

Current Knowledge and Management of Hypersensitivity Reactions to Monoclonal Antibodies



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Hypersensitivity reactions (HSRs) to monoclonal antibodies (mAbs) are increasingly frequent as this class of therapeutic agents is rapidly expanding. Immediate and nonimmediate HSRs have been reported with mAbs. Immediate HSRs can be explained by 3 main mechanisms: cytokine release syndrome, IgE-mediated, and IgG-mediated reactions. Importantly, IgE-mediated reactions can occur on first exposure due to preformed specific IgEs, as shown for cetuximab. Almost all patients with an immediate HSR can be safely re-exposed either through desensitization or challenge depending on the severity and mechanism of the initial reaction. An algorithm detailing the general approach to these HSRs and the preferred method of re-exposure is presented in this review. Also, the mAbs that are most frequently implicated in HSRs are discussed individually. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:600-9)

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Monoclonal antibodies (mAbs) are a rapidly expanding class of targeted biological agents. In contrast to most other drugs, which are small chemical molecules, mAbs are proteins (many with sequences of murine origin). Therefore, immunogenicity is an important issue that impacts the development of these agents because it may reduce their efficacy (because of neutralizing anti-mAbs) and/or their safety (by being responsible for hypersensitivity reactions [HSRs]).¹ Fully human mAbs are considered less immunogenic than humanized or chimeric mAbs, which contain variable amounts of sequences of mouse origin.¹ However, even fully human proteins can elicit an unwanted immune

response.^{1,2} The World Health Organization established guidelines for the nomenclature of mAbs so that the source of the different parts of the antibody can be easily determined (Table I).³

HSRs to mAbs are an increasingly frequent clinical problem and the allergist has a key role to play in their management. In this review, the nomenclature put forward by the International Consensus on drug allergy will be used. It stipulates that HSRs are adverse effects of drugs that clinically resemble allergic reactions.⁴ HSRs are classified as immediate (when they occur within an hour of administration) or nonimmediate (when they occur more than an hour after administration). When an immunologic mechanism (eg, IgE- or T-cell-mediated) has been demonstrated, these reactions are termed drug allergies. Therefore, acute infusion reactions will be referred to as immediate HSRs and delayed infusion reactions as nonimmediate HSRs.

This review will first describe the clinical presentations, discuss the mechanisms, and provide a general management strategy for HSRs to mAbs. In the second part, it will discuss in detail the agents most frequently implicated in HSRs.

MECHANISMS AND CLINICAL PRESENTATIONS OF HSRs TO mAbs

Immediate HSRs

Three main mechanisms have been implicated in immediate HSRs to mAbs: cytokine release syndrome, IgE-mediated, and IgG-mediated reactions (Table II). It should be kept in mind that mixed reactions could occur with mAbs. These HSRs would be characterized by features of a cytokine release syndrome (eg, fever) as well as features of an IgE-mediated reaction (eg, elevated tryptase when measured shortly after the reaction and/or a positive skin test result).

Reactions due to cytokine release syndrome typically occur on the first administration and generally wane rapidly with subsequent exposures.⁵ They are characterized by the rapid destruction of cells targeted by the mAb through complement-mediated and/or antibody-mediated cell death (ADCC).⁶ This rapid destruction leads to the release of proinflammatory cytokines such as TNF- α and IL-6.⁶ Their clinical features are varied and range from nonspecific symptoms (flushing, dyspnea, throat tightness, dizziness/hypotension, and gastrointestinal symptoms) to more distinctive features (headache, increased blood pressure, chest and back pain, fever, chills, and rigors).⁷ These reactions can be attenuated or prevented by premedication with corticosteroids and acetaminophen and a slow increase in the infusion rate.^{5,8}

IgE-mediated reactions to mAbs typically occur after at least one uneventful administration because sensitization has to take place before a reaction can develop.^{9,10} However, there is at least

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Abbreviations used

ADCC-Antibody-mediated cell death

HER2-Human epidermal growth factor receptor 2

HSR-Hypersensitivity reaction

mAb-Monoclonal antibody

SDRIFE-Symmetrical drug-related intertriginous and flexural exanthema

SJS-Stevens-Johnson syndrome

SSLR-Serum sickness-like reaction

Th2-T helper 2

one notable exception: cetuximab. As discussed later, in the case of cetuximab, preformed IgE antibodies are responsible for immediate HSRs that occur on first exposure to this mAb.¹¹ Even though this phenomenon has not been demonstrated for other mAbs, one should keep in mind this possibility when faced with a reaction compatible with anaphylaxis on first exposure.¹² Symptoms of an IgE-mediated reaction can range from isolated skin symptoms to anaphylactic shock and may sometimes overlap with symptoms of cytokine release (eg, fever, rigors, chills).^{12,13} A skin test with a nonirritating concentration of an mAb that is positive on immediate reading is strongly suggestive of an IgE-mediated allergy.^{12,13} Also, an elevated serum tryptase level measured at the time of the HSR indicates mast cell degranulation and suggests the possibility of an IgE-mediated reaction.¹⁴

