Hypersensitivity to Biological Agents—Updated Diagnosis, Management, and Treatment

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List of Design Committee Members: Violeta Régnier Galvão, MD, and Mariana Castells, MD, PhD

Activity Objectives

1. To comprehend indications and contraindications of specific desensitization to biological agents.
2. To recognize the clinical presentations of hypersensitivity reactions to biological agents.
3. To understand the management of hypersensitivity reactions to biological agents.
4. To become acquainted with monoclonal antibodies' targets and origins.

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Biological agents are used in the treatment of neoplastic, autoimmune, and inflammatory diseases and their clinical applications are becoming broader. Following their increased utilization, hypersensitivity reactions linked to these drugs have become more frequent, sometimes preventing the use of first-line therapies. The clinical presentation of hypersensitivity reactions to biological agents ranges from mild cutaneous manifestations to life-threatening reactions. In this scenario, rapid desensitization is a groundbreaking procedure that enables selected patients to receive the full treatment dose in a safe way, in spite of their immediate hypersensitivity reaction to the drug, and protects them against anaphylaxis. The aim of this review is to update and discuss some of the main biological agents used in clinical practice (rituximab, trastuzumab, cetuximab, ofatumumab, tocilizumab, brentuximab, omalizumab, and tumor necrosis factor alpha inhibitor agents) and their associated hypersensitivity reactions, including clinical presentations, diagnosis, and treatment in the acute setting. In addition, novel management options with rapid desensitization are presented. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:175-85)

Key words: *Hypersensitivity reactions; Drug allergy; Anaphylaxis; Biological agents; Monoclonal antibodies; Tryptase; Epinephrine; Skin testing; Rapid desensitization*

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Abbreviations used
AS- Ankylosing spondylitis
ASA- Acetylsalicylic acid
BAT- Basophil activation test
CD- Crohn's disease
CLL- Chronic lymphocytic lymphoma
EGFR- Epidermal growth factor receptor
HER-2- Human epidermal growth factor receptor 2
IBD- Inflammatory bowel disease
IDT- Intradermal test
IgE- Immunoglobulin E
ISR- Injection site reactions
IV- Intravascular
JIA- Juvenile idiopathic arthritis
MPA- Microscopic polyangiitis
NHL- Non-Hodgkin's lymphoma
PA- Psoriatic arthritis
PO- Per os
PsO- Plaque psoriasis
RA- Rheumatoid arthritis
SpO_2- Peripheral oxygen saturation
TCZ- Tocilizumab
TNF-α- Tumor necrosis factor alpha
UC- Ulcerative colitis
WG- Wegener's granulomatosis

Biological agents are applied in the treatment of neoplastic, autoimmune, and chronic inflammatory diseases, and their clinical applications are increasing and becoming broader. Hypersensitivity reactions linked to these drugs have become more frequent, sometimes preventing the use of first-line therapies on diseases that require precise management. Examples of immune-mediated and inflammatory diseases that respond to biological agents include rheumatoid arthritis (RA), Crohn's disease (CD), ulcerative colitis (UC), juvenile idiopathic arthritis (JIA), psoriasis and psoriatic arthritis (PA), Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), ankylosing spondylitis (AS), plaque psoriasis (PsO), and asthma. Neoplastic diseases include non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and colorectal, breast, gastric, and lung cancer.[1]

Hypersensitivity reactions to biological agents can occur on the first exposure (ie, cetuximab, trastuzumab) or after multiple exposures, similarly as what can be seen with platinum compounds.[2] The clinical presentation of hypersensitivity reactions secondary to biological agents may include cutaneous (erythema, flushing, pruritus, urticaria, angioedema, itching), cardiovascular (chest pain, tachycardia, presyncope, syncope, hypotension), respiratory (dyspnea, wheezing, oxygen desaturation, throat tightness), gastrointestinal (nausea, vomiting, diarrhea, abdominal pain), and neurological (mental confusion, visual disturbances, and numbness and/or weakness) signs and symptoms. Atypical manifestations such as fever, chills, rigors, back, and neck pain can also occur.

Immediate reactions can be considered mild, moderate, or severe and are classified according to Brown's grading system for immediate hypersensitivity reactions.[3] Mild (grade 1) reactions compromise skin and subcutaneous tissues only, whereas moderate (grade 2) and severe (grade 3) reactions may affect cardiovascular, respiratory, and neurological systems. In a study from 2009, Brennan et al[4] evaluated 105 desensitization procedures to monoclonal antibodies (infliximab, rituximab, and trastuzumab) in 23 patients. Initial reactions were considered mild in 26%, moderate in 48%, and severe in 26%. Reactions that involve cutaneous signs and/or symptoms were the most prevalent, followed by cardiovascular and respiratory reactions. Severe reactions to trastuzumab did not occur, possibly due to the fact that it is a humanized monoclonal and therefore presents less immunogenicity than rituximab and infliximab. Delayed hypersensitivity reactions to biologicals have been reported, with reports of rash, serum-sickness-like symptoms, vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.[5-9]

When a patient presents a hypersensitivity reaction to a biological, rapid desensitization is a groundbreaking procedure that will enable the patient to receive the full treatment dose while protecting him from anaphylaxis. A standard desensitization protocol to monoclonal antibodies has been developed with 3 intravenous dilution bags, 12 steps, and an approximate total duration of 6 hours.[10] High-risk patients can be desensitized with additional dilutions and/or steps (16 or 20 steps).

The aim of this review is to discuss some of the main biological agents in clinical practice (rituximab, trastuzumab, cetuximab, ofatumumab, tocilizumab, brentuximab, omalizumab, and tumor necrosis factor alpha [TNF-α] inhibitor agents) (Table I), their associated hypersensitivity reactions, including clinical presentation, diagnosis, and treatment in the acute setting, and provide up-to-date management options, including novel desensitization protocols.

SPECIFIC AGENTS—CLINICAL PRESENTATION PARTICULARITIES

Rituximab

Rituximab is a chimeric mouse-human monoclonal antibody against CD20 used in the treatment of NHL, CLL, RA, WG, and MPA.[11,12] Infusion reactions may present with urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or non—immunoglobulin E (IgE)-mediated reactions.[12] Reactions consistent with immediate hypersensitivity, potentially IgE-mediated, are estimated to account for 5% to 10%.[4,13] Severe reactions tend to occur during the first infusion with time to onset of 30-120 minutes.[12] There is a report of a possible Stevens-Johnson syndrome associated with rituximab,[5] but other authors argued that the diagnosis was more consistent with paraneoplastic pemphigus due to clinical description and time course of the reaction.[14] A fatal case of Stevens-Johnson and/or toxic epidermal necrolysis overlap syndrome associated with the concomitant administration of rituximab, allopurinol, and bendamustine has also been reported.[15]

Trastuzumab

Trastuzumab is a humanized mouse IgG1 monoclonal antibody against the extracellular domain of the human epidermal growth factor receptor 2 (HER-2) receptor, indicated for the treatment of HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.[16] Typical first-time infusion reactions include chills and/or fever and occur in approximately 40% of patients.[17] Serious infusion reactions are reported to be relatively rare (0.5%).[18] One case of a serious adverse event to trastuzumab was observed in a 56-year-old woman with breast cancer.[19] During the first infusion and following premedication with paracetamol and antihistamines, she developed generalized tremor,