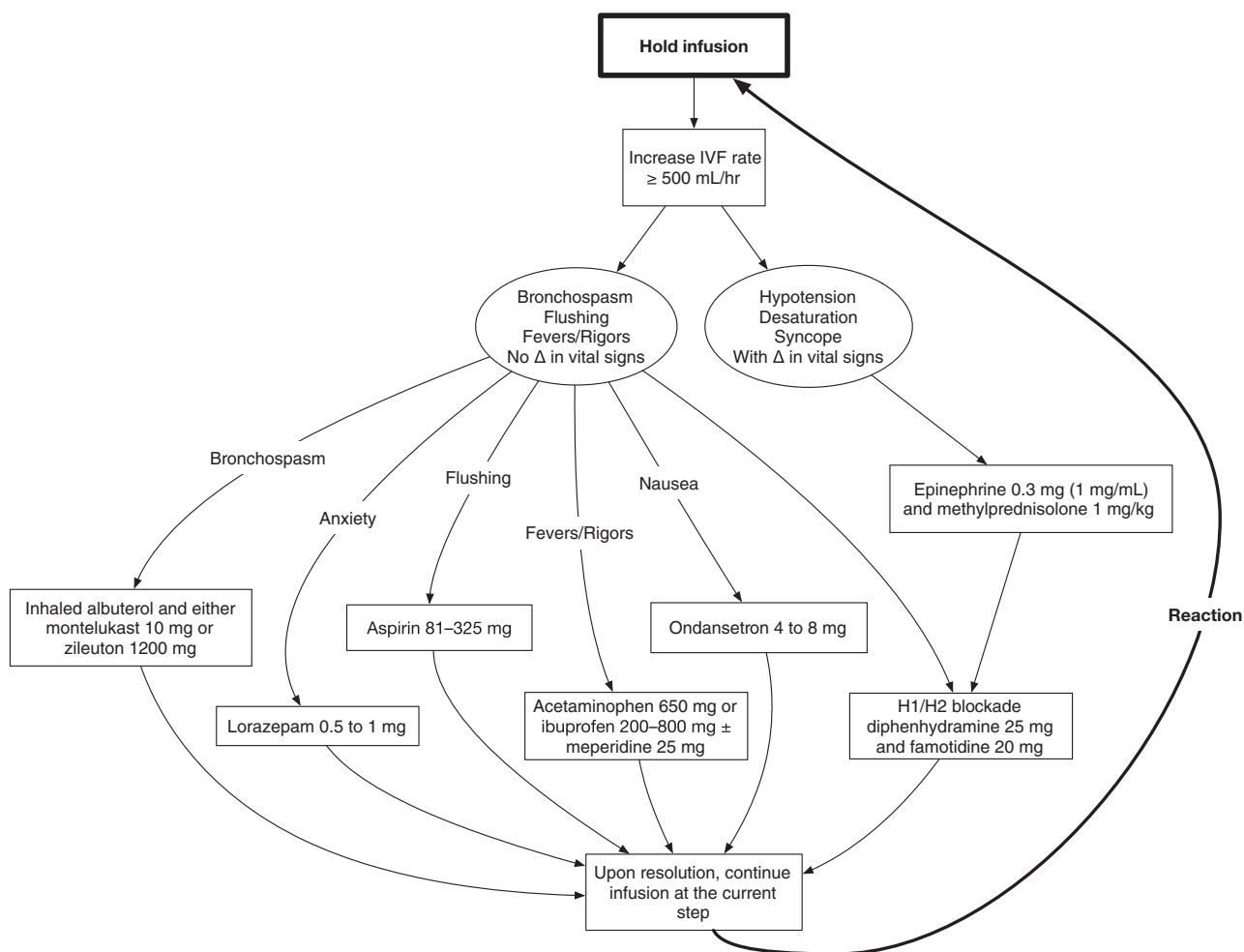


Figure 2. Guidelines for the management of breakthrough reactions during rituximab desensitization.

For desensitization, she was premedicated with cetirizine 10 mg orally, famotidine 20 mg orally, montelukast 10 mg orally, and ibuprofen 400 mg orally. During step 11, she began to have throat pain and chills. The infusion was paused, and intravenous fluids were increased. Intravenous diphenhydramine 25 mg and famotidine 20 mg were administered. The infusion was restarted 30 minutes later, and within 5 minutes, she developed chills, and intravenous meperidine 25 mg and methylprednisolone 40 mg was administered. She was then found to have a fever of 102.1°F, so oral acetaminophen 650 mg was administered.