IgG-mediated reactions to mAbs have not been clearly demonstrated. However, in the case of infliximab, anti-mAb IgGs are associated with 2 main problems: reduced efficacy (through increased clearance and/or by blocking the antibody-binding site) and HSRs.^{15,16} In contrast, this association has not been found for another chimeric mAb: rituximab.¹⁷ Although this remains to be shown in humans, it is hypothesized that the mAb could stimulate anti-mAb IgGs bound to Fc-gamma-receptors on macrophages, basophils, and neutrophils triggering the release of platelet-activating factor, as shown in the mouse model of IgG-dependent anaphylaxis.¹⁸ In addition, the complement system could be activated by the formation of large immune complexes thereby generating anaphylatoxins (C3a and C5a).^{18,19} Symptoms of IgG-mediated reactions would thus be quite similar to those observed in IgE-mediated reactions as both involve mast cell/basophil activation.¹² Also, they should typically occur after at least one uneventful infusion as sensitization would be required. Notably, skin testing should be negative in those patients.⁹

Some reactions with clinical features of an immediate HSR may develop several hours after administration especially when the mAb is administered subcutaneously.^{20,21} These reactions should be considered as immediate HSRs.

Nonimmediate HSRs

The most common manifestation of a nonimmediate HSR to mAbs is a serum sickness-like reaction (SSLR). Onset is typically from 5 to 7 days after infusion and it may present with fever, malaise, arthralgia/arthritis, jaw pain or tightness, an erythematous (sometimes urticarial) skin eruption, purpura, and conjunctival hyperemia.^{22,23} In a few cases, immediate HSRs may precede or follow SSLR.^{22,24,25} These reactions may occur with the first exposure to the mAb although they most frequently develop after at least one uneventful infusion.^{22,25} They are

thought to be caused by the deposition of immune complexes composed of the mAb and anti-mAb IgGs in small blood vessels.²² A wide range of rare nonimmediate HSRs have been attributed to mAbs from symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis although the causality often remains uncertain.²⁶⁻²⁸

MANAGEMENT OF HSRs TO mAbs

General approach

The first step in the evaluation of a patient with an HSR to an mAb is to determine the most likely mechanism of the reaction (Table II and Figure 1). A positive skin test result to a nonirritating concentration of a mAb (Table III) strongly suggests an IgE-mediated mechanism and warrants re-exposure only through desensitization given the risk of anaphylaxis.^{12,13}

On the other hand, for non-IgE-mediated reactions, the method of re-exposure should be based on the severity of the initial HSR (Table IV).^{7,12} Desensitization is generally favored for patients with severe reactions, whereas a challenge may be attempted in those with mild reactions.^{7,12} In patients with a moderate HSR, the decision between challenge and desensitization should be made on a case-by-case basis taking into consideration the likelihood of a recurrent reaction and its potential impact on the patient.

If desensitization is well tolerated, the protocol can be progressively shortened to 2 bags and then to 1 bag.¹³ The final infusion rate can also be safely increased up to 160 mL/h.¹³ In patients with non-IgE-mediated reactions, a challenge can be considered in those who tolerate short desensitization protocols, as some may be able to tolerate regular infusions.^{7,29}

Premedication

Premedication is generally used as an adjunct to desensitization and it should be tailored to the clinical features of the initial HSR. H1 and H2 antihistamines are generally administered to prevent cutaneous symptoms, montelukast can be used in patients with prominent respiratory symptoms, and aspirin is sometimes used to prevent flushing.^{12,13} In addition, acetaminophen, nonsteroidal anti-inflammatory drugs, and corticosteroids can be used to prevent fever.^{12,13} A benzodiazepine such as lorazepam can also be helpful to alleviate the anxiety associated with desensitization.¹² Premedication is generally administered 30 minutes to 1 hour before the start of the infusion.^{12,13}

Desensitization

The best-studied desensitization protocol for mAbs is the 12-step/3-bag protocol developed at Brigham and Women's Hospital (Table V).^{12,13,30} Desensitization procedures should be performed in a facility equipped to treat anaphylactic reactions, with a one-to-one nurse-to-patient ratio and under the supervision of an allergist.^{12,13} Breakthrough reactions occur in around 30% of desensitizations, most commonly during the last step of the protocol, and are generally mild.¹² When a breakthrough reaction occurs, the infusion should be paused and treatment tailored to the patient's symptoms. H1 and H2 antihistamines, intravenous fluids, montelukast, inhaled β -agonist, and corticosteroids can be used.¹² Intramuscular epinephrine is rarely needed but should be given if anaphylaxis occurs.^{12,13} Meperidine can be useful to treat rigors and chills.³¹ After resolution of the HSR, the infusion is resumed where it was stopped and

