Hypersensitivity Reactions to Biologic Agents

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KEYWORDS

• Antidrug antibodies • Biologic agents • Drug allergy • Hypersensitivity reactions • Immunogenicity

KEY POINTS

- Biologic agents (BAs) are important therapeutic tools, but their use may be limited by adverse drug reactions.
- Procedures for management of BA-induced reactions, including preventive, diagnostic work-up and desensitization, are becoming available in the clinical setting.
- The knowledge of such procedures for management of BA-induced reactions may be useful to increase the safety profile of current and forthcoming BAs.

INTRODUCTION

Many BAs have become available as new therapeutic tools, including monoclonal antibody (mAb), cytokines, and fusion proteins. Since their approval, BA therapy had a positive impact on the long-term outcomes, such as disability and mortality, associated with both inflammatory chronic diseases and cancers; thus, in a short period of time, they have entered the mainstream of their treatment.[1,2] There is a large amount of research and development being undertaken to create BAs for many serious diseases, such as rheumatoid arthritis, multiple sclerosis, bowel inflammatory diseases, and different types of cancers.[3] These medications each have their unique profile in terms of efficacy, tolerability, and adverse effects; they are not deprived in toxicity, which can impair quality of life and may occasionally be life-threatening or, more frequently, lead to the interruption of treatment.[4]

DEFINITIONS

Generally, adverse events (AEs) are defined as any untoward medical occurrences associated with the use of a drug in humans, whether or not considered drug related,

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whereas any AE caused by an injected drug is defined as an infusion reaction. The term, *allergic hypersensitivity reactions (HRs)*, refers to antibody- or cellular-mediated infusion reactions. Infusion reactions may be divided into local and systemic reactions.[5] Local infusion reactions, which are induced by subcutaneous BAs, are referred to as injection site reactions (ISRs). Lastly, acute infusion reactions occur during or within 1 hour after infusion or within a few minutes after subcutaneous injection, whereas delayed reactions occur from 1 hour to 14 days after.[6,7]

CLINICAL PRESENTATION: SYMPTOMS AND MANAGEMENT

The clinical manifestations of both acute and delayed reactions vary considerably, ranging from mild to severe and life threatening; thus, important clinical consequences, such as drop-out therapy or fatal cases, may occur.

Acute Infusion Reactions

Acute reactions include mainly cutaneous symptoms, such as itching, urticaria, and flushing, but sometimes anaphylaxis may occur characterized by respiratory distress, laryngeal edema, and bronchospasm, accompanied by gastrointestinal and cardiovascular involvement. In some cases, patients may display fever, skills, or myalgia.[7] The severity of the reaction should be determined to better define the clinical management of such infusion. Mild to moderate events may be managed by reducing the infusion rate (after a temporary interruption) and administering H_1 antihistamines and corticosteroids for symptom control. In cases of severe reactions, the infusion must be stopped and rescue treatment promptly administered, such as epinephrine, liquids, oxygen supply, H_1 antihistamines, and high doses of intravenous steroids, according to the clinical features of the reaction.[8]

Acute infusion reactions may occur at the first dose or during the course of treatment, thus suggesting different underlying pathogenic mechanisms. Matucci and colleagues[9] have recently analyzed the clinical characteristics of infliximab-induced immediate infusion reactions: severe events were 1 in 3 reactions; a majority of reactions occurred within 15 minutes after the beginning of the infusion; and cutaneous and respiratory symptoms were the most frequent clinical features.

Delayed Infusion Reactions

Delayed reactions usually occur within the first 2 weeks after the administration of a BA. They usually present with arthralgia, myalgia, exanthems, fever, urticaria, and itching.[10] The clinical presentation of delayed reactions may be consistent with a classic serum sickness characterized by the production of antibody to foreign immunoglobulin with formation of antigen-antibody complexes. Patchy lung infiltrates and skin necrotizing vasculitis may be present, sustained by inflammatory infiltrates involving small blood vessels and complement deposition at immunofluorescence staining. In addition, there can be lymphadenopathy, splenomegaly, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and melena), and extremity weakness.[11] It has been reported that approximately 2.5% of patients receiving infliximab infusion develop serum sickness–like reactions,[12] but other chimeric molecules used to treat various conditions, such as abciximab for acute coronary syndromes, trastuzumab for breast cancer, rituximab for lymphoma, omalizumab for asthma, and natalizumab for multiple sclerosis, have been associated to these reactions.[12–15] Some delayed reactions associated with mAb infusions may be characterized by a prevalent hematologic involvement, such as hemolytic anemia and immune thrombocytopenia.[16,17] The course of delayed reactions is usually self-limiting, but severe acute respiratory