Clinical Management Review

Current Knowledge and Management of Hypersensitivity Reactions to Monoclonal Antibodies

Matthieu Picard, MD[a], and Violeta Régnier Galvão, MD[b] *Montréal, Québec, Canada; and São Paulo, Brazil*

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 2016;■:■-■)

Key words: *Hypersensitivity; Allergy; Infusion reaction; Monoclonal antibody; Desensitization; Challenge; Skin test; IgE; IgG; Cytokine release*

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

[a]Division of Allergy and Immunology, Department of Medicine, Hôpital Maisonneuve-Rosemont, Université de Montréal, Montréal, Québec, Canada
[b]Division of Allergy and Immunology, Department of Medicine, University of São Paulo Medical School, São Paulo, Brazil
No funding was received for this work.
Conflicts of interest: M. Picard has received consultancy fees from Algorithme Pharma; and has received lecture fees from Sanofi and Nestle. V. R. Galvão declares no relevant conflicts of interest.
Received for publication October 17, 2016; revised November 19, 2016; accepted for publication December 2, 2016.
Available online ■■
Corresponding author: Matthieu Picard, MD, Division of Allergy and Immunology, Department of Medicine, Hôpital Maisonneuve-Rosemont, Université de Montréal, 5415 Boulevard de l'Assomption, Montréal, Québec H1T 2M4, Canada. E-mail: matthieu.picard@umontreal.ca.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.12.001

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