TABLE I. Monoclonal antibodies nomenclature³

	Antibody structure	Suffix	Examples
Chimeric	Constant region: human Variable region: mouse	-ximab	Rituximab
Humanized	Constant region: human Variable region: human except the complementary determining regions (mouse)	-zumab	Trastuzumab
Fully human	Constant region: human Variable region: human	-mumab	Adalimumab
Receptor molecule fused with the Fc portion of IgG	Receptor molecule: human Fc region of IgG: human	-cept	Etanercept

TABLE II. Mechanisms of immediate HSRs to mAbs

Mechanism	Clinical features	Skin test	Examples of mAbs	Re-exposure
IgE mediated	May occur on first exposure but onset usually after at least one exposure; Elevated tryptase	Positive	Cetuximab, Infliximab, Rituximab, Tocilizumab, Bevacizumab	Desensitization only
IgG mediated	Onset usually after several exposures	Negative	Infliximab	Rechallenge or desensitization
Cytokine release syndrome	Fever and chills	Negative	Rituximab	Rechallenge or desensitization
			Ofatumumab	
	Onset usually on first exposure		Trastuzumab	

HSR, Hypersensitivity reaction; mAb, monoclonal antibody.

almost all patients are then able to complete the protocol.^{12,13} In patients with breakthrough reactions, premedication is usually adjusted for subsequent desensitizations. For example, if a patient had a reaction during step 11, an additional dose of H1 antihistamine could be administered at the beginning of step 10. Other interventions that can help prevent breakthrough reactions include adding an intermediate step before the one where the reaction occurred, infusing normal saline at rates between 100 and 250 mL/h in parallel to the desensitization, limiting the final infusion rate of the mAb to 40 or 60 mL/h, and using a 4-bag/16-step desensitization protocol in patients with a very low reaction threshold.^{12,13}

Challenge

There is no standardized procedure for a challenge to mAbs. As a general rule and to abide by the principles of a graded drug challenge,³² we would recommend starting the mAb infusion at one-tenth the target infusion rate for 15 minutes and, if well tolerated, then increasing the rate to its target according to the manufacturer's instructions. For mAbs where the infusion rate has to be slowly increased, we would use the regular infusion protocol.

TNF- α INHIBITORS

Infliximab is a chimeric mAb directed against TNF- α used in the treatment of rheumatoid arthritis, ankylosing spondylarthritis, psoriasis, Crohn's disease, and ulcerative colitis.³³ It is administered intravenously, whereas all the other anti-TNF- α biologics are administered subcutaneously. Certolizumab is an antigen-binding fragment (Fab) of a humanized mAb linked to

polyethylene glycol, adalimumab and golimumab are fully human mAbs, and etanercept is composed of 2 TNF- α receptors linked to the Fc fragment of IgG.³⁴⁻³⁷

Immediate HSRs to infliximab

Immediate HSRs to infliximab occur in around 10% of patients.³⁸⁻⁴⁰ Their clinical features are varied and range from symptoms suggestive of mast cell/basophil activation (flushing, pruritus, dyspnea, dizziness/hypotension) to nonspecific symptoms (headache, increased blood pressure, chest and back pain, fever, and chills).^{9,12,38,40} Immediate HSRs may occur with the first exposure, but their incidence peaks around the seventh infusion.^{12,40}

Multiple mechanisms may account for these reactions.²³ Patients with anti-infliximab IgGs are at increased risk (relative risk varies from 2.4 to 4.0) of immediate HSRs compared with patients without such antibodies.^{15,16} Anti-infliximab antibodies are also associated with loss of efficacy owing to their neutralizing effect and accelerated elimination of infliximab.¹⁶ Concomitant use of other immunosuppressive drugs such as methotrexate or azathioprine and treatment at fixed time intervals as compared with episodic therapy appear to reduce the chance of developing anti-infliximab antibodies and immediate HSRs.²³ IgE-mediated reactions account for a subset of immediate HSRs to infliximab. An immediate positive skin test response to infliximab and anti-infliximab IgEs were seen on average in 28% (range: 4%-67%) and 21% (range: 13%-27%) of reactive patients, respectively.^{9,12,13,41,42} In comparison, anti-infliximab IgEs and an immediate positive skin test response to infliximab occur in 10% and 3% of tolerant patients, respectively.⁹ In addition, infliximab-specific T cells with a T helper

