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Hypersensitivity and immunologic reactions to biologics: opportunities for the allergist

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ABSTRACT

Objective: There has been a great expanse in the use of biological agents during the past decade. However, there are significant differences between biologics and typical pharmaceutical drugs. This review focuses on 3 separate types of adverse reactions to biologics, namely high cytokine reactions, hypersensitivity reactions, and secondary immunodeficiency.

Data Sources: A PubMed literature search restricted to the previous 10 years using combinations of search terms, including *omalizumab, rituximab, TGN1412, biologic agent, anaphylaxis, hypogammaglobulinemia, desensitization*, and *cytokine storm*, was performed. The results were manually filtered to identify relevant articles with additional references identified from bibliographies.

Study Selection: Reports were selected for TGN1412 cytokine storm, omalizumab anaphylaxis and desensitization, rituximab-induced hypogammaglobulinemia, rituximab anaphylaxis and serum sickness, and monoclonal antibody desensitization.

Results: A phase 1 clinical trial using a humanized anti-CD28 monoclonal antibody (TGN1412) caused severe cytokine storm reactions in all 6 subjects, resulting in multiorgan failure. Omalizumab has been reported to cause anaphylaxis in fewer than 0.1% of patients, many with delayed reactions. The mechanism for this anaphylactic reaction is unclear. Rituximab has been associated with hypogammaglobulinemia, serum sickness-like reactions, and anaphylaxis. Rapid drug desensitizations to monoclonal antibodies, including rituximab, suspected of causing immunoglobulin E-mediated reactions have been found to be generally safe and effective.

Conclusion: Hypersensitivity reactions and immune dysregulation from biologic agents are not rare. The allergist and immunologist should be involved in managing these patients for optimal care.

Introduction

Biological agents are immune modulators used to treat different diseases, including inflammatory diseases and malignancies. There has been a great expanse in the use of biological agents during the past decade. These agents are typically proteins such as cytokines, monoclonal antibodies, and fusion receptors. Many of these agents have revolutionized the therapies for diseases such as rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, and lymphoproliferative disorders. More recently, allergic disorders, including allergic asthma, eosinophilic asthma, and chronic urticaria, also have been targets for biological agents.

Like other pharmaceutical agents, biological agents can cause adverse drug reactions. However, there are significant differences between biologics and typical pharmaceutical drugs.[1] Biological agents are structurally similar to autologous proteins, whereas drugs are generally synthesized chemicals. Biologic agents are not metabolized like drugs, but rather are processed like other proteins. Most biologics are administered parenterally, some over minutes, whereas others require longer infusions over hours. Like other pharmaceuticals, biologic agents can cause hypersensitivity reactions that are unexpected. In sharp contrast to typical drugs, biologics have inherent immune-mediated effects, which by themselves can cause unintended adverse effects.

Because of these inherent differences between biological agents and other pharmaceutical drugs, different classification schemes have been suggested to categorize adverse reactions to biologics.[1] Classification of adverse reactions to biologics has been noted in the drug allergy practice parameters as listed in Table 1.[2–9] This review focuses on 3 separate types of adverse reactions to biologics,

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Table 1
Classification of Adverse Reactions to Biological Agents[2]

Type of adverse reaction	Clinical example	Biologic example
High cytokine	cytokine release syndrome (aka cytokine storm)	TGN1412[3]
Hypersensitivity	delayed injection reactions	etanercept, adalimumab[4]
Secondary Immunodeficiency	tuberculosis with anti-TNF	infliximab, etanercept[5]
Autoimmunity	SLE	interferon-α[6]
Atopic disorders	atopic dermatitis	infliximab[7]
Cross-reactivity	acne from anti-epidermal growth factor receptor	gefitinib[8]
Nonimmunologic side effects	depression from interferons	interferon-α[9]

Abbreviations: SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.

namely high cytokine reactions, hypersensitivity reactions, and secondary immunodeficiency.