In all reactions that occur during desensitization, the infusion is promptly held (Fig 2). The next step is to classify the severity into mild, moderate, or severe.⁴ Mild reactions consist of primarily cutaneous symptoms, such as isolated itching, flushing, hives, or angioedema. Moderate reactions show signs of additional organ system involvement and include symptoms of subjective fever, measured temperature of less than 38°C, mild chest tightness, nausea, abdominal pain, or back pain with otherwise normal vital signs. Both mild and moderate reactions are treated with diphenhydramine, COX inhibitors, and intravenous fluids.

Severe reactions include symptoms of hypotension, acute encephalopathy, syncope, bronchospasm, throat swelling, wheezing, or respiratory distress, and they include changes in vital signs and are treated aggressively. Intramuscular epinephrine, intravenous diphenhydramine and methylprednisolone, oxygen, nebulized albuterol, and intravenous fluids are given.⁹ If the patient has been on β -agonist blockade therapy, intravenous glucagon is administered as a bolus followed by an infusion.

Regardless of the severity, the remaining management is targeted to specific symptoms (Fig 2). Bronchospasm is treated with inhaled beta agonists and either montelukast or zileuton. Flushing is treated with aspirin. Anxiety is treated with low-dose

benzodiazepines; nausea with ondansetron; fever and chills with acetaminophen and meperidine. The patient is observed until the reaction subsides and it is safe to continue. The protocol is then resumed at the point the infusion was stopped (at the exact rate and dose of the current step). There is no going back to previous steps, and resolution of 80% of symptoms is sufficient to resume the infusion. Patients who receive epinephrine and remain stable can continue their protocol.

The tryptase level was found to be 7.6 ng/mL (normal, <11.5 ng/mL). Interleukin (IL)-6 levels both during and after the desensitization were 400 pg/mL and 190 pg/mL (normal, ≤ 1.8 pg/mL), respectively. Baseline IL-6 was 1.1 pg/mL.

Infusion reactions during desensitization can be classified into 1 of 3 different types: type I IgE/non-IgE-mediated immediate hypersensitivity, cytokine-release, or mixed.⁷ Serum tryptase levels drawn during a reaction are a measurement of mast cell involvement. Elevated levels are strongly suggestive of a type I hypersensitivity reaction, which presents with symptoms of itching, hives, hypotension, and bronchospasm. Tryptase levels should also be drawn 3 weeks after a reaction to screen for mastocytosis.¹⁰ Elevated serum IL-6 levels (along with tumor necrosis factor α and IL-1 β) signify a cytokine-release type of reaction that is attributed to massive B-cell lysis,¹¹ although activation of other immune cells (macrophages and monocytes) cannot be ruled out. Its levels correlate with the severity of reaction and is associated with symptoms of flushing, fever, chills, hypertension, nausea, vomiting, and syncope. A mixed reaction has a positive skin test, and IL-6 and tryptase can be elevated. In addition, IL-6 can be released from mast cells.⁷

She successfully completed her next rituximab desensitization with the premedication addition of oral ibuprofen 800 mg and intravenous normal saline at 250 mL/hr throughout.

Case 3

A 61-year-old man completed 7 treatments with rituximab for marginal zone lymphoma at an outside hospital, which he tolerated well. Within seconds of receiving his 8th lifetime infusion, he

experienced sweating, intense flushing, and chest pain. The infusion was stopped and then resumed after 10 minutes, but the symptoms recurred within seconds. His symptoms resolved within

Table 2
Example of 3-Bag, 12-Step Desensitization Protocol That Was Used in Case #3

Name of medication:					Rituximab	
Target dose (mg)					858.75	
Standard volume per bag (mL)					250	
Final rate of infusion (mL/hr)					80	
Calculated target concentration (mg/mL)					3.435	
Standard time of infusion (minutes)					187.5	
					Total mg per bag	Amount of bag infused (mL)
Solution 1	250	mL of	0.034	mg/mL	8.588	9.25
Solution 2	250	mL of	0.344	mg/mL	85.875	18.75
Solution 3	250	mL of	3.408	mg/mL	851.992	250.00
Step	Solution	Rate (mL/hr)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0172	0.0172
2	1	5.0	15	1.25	0.0429	0.0601
3	1	10.0	15	2.50	0.0859	0.1460
4	1	20.0	15	5.00	0.1718	0.3177
5	2	5.0	15	1.25	0.4294	0.7471
6	2	10.0	15	2.50	0.8588	1.6059
7	2	20.0	15	5.00	1.7175	3.3234
8	2	40.0	15	10.00	3.4350	6.7584
9	3	10.0	15	2.50	8.5199	15.2783
10	3	20.0	15	5.00	17.0398	32.3181
11	3	40.0	15	10.00	34.0797	66.3978
12	3	80.0	174.375	232.50	792.3522	858.7500
Total time (minutes) =			339.375	= 5.66 hr		

minutes, and without additional medical treatment. His vital signs were normal throughout. He was unable to complete the remainder of the infusion.