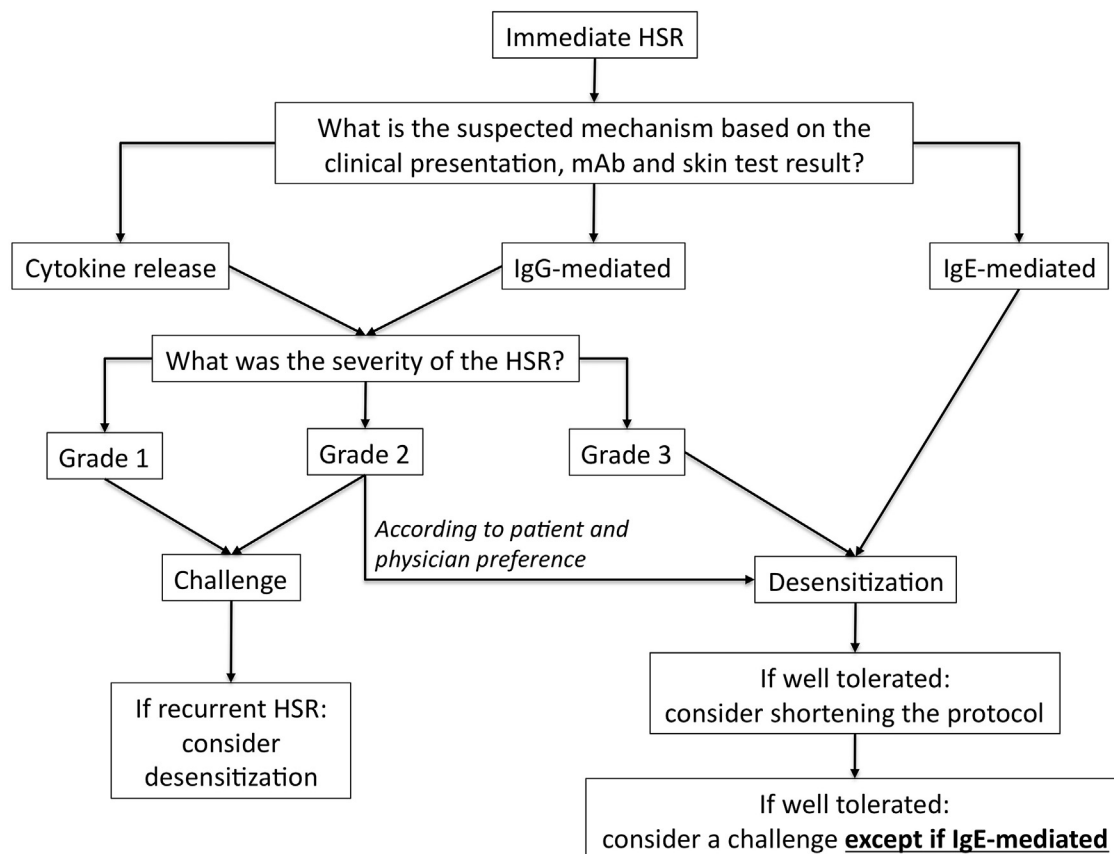


FIGURE 1. Suggested algorithm for the management of immediate hypersensitivity reactions to monoclonal antibodies. *HSR*, Hypersensitivity reaction; *mAb*, monoclonal antibody.

2 (Th2) cytokine profile were recently described in patients with anti-infliximab IgEs.⁴³ Lastly, cytokine release could also explain some of the features of immediate HSRs such as fever because infliximab can cause T-cell apoptosis by binding to transmembrane TNF.^{23,44}

Patients with an immediate HSR to infliximab comprising clinical features suggestive of mast cell/basophil activation should be skin tested to identify those with an IgE-mediated allergy. Intradermal testing may be performed directly, as no patient has been reported with a positive skin prick test.^{9,42} Caution should be exercised if skin testing is performed several months after the last exposure because skin test positivity has been shown to wane quickly over time.⁹ Patients with a positive skin test result or with a severe initial HSR or with recurrent reactions despite added premedication and/or a slowed infusion rate should undergo desensitization, which is usually well tolerated.^{12,13,38,42} In others, retreatment using the protocol developed by Cheifetz et al²⁵ (premedication with an H1 antihistamine and acetaminophen followed by a slow increase of the infusion rate) can be used and appears to be safe.^{38,42} The risk of a recurrent reaction with subsequent exposures is around 33% on the first re-exposure and it progressively decreases thereafter.²⁵ Therefore, in patients who tolerate desensitization well, it may be reasonable to progressively shorten desensitization protocols and eventually proceed to a challenge procedure except in those with an IgE-mediated allergy.

