# Monoclonal Antibodies Hypersensitivity

## Prevalence and Management

Rafael Bonamichi Santos, MD, Violeta Régnier Galvão, MD, PhD*

**KEYWORDS**

• Monoclonal antibodies • Biological agents • Rapid drug desensitization
• Drug allergy • Skin test • Immunoglobulin E • Tryptase

**KEY POINTS**

- Monoclonal antibodies (mAbs) are effective in the treatment of autoimmune, neoplastic, and inflammatory diseases.
- Hypersensitivity reactions (HSR) secondary to mAbs are being more reported.
- Some of the main mAbs in clinical use and their associated HSR are reviewed.
- The authors propose algorithms for the treatment of mAb-related HSR and for desensitization indications.

### INTRODUCTION

The first monoclonal antibodies (mAbs) were created in the mid 1970s to target specific mutations and defects in protein structures expressed in several diseases and conditions. They are now part of mainstream treatments for neoplastic, autoimmune, and chronic inflammatory diseases, which led to an increase in the reports of hypersensitivity reactions (HSR) secondary to this drug class.

First-generation mAbs are monospecific/bifunctional antibodies, with one binding site to a specific antigen and an intact Fc-part binding to an Fc receptor on accessory cells. In 2009, catumaxomab, a bispecific/trifunctional mAb, was approved for the treatment of malignant ascites in patients with cancer.[1]

There are 3 types of bispecific mAbs, as follows:

- Trifunctional antibody: presents binding sites for 2 different antigens. In addition, its intact Fc-part can bind to an Fc receptor, on monocytes/macrophages,

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Division of Clinical Immunology and Allergy, University of São Paulo Medical School, Av. Dr. Arnaldo, 455-Cerqueira César, São Paulo, São Paulo 01246-903, Brazil
* Corresponding author.
*E-mail address:* violeta_galvao@yahoo.com.br

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natural killers, dendritic cells, or other Fc receptor–expressing cells to the tumor cells, leading to their destruction.[2]
- Chemically linked Fab: consists only of Fab regions. It is considered non–mmunoglobulin G (IgG)-like.
- Bispecific T-cell engager: fusion proteins consisting of 2 single-chain variable fragments. The protein sources are different antibodies, or amino acid sequences from 4 different genes, on a single peptide chain.

Some of mAbs' mechanisms of action include the following:

- Neutralization of targeted molecule's functions (infliximab: anti–tumor necrosis factor-α [TNF-α]).
- Modulating signaling pathways by blocking targeted cell receptors, also known as checkpoint therapy (ipilimumab: anti–CTLA-4).
- Cell apoptosis mechanisms:
  - Antibody-dependent cell-mediated cytotoxicity
  - Complement-mediated cell lysis
  - Toxic effect of a conjugate drug molecule linked to the mAb Fc region (tositumomab: radioactively conjugated and brentuximab vedotin: cytotoxic-conjugated).

## PHENOTYPES AND ENDOTYPES

### *Type I Hypersensitivity*

Type I hypersensitivity typically occurs within 30 to 120 minutes of the infusion. This type of reaction usually requires a previous exposure to the drug for sensitization to occur,[3] but a notable exception to this rule is a cetuximab-induced HSR.[4] IgE-mediated reactions to this drug might occur because of a previous tick bite (lone star tick, *Amblyomma americanum*) and the consequent development of an anti-α-1,3-galactose antibody.[4]

Various systems can be involved (cutaneous, respiratory, gastrointestinal, cardiovascular, and neurologic), and the severity can range from mild cutaneous symptoms to life-threatening reactions.[5]

Applied subcutaneously, mAbs may cause an IgE-mediated injection-site reaction (ISR), characterized by local redness, warmth, burning, stinging, itching, urticaria. These symptoms usually appear within the first hour of the injection.

### *Immunoglobulin G–Mediated Reactions*

IgG-mediated HSRs are still being studied. On animal models, it was demonstrated that mAbs can stimulate anti-mAb IgGs bound to Fc-gamma-receptors, found on macrophages, basophils, and neutrophils, leading to the release of platelet-activating factor.[6]

Another mechanism could be the activation of the complement system by large immune complexes, generating anaphylatoxins.[6,7] In this case, the clinical presentation would be like that of an IgE-mediated HSR.

### *Type III Hypersensitivity Reactions*

Type III HSRs are secondary to immune complex deposition (mAb + anti-mAb IgG) in small blood vessels located in the skin, kidney, and other organs. This deposition typically occurs 5 to 7 days after the drug exposure.[8,9] Symptoms can include fever, malaise, myalgia, arthralgia/arthritis, jaw pain or tightness, rash, pruritus, erythematous (sometimes urticarial) skin eruption, edema, purpura, and conjunctival hyperemia.[10,11]