The patient was referred to the allergy clinic, and the skin test was positive at the intradermal level to rituximab 1 mg/mL. Using risk stratification classifying this as a moderate reaction, a 3-bag, 12-step protocol for desensitization was recommended (Table 2), along with premedication with montelukast 10 mg orally, aspirin 325 mg orally, cetirizine 10 mg orally, methylprednisolone 40 mg intravenously, acetaminophen 650 mg orally, and famotidine 20 mg orally.

In this case, the reaction had features of both type I IgE-mediated reaction and cytokine-mediated reaction. This was confirmed by positive skin testing. A change of more than half of all reactions from type I to cytokine release is seen when comparing the initial reactions with the reactions that occur during desensitization; the mechanism of this is unclear.⁷ The desensitization protocol may prevent the symptoms of type I reaction, unmasking cytokine-release symptoms. Desensitization has been shown to be helpful for both kinds of reactions, possibly because of this type-switching phenomenon.

Conclusion

Rituximab is a chimeric monoclonal anti-CD20 antibody that has a clinically significant incidence of hypersensitivity reactions that can limit its use. Through rapid desensitization, one can overcome the hypersensitivity and receive treatment. Once a reaction is identified, the patient is risk stratified to determine the viability of desensitization. If so, a protocol is then selected and

During the last step of desensitization, he developed flushing, chills, and a sensation of restlessness. The infusion was held for 15 minutes, and the rate of normal saline was increased to 250 mL/hr. An hour after the infusion was continued, he had a fever of 102.4°F. He was given another oral dose of acetaminophen 650 mg, intravenous meperidine 25 mg, diphenhydramine 25 mg, and famotidine 20 mg.

After the desensitization, his tryptase level was 10.2 ng/mL (normal, <11.5 ng/mL), and his IL-6 level was >3000 (normal, <17.4 pg/mL). A month later, his repeat baseline tryptase was measured to be 6.1 ng/mL, and baseline IL-6 was <2.9 pg/mL.

A baseline tryptase is important in this situation, because the initial tryptase was noted to be normal at 10.2. However, the minimal elevation of tryptase based on the baseline tryptase is 9.32 ($2 + 1.2 \times \text{baseline tryptase level}$), making the tryptase level in this case significant.¹²

The patient later underwent 2 more administrations of rituximab via desensitization with the addition of normal saline running at 250 mL/hr for the entirety of the infusion, without reaction.

further tailored to overcome the specific symptoms experienced by that patient during their initial reaction with appropriate premedication. When reactions occur during desensitization, they are managed in real time based on the type and severity of the reaction. Desensitization is thus a paragon of modern personalized medicine.

References

- Ataca P, Atilla E, Kendir R, Bavbek S, Ozcan M. Successful desensitization of a patient with rituximab hypersensitivity. *Case Reports Immunol*. 2015;2015:524507.
- Wong JT, Long A. Rituximab hypersensitivity: evaluation, desensitization, and potential mechanisms. *J Allergy Clin Immunol Pract*. 2017;5:1564–1571.
- Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol*. 2008;122:574–580.
- Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol*. 2004;114:371–376.
- Brennan PJ, Rodríguez Bouza T, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol*. 2009;124:1259–1266.
- Ozturk E, Ozyigit LP, Ozturk AB, Akay MO, Cetiner M, Ferhanoglu B. Rituximab desensitization in three patients with severe rituximab allergy. *Curr Probl Cancer*. 2017;41:349–354.
- Isabwe GAC, Garcia Neuer M, de Las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: phenotypes and endotypes. *J Allergy Clin Immunol*. 2018;142:159–170.
- Sloane D, Govindarajulu U, Harrow-Mortelliti J, et al. Safety, costs, and efficacy of rapid drug desensitizations to chemotherapy and monoclonal antibodies. *J Allergy Clin Immunol Pract*. 2016;4:497–504.
- Sheikh A, Shehata YA, Brown SG, Simons FE. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock. *Cochrane Database Syst Rev*. 2008;CD006312.
- Hsu Blatman KS, Castells MC. Desensitizations for chemotherapy and monoclonal antibodies: indications and outcomes. *Curr Allergy Asthma Rep*. 2014;14:453.
- Picard M, Galvao VR. Current knowledge and management of hypersensitivity reactions to monoclonal antibodies. *J Allergy Clin Immunol Pract*. 2017;5:600–609.
- Sprung J, Weingarten TN, Schwartz LB. Presence or absence of elevated acute total serum tryptase by itself is not a definitive marker for an allergic reaction. *Anesthesiology*. 2015;122:713–714.