Cross-reactivity of infliximab with adalimumab

Anti-infliximab antibodies do not cross-react with adalimumab.⁴⁵ However, patients who develop anti-infliximab antibodies are more prone to develop anti-adalimumab antibodies and have a higher treatment failure rate with adalimumab.⁴⁶ Also, rare cases of patients with an immediate HSR to infliximab have been described who also reacted to adalimumab (injection site reaction or SSLRs).^{42,47} Despite these caveats, switching to adalimumab after an HSR to infliximab can be attempted.^{38,42}

Injection site reactions

Injection site reactions occur in around 20% of patients treated with adalimumab or etanercept and in 2% to 6% of patients treated with certolizumab or golimumab.^{48,49} Reactions to etanercept occur in median on the fourth injection, have their onset 1 to 2 days after injection, last 2 to 3 days, and may be accompanied by recall reactions (local reactions at the site of previous injections).⁴⁸ These reactions usually wane over time.⁴⁸ It is thought that they represent a T-cell-mediated HSR as CD8+ T cells were shown to be the main immune cell type present in those lesions.⁴⁸ A similar phenomenon has also been shown in 2 patients with injection site reactions to adalimumab with onset 12 to 24 hours after injection and lasting up to 4 days with a positive skin test read at 24 to 48 hours.⁵⁰ Injection site reactions are usually

TABLE III. Suggested skin testing concentrations for mAbs

Agent	SPT	IDT
Adalimumab* ²⁰	40 mg/mL (full strength)	0.4 mg/mL (1/100 dilution)
Bevacizumab* ^{13,29}	25 mg/mL (full strength)	2.5 mg/mL (1/10 dilution) [†]
Brentuximab vedotin	NA	NA
Certolizumab	NA	NA
Cetuximab* ^{13,29}	2 mg/mL (full strength)	0.2 mg/mL (1/10 dilution) [‡]
Etanercept* ²⁰	50 mg/mL (full strength)	0.5 mg/mL (1/100 dilution)
Golimumab	NA	NA
Infliximab* ^{9,29}	10 mg/mL (full strength)	1 mg/mL (1/10 dilution)
Obinutuzumab	NA	NA
Ofatumumab	NA	NA
Omalizumab* ⁹⁸	125 mg/mL (full strength) [§]	0.00125 mg/mL (1/100,000 dilution)
Pertuzumab ⁷⁶	1.6 mg/mL ($\approx$ 1/20)	0.16 mg/mL ($\approx$ 1/200 dilution) [‡]
Rituximab* ^{12,29}	10 mg/mL (full strength)	1 mg/mL (1/10 dilution) [¶]
Tocilizumab* ⁹⁰	20 mg/mL (full strength)	20 mg/mL (full strength)
Trastuzumab ¹²	21 mg/mL (full strength)	2.1 mg/mL (1/10 dilution)

IDT, Intradermal test; NA, not available; SPT, skin prick test.

All dilutions should be made in normal saline.

*Concentrations shown to be nonirritating by testing on healthy control subjects.

[†]A concentration of 25 mg/mL was also shown to be nonirritating.²⁹

[‡]A concentration of 0.5 mg/mL was shown to be nonirritating in 8 controls⁹⁹ and another group reported a concentration of 5 mg/mL to be nonirritating.²⁹

[§]Omalizumab should be reconstituted with normal saline to avoid false positive results.⁹⁸

^{||}Full strength concentration is 30 mg/mL. Pertuzumab was only tested on one reactive subject with negative results at 1.6 mg/mL (SPT) and up to 0.16 mg/mL (IDT). Higher concentrations could be nonirritating.

[¶]Although 1 mg/mL (IDT) is more commonly used, a maximal concentration of 10 mg/mL (full strength) for rituximab IDT is recommended by the European Network on Drug Allergies and does not seem irritating.²⁹

managed with ice, an oral antihistamine, topical corticosteroids, and analgesics.⁴⁹

IgE-mediated reactions may also be the cause of some injection site reactions and also of rare systemic reactions to adalimumab and etanercept. In the largest case series, all 12 patients had a positive skin test response on immediate reading to the culprit mAb strongly suggesting an IgE-mediated reaction.²⁰ Most of these reactions developed after several uneventful injections (most commonly on the fourth injection) although 3 of 12 patients reacted on the first administration.²⁰ An underlying immunological phenomenon should also be considered in patients with progressive worsening of the injection site reactions.⁵¹ In patients with important injection site reactions and in those with systemic reactions, desensitization can be used to alleviate symptoms followed by weekly administration to maintain the desensitized state.²⁰

TABLE IV. Severity grading of immediate hypersensitivity reactions¹⁰⁰

Grade	Severity	Description
1	Mild	Symptoms are limited to the skin (eg, flushing) or involve a single organ/system and are mild (eg, mild back pain)
2	Moderate	Symptoms involve at least 2 organs/systems (eg, flushing and dyspnea), but there is no significant drop in blood pressure or in oxygen saturation
3	Severe	Symptoms typically involve at least 2 organs/systems and there is a significant drop in blood pressure (systolic $\leq$ 90 mm Hg and/or syncope) and/or oxygen saturation ($\leq$ 92%)