High Cytokine (Cytokine Release and Storm) Reactions

The most infamous example of a severe reaction to a biologic agent occurred in 2006. TGN1412 was a novel monoclonal antibody designed as a humanized super-agonist anti-CD28 monoclonal antibody. The company that owned this antibody, TeGenero, had performed preclinical studies that demonstrated that stimulation of CD28 with TGN1412 preferentially activated and expanded T-helper type 2 cells, in particular $CD4^+CD25^+$Treg cells.[10,11] In these preliminary preclinical studies, they did not detect significant toxic or proinflammatory effects in rodent or macaque monkey models.[12] In a phase 1 clinical study, 6 healthy men received TGN1412 as a single intravenous bolus (100 μg/kg). Each subject received this study drug 10 minutes apart. Approximately 1 hour later, subjects developed severe headaches, low back pain, nausea, vomiting, diarrhea, and fever.[3] All subjects went on to develop hypotension and bilateral pulmonary infiltrates. All were admitted to a local intensive care unit and 2 subjects required intubation and mechanical ventilation. Most patients went on to have multiorgan failure, including cardiovascular symptoms of capillary leak, lactic acidemia, acute renal injury, transaminitis, diffuse erythema followed by desquamation, delirium, amnesia, headaches, and gastrointestinal symptoms. Laboratory evaluation showed evidence of increased inflammatory markers, including C-reactive protein and sedimentation rate. Lymphopenia, monocytopenia, thrombocytopenia, and disseminated intravascular coagulation were common. Evaluation of cytokine levels showed elevations in tumor necrosis factor-α, interferon-γ, interleukin (IL)-10, IL-6, and IL-2. All these features were consistent with the clinical picture of a cytokine storm (aka cytokine release syndrome).

Subsequent analysis of the available data suggested that CD4 effector memory T cells in the tissues were activated by the CD28 super-agonist and caused immediate cytokine release. It was hypothesized that the laboratory rodents did not display this reaction because they were raised in clean conditions and lacked the necessary quantity of T memory cells.[12] Macaque monkey CD4 T cells lose CD28 expression during differentiation to T effector memory cells, also making this animal model inadequate. Subsequent determinations found that the dose of TGN1412 used occupied 90% of CD28 receptors.

Different critiques of TGN1412 studies have been proposed, including that low-level cytokine release in the primate studies should have promoted caution; that there were insufficient in vitro human studies; the choice of starting dose was based on primate studies; the dosing interval was too short between the subjects; and there was inadequate preparation for adverse effects.[13] This horrific outcome from a phase 1 clinical trial demonstrates the potential for severe adverse reactions to biologic agents and emphasizes the importance of careful preclinical and clinical evaluations to ensure safety.

The company TeGenero went bankrupt after a legal battle with the subjects, all of whom had lasting injuries and 1 who had lost fingertips and toes from necrosis.[14] TheraMAB, a Russian biotech company, bought the rights and renamed the antibody TAB08. Despite the prior disaster, they performed another clinical trial in humans starting with much lower doses (1,000 times lower) with a slower infusion and found no evidence of cytokine storm and subjects tolerated the infusion much better.[15]

Common Acute Infusion Reactions

Because most biological agents are administered parenterally, infusion reactions can occur. There is no consistent terminology for acute infusion reactions that differentiates immunoglobulin (Ig) E-mediated hypersensitivity reactions from more typical, predictable, and common non-hypersensitivity reactions. The term *common acute infusion reactions* denotes acute reactions that are predictable and common.[16] Common acute infusion reactions represent most reactions to monoclonal antibodies. They are usually mild and certainly can occur with the first dose. Different symptoms and signs can be seen with common acute infusion reactions, including fevers, rigors, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, and changes in heart rate or blood pressure. The mechanism for these infusion reactions is not well understood but many are related to rate, suggesting a nonimmunologic mechanism. For some infusion reactions, such as with rituximab, release of proinflammatory cytokines tumor necrosis factor-α and IL-6 could have a role in these reactions. Management of common acute infusion reactions typically involves premedication with corticosteroids, antihistamines, analgesics, and slower infusion rates.

Hypersensitivity Reactions

Immediate hypersensitivity reactions to biologic agents are believed to be due to IgE-mediated mechanisms. These agents are complete allergens and are large-molecular-weight proteins capable of inducing IgE-mediated response against different epitopes that might be foreign (eg, murine) or neoepitopes owing to conformational changes in humanized antibodies. In the case of cetuximab anaphylaxis, pre-existing antibodies to the carbohydrate galactose-α-1,3-galactose IgE antibodies were found to be causative.[17] Hypersensitivity reactions to biologic agents are less common than standard infusion reactions. Although some clinical signs and symptoms are more unique to hypersensitivity reactions, many are similar. Hypersensitivity and standard infusion reactions can have gastrointestinal symptoms, dyspnea, flushing, pruritus, and back pain. Symptoms that are more suggestive of a hypersensitivity reaction would include urticaria, wheezing, frequent coughing, and anaphylactic symptoms. The frequency of hypersensitivity reactions and standard infusion reactions vary based on the biological agent. Rituximab has some of the highest reported infusion reactions, with up to 77% reported with the first infusion.[18] It also has a relatively high rate of hypersensitivity reactions reported with 5% to 10% of infusions.[19]