Nonimmediate HSRs

SSLRs have been described with infliximab and adalimumab although they are much less frequent than immediate HSRs.⁴⁹ Onset is typically from 5 to 7 days after infusion and the HSR may involve fever, malaise, arthralgia/arthritis, and an erythematous (sometimes) urticarial skin eruption.⁵² Desensitization is not a safe method of preventing such reactions, but the optimal approach remains unclear. Switching to another TNF- α has not been adequately studied although some authors have reported that re-exposure to the suspected culprit drug may not necessarily lead to a recurrent reaction.^{25,53}

Many different types of skin eruptions may develop during treatment with TNF- α inhibitors.⁵⁴ Most notably, psoriasiform and eczematous skin eruptions appear to be frequent although they rarely necessitate discontinuation of the mAb.⁵⁴ Other rare reactions that may occur include SDRIFE,²⁶ erythema multiforme,⁵⁵ SJS,⁵⁶ and a variety of autoimmune diseases such as drug-induced lupus.⁵⁷

RITUXIMAB

Immediate HSRs

Rituximab is a chimeric mAb against CD20, a surface marker expressed by B cells.²³ It is used in the treatment of B-cell malignancies and multiple autoimmune diseases.²³ Its mechanism of action implies B-cell lysis through ADCC and complement activation.²³ Immediate HSRs are quite common on first exposure to rituximab occurring in around half of patients with a B-cell malignancy despite premedication with acetaminophen, antihistamines, and, often, corticosteroids.^{5,23} These reactions are usually less common in patients with inflammatory disorders such as rheumatoid arthritis where they occur in around 25% on first exposure.¹⁷ Most of these reactions are consistent with a cytokine release syndrome caused by massive B-cell lysis.⁶ TNF- α and IL-6 serum levels were shown to correlate with the severity of these reactions.⁶ Higher B-cell counts are associated with a higher likelihood of reaction and corticosteroids are effective at preventing these reactions.^{5,6} Importantly, these reactions may present solely with cutaneous and respiratory symptoms without any signs of fever, chills, or rigors.⁷ Most of these reactions are mild or moderate and do not recur on further exposures, which are often given with added premedication and/or a more progressive increase in the infusion rate.^{5,7,17,23} On the other hand, patients with severe reactions on first exposure could benefit from desensitization because the chance of a recurrent

TABLE V. Example of a desensitization protocol to infliximab (12-step/3-bag)¹³

Drug: infliximab						
Target dose: 400 mg						
Bag	Volume (mL) per bag	Concentration (mg/mL) per bag	Amount (mL) of bag infused	Dose infused (mg) per bag		
Solution 1	250	0.016	9.25	0.148		
Solution 2	250	0.16	18.75	3		
Solution 3	250	1.587	250	396.75		
Step	Solution	Rate (mL/h)	Time (min)	Volume infused (mL)	Dose infused (mg) per step	Cumulative dose (mg)
1	1	2	15	0.5	0.008	0.008
2	1	5	15	1.25	0.02	0.028
3	1	10	15	2.5	0.02	0.068
4	1	20	15	5	0.08	0.148
5	2	5	15	1.25	0.20	0.348
6	2	10	15	2.5	0.40	0.748
7	2	20	15	5	0.80	1.548
8	2	40	15	10	1.6	3.148
9	3	10	15	2.5	3.969	7.117
10	3	20	15	5	7.937	15.054
11	3	40	15	10	15.874	30.928
12	3	80	174.4	232.5	369.072	400
Total time (h) = 5.7 h						

reaction appears to be high.⁷ Also, several of these patients may have a positive skin test result suggesting an IgE-mediated reaction, thus reinforcing the indication for desensitization.^{7,12} Desensitization would also be indicated for a patient with recurrent reactions despite added premedication and a slower infusion rate.⁷

Some patients who initially tolerate rituximab then develop immediate HSRs on subsequent exposures.^{10,12} These reactions should be considered IgE-mediated until proven otherwise. A recent case report clearly showed the presence of rituximab-specific IgEs and Th2 cells as well as a positive skin test result in such a patient.¹⁰ In this case report, the patient had a first HSR on the fourth exposure. She tolerated the fifth infusion, which took place 10 months after the fourth, but soon after she had a recurrent HSR on the sixth infusion illustrating the “wax and wane” nature of IgEs to rituximab.¹⁰ Desensitization should be used to re-expose those patients to rituximab.^{12,13} To minimize the risk of breakthrough reactions in pediatric patients, the desensitization protocol should be adapted to the patient’s weight, so that the increase in the infusion rate is not faster than 0.5 mg/kg/h and the final infusion rate is not higher than 2 mg/kg/h.⁵⁸

Serum sickness-like reactions

There are at least 34 case reports of SSLRs to rituximab.²² Most cases have been reported in patients receiving rituximab to treat autoimmune diseases.²² Re-exposure was attempted in 4 patients who were premedicated with high-dose corticosteroids.²² Two patients tolerated re-exposure, whereas one had a recurrent SSLR and the other had a severe immediate HSR.²²

OFATUMUMAB AND OBINUTUZUMAB

Ofatumumab is a fully human whereas obinutuzumab is a humanized mAb, and both have the same molecular target as rituximab (CD20) and are used in B-cell malignancies.^{59,60} Both

mAbs cause immediate HSRs, thought to be caused by cytokine release, in more than 50% of patients on first exposure despite a gradual increase in the infusion rate and premedication with acetaminophen, an antihistamine, and a corticosteroid.^{59,61-63} Although the incidence of HSRs rapidly decreases with subsequent infusions, severe reactions that led to drug discontinuation and even fatal HSRs, in the case of ofatumumab, have been reported.^{59,62,63} Skin testing to these mAbs has not been studied. The same approach used for rituximab HSRs can be applied to these agents.

BRENTUXIMAB VEDOTIN

Brentuximab vedotin is a chimeric mAb coupled with a microtubule-disrupting agent used in the treatment of CD30+ lymphomas.⁶⁴ Several cases of anaphylaxis were reported occurring on second exposure in most patients.⁶⁵⁻⁶⁸ Skin testing to brentuximab vedotin has not been reported. Desensitization appears to be the method of choice for re-exposure in patients with anaphylaxis.⁶⁵⁻⁶⁷

TRASTUZUMAB

Trastuzumab, which is used in the treatment of breast cancer, is a humanized mAb targeted against the human epidermal growth factor receptor 2 (HER2).⁶⁹ Between 16% and 40% of patients experience an immediate HSR during the first exposure with clinical features consistent with a cytokine release syndrome.^{70,71} Most of these patients will tolerate future infusions after premedication with an antihistamine and a corticosteroid.⁶⁹⁻⁷¹ However, a subset of patients may experience a severe HSR most commonly complicated by respiratory symptoms and some may not tolerate future exposures.⁷¹ Also, patients with reactions after several exposures have also been reported with a positive skin test suggesting that IgE-mediated reactions may also

occur with trastuzumab.^{12,13} Desensitization is considered a safe method of re-exposing patients with an IgE-mediated reaction to trastuzumab.^{12,13} In contrast, most patients with a reaction consistent with a mild-to-moderate HSR due to cytokine release will tolerate re-exposure without desensitization.^{70,71} However, desensitization may be considered for those with a severe cytokine release reaction, and progressive shortening of the protocol may then be considered if well tolerated.^{12,13} Papulopustular acneiform skin eruptions have been reported in some patients treated with trastuzumab. All were able to continue treatment with trastuzumab and responded well to acne treatment.⁷²

PERTUZUMAB

Pertuzumab is a humanized mAb directed against HER2 that recognizes a different epitope of HER2 compared with trastuzumab.⁷³ These 2 mAbs are used in combination in the treatment of breast cancer.⁷³⁻⁷⁵ Very few patients experience immediate HSRs to pertuzumab.⁷⁴ However, there is a recent case report of a patient with anaphylaxis on the second exposure to pertuzumab who was successfully re-exposed through desensitization.⁷⁶ Interestingly, serum tryptase was elevated from baseline shortly after the HSR although it remained within the normal range.⁷⁶ Skin testing to pertuzumab was negative, but a basophil activation test was positive suggesting an IgE-mediated mechanism.⁷⁶

BEVACIZUMAB

Bevacizumab is a humanized mAb directed against vascular endothelial growth factor used in the treatment of many types of cancer.⁷⁷ Immediate HSRs to bevacizumab are rare occurring in less than 3% of patients and are usually mild.⁷⁸ Among the rare patients with an immediate HSR, most tolerate subsequent exposures with premedication with an antihistamine and a reduction in the infusion rate.⁷⁹ However, in a recent study by Sloane et al,¹³ 2 patients with an immediate HSR to bevacizumab had a positive skin test result and were managed with desensitization. Therefore, an IgE-mediated mechanism should be suspected in those with recurrent HSRs or with a severe immediate HSR.

CETUXIMAB

Cetuximab is a chimeric mAb used in the treatment of colorectal, head and neck, lung and skin cancer, which binds to the epidermal growth factor receptor. Immediate HSRs to cetuximab on first exposure are generally rare (<3%) except in the southeastern United States where the prevalence is around 22%.⁸⁰ In 2008, Chung et al¹¹ showed that most patients (17 of 25; 68%) with a severe immediate HSR on their first exposure to cetuximab had pre-existing IgE antibodies directed against an oligosaccharide present on the murine F(ab')₂ portion of cetuximab: galactose- α -1,3-galactose (α -gal). Soon after, IgE antibodies to α -gal were shown to be the cause of delayed allergic reactions to red meat (beef, pork, lamb).⁸¹ The peculiar geographic distribution of these 2 phenomena (both are especially prevalent in the southeastern United States) led to further investigations, which revealed that bites of the Lone Star tick (*Amblyomma americanum*) were the main cause of sensitization to α -gal in the United States.⁸² Other tick species in Europe and Australia can elicit IgE antibodies to α -gal and thereby allergy to red meat and cetuximab.⁸³

Preemptive skin testing or measurement of IgE antibodies to cetuximab before its initiation is not currently used in daily practice. A retrospective study involving multiple centers across the United States found that 15 of 21 (71%) patients with a severe HSR to cetuximab had pre-existing IgE antibodies to cetuximab compared with 23 of 524 (4%) patients without a severe HSR.⁸⁴ Interestingly, almost all patients with a severe reaction (14 of 15; 93%) had anti-cetuximab IgE levels >0.35 kU_A/L, whereas most patients (16 of 23; 70%) who did not react but had detectable anti-cetuximab IgEs had levels between 0.1 and 0.35 kU_A/L.⁸⁴ This study thus confirmed the association between anti-cetuximab IgE levels and the risk of HSR. Further studies are needed to establish the optimal strategy to preemptively detect cetuximab allergic patients.

Patients with an immediate HSR to cetuximab should be skin tested or have cetuximab-specific IgEs measured to detect those with an IgE-mediated allergy. If skin testing or specific IgEs are positive and cetuximab treatment is to be continued, desensitization should be used.^{13,85,86} A rechallenge with premedication and a slower infusion rate can be considered in those with a negative result and has been shown to be successful in 4 of 5 patients in the study by Chung et al.¹¹ Alternatively, panitumumab, a fully human mAb with the same molecular target as cetuximab, could be used instead because it does not contain α -gal and appears to be equally effective.^{87,88}

TOCILIZUMAB

Tocilizumab is a humanized mAb that binds to IL-6 receptors to block IL-6 signaling.⁸⁹ It is used to treat rheumatoid arthritis and systemic or polyarticular juvenile arthritis.⁸⁹ Immediate HSRs to tocilizumab are rare although several cases of anaphylaxis have been reported occurring from the second exposure onward.^{90,91} Most patients who were evaluated had a positive skin test result to tocilizumab supporting an IgE-mediated reaction.^{13,90,91} Desensitization should be considered the method of choice to re-expose those patients to tocilizumab.^{13,91}

OMALIZUMAB

Omalizumab is a humanized mAb that binds free IgE antibodies.⁹² It is administered subcutaneously and is used in the treatment of moderate-to-severe allergic asthma and chronic idiopathic urticaria.⁹² Anaphylaxis to omalizumab is rare and is estimated to occur in 0.1% to 0.2% of patients.⁹³ A history of anaphylaxis, regardless of the cause, was recently shown to increase the risk of developing anaphylaxis to omalizumab to 0.6%.⁹⁴ Most cases (70%) are immediate (occurring less than an hour after injection) although delayed reactions (>24 hours after the injection) and a protracted course with symptoms progressively developing over the course of several hours have been reported.^{21,94} Two patients with symptom onset >24 hours after the injection were rechallenged and both had recurrent reactions strengthening the causality of omalizumab in these reactions.²¹ The mechanism of immediate HSRs to omalizumab is still unknown. Serum tryptase was normal in all patients with anaphylaxis to omalizumab in whom it was measured.^{95,96} Specific IgE or IgG against omalizumab was not detected in 21 cases of anaphylaxis.⁹⁴ Skin testing to nonirritating concentrations of omalizumab was negative in all tested patients.⁹⁴ Two cases of anaphylaxis to omalizumab were attributed to the excipient polysorbate but since then no other groups have identified such patients.⁹⁵ Further research is needed

to identify the mechanism of these peculiar reactions. The approach to patients with anaphylaxis to omalizumab remains uncertain although rechallenge is not recommended especially in patients with severe reactions. Desensitization may be attempted followed by weekly or biweekly administration to preserve the desensitized state and may allow for continued administration in some patients.⁹⁷

CONCLUSIONS

HSRs to mAbs are a growing problem as they are increasingly used and as new mAbs are constantly being developed. There is still a lot to be learned on the mechanisms of these reactions and on the optimal management strategy of patients with HSRs to mAbs. In daily practice, desensitization remains an essential tool that allows the safe readministration of any mAb to a reactive patient and efforts should be made to make it widely accessible.

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