Adverse Reactions to Biologic Therapy

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KEYWORDS

• Biologic agents • Monoclonal antibodies • Infusion reaction • Delayed reaction
• Drug desensitization • Omalizumab • Rituximab

KEY POINTS

- At the current time, the diagnostic tools, including skin testing and in vitro testing, to evaluate for immediate hypersensitivity reactions for biologic agents are insufficient.
- Desensitization can be considered for reactions suggestive of immunoglobulin E-mediated mechanisms, but allergists/immunologists should be involved in managing these patients.
- Because reactions to desensitizations for biologics occur in approximately one-third of patients, steps to reduce these reactions for subsequent desensitizations are important.

INTRODUCTION

In recent years, there has been a rapid increase in the number of US Food and Drug Administration (FDA) -approved biological agents used to treat a variety of inflammatory conditions and malignancies. As these agents become more widespread in their use, more is likely to be learned about adverse reactions associated with their use, diagnostic approaches, and management strategies. In this review, the authors summarize proposed classification schemes and known adverse reactions to some notable biologic therapies and discuss potential management strategies that are available to physicians with allergist/immunologist involvement.

TYPES OF BIOLOGIC AGENTS

Biologic agents have become a very important therapeutic option for many to help treat inflammatory diseases, autoimmune diseases, and malignancies. Despite their therapeutic potential, the risk of immune-mediated effects by virtue of their mechanism of action is potentially significant.

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The various biologic agents can be grouped into 3 main categories, including cytokines, antibodies, and fusion proteins. Cytokines are normally secreted proteins with growth, differentiation, and activation functions that regulate and direct the nature of the immune responses.[1] Examples of cytokines used in the form of biologic agents include interferon-α (IFN-α), IFN-β, and interleukin-2 (IL-2). When developed as biologic agents, they are often modified to prolong their half-life in vivo. Biologic agents in the form of monoclonal antibodies have also been developed to soluble proteins like cytokines, to cell surface molecules, to immunoglobulin E (IgE), and to tumor antigens. With advancement in molecular biology techniques, antibody formation has shifted from using monoclonal antibodies derived from mouse origin to chimeric, humanized, or fully humanized monoclonal antibodies. Finally, fusion proteins are essentially soluble forms of natural receptors or ligands that have high affinity for their respective ligands or antibodies. They are designed by fusing proteins with the Fc portion of immunoglobulin (IgG1). Examples of each respective type are shown in **Table 1**.[2]

DIFFERENCES BETWEEN DRUGS AND BIOLOGIC AGENTS

To better understand adverse reactions to biologic agents, it is important to consider some key differences between drugs and biologic agents. Unlike most drugs, which are small compounds with molecular weights less than 1 kDa, biologic agents are larger sized proteins that are designed to be structurally similar to autologous proteins with molecular weights much greater than 1 kDa.[3] Drugs are synthetic compounds, whereas biologic agents are produced with molecular genetic technique and purified from engineered cells.[3] Most biologic agents are administered parenterally as they would otherwise be digested and broken down in the gastrointestinal (GI) tract. Most drugs, however, can be administered either orally or parenterally and are metabolized. The metabolism of drugs is thought to sometimes yield immunogenic intermediates. On the other hand, biologic agents do undergo processing but are not metabolized. Finally, biologic agents have inherent immune-mediated effects as

Table 1
Types of biologic agents and examples

Type of Biologic Agents	Examples
Cytokines	IFN-α, IFN-β, IL-2
Antibodies directed to:	Soluble proteins like cytokines: anti-TNF-α (infliximab, adalimumab, certolizumab, and golimumab), anti-IL-2 (daclizumab), anti-IL-5 (mepolizumab, reslizumab) Cell surface molecules: anti-CD20 (rituximab); anti-IL-2 receptor (basiliximab); anti-LFA-1 (efalizumab) IgE (omalizumab) Tumor antigens (eg, EGFR-, cetuximab, anti-HER2-trastuzumab) Receptors (eg, IL-5Rα, benralizumab)
Fusion proteins (soluble receptors for cytokines or soluble cellular ligands)	TNF-αRII (etanercept), CTLA4-Ig (abatacept), IL-1 receptor antagonist (anakinra, which is not a fusion protein but has a similar mechanism of action)

Modified from Pichler WJ. Adverse side-effects to biological agents. Allergy 2006;61(8):913; with permission.

they originate from foreign non-self proteins, which are typically not expected to be seen with drugs because they are smaller synthetic compounds.[2,3]

PROPOSED CLASSIFICATION OF ADVERSE REACTIONS TO BIOLOGIC AGENTS

Adverse reactions to drugs can be classified according to their action. One such classification scheme categorizes adverse reactions to drugs in types A through E. Type A reactions are thought to correspond to the drug's pharmacologic activity, are dose-dependent, and are predictable. Type B reactions are not related to the drug's pharmacologic activity, are unpredictable, and include immune-mediated side effects and hypersensitivity reactions. Type C reactions are due to the chemical structure of the drug itself and its metabolism. Type D reactions are delayed reactions that appear many years after treatment. Finally, type E reactions are those that occur after withdrawal of a specific drug.[4]

Because of the differences highlighted above between drugs and biologic agents, there have been attempts to alternatively classify adverse reactions to biologic agents using classification schemes that focus on their immune target-related adverse reactions. Pichler[2] in 2006 provided such a classification scheme that was further elaborated on by Haussman and colleagues.[5] As shown in **Table 2**, each type of reaction is classified by Greek letters: α, β, γ, δ, and ε.[2,5] Further details about each of the respective types are discussed in the following sections.

Type α: Overstimulation

Type α reactions of biologic agents are similar to type A reactions of drugs in that they are predictable based on the biologic agent's intended pharmacologic activity. It is thought that these types of reactions are due to cytokines administered in high systemic doses in order to achieve a specific therapeutic effect or to the release of high concentrations of cytokines as a result of the specific agent's mechanism of action.[2] This type of reaction was first seen in humans with anti-CD3 monoclonal antibody (muromunab), which was one of the first monoclonal antibodies approved for

Table 2
Proposed classification of adverse reactions to biologic agents

Type	Example Reaction (Causative Medication)
α: Overstimulation	Cytokine release syndrome (cytokine storm) (muromunab, TGN1412)
β: Hypersensitivity	Common acute infusion reactions (rituximab), delayed infusion reactions (etanercept, adalimumab), anaphylaxis (muromunab, cetuximab, omalizumab)
γ: Cytokine or immune imbalance	
Immunodeficiency	Increased risk of tuberculosis (anti-TNF agents) Hypogammaglobulinemia (rituximab)
Autoimmunity	Systemic lupus erythematosus or vasculitis (IFN-γ)
Atopic disorders	Atopic dermatitis (anti-TNF agents)
δ: Cross-reactivity	Acne from anti-EGFR (cetuximab)
ε: Nonimmunologic side effects	Neuropsychiatric side effects including confusion or depression (IFN-α)

Modified from Pichler WJ. Adverse side-effects to biological agents. Allergy 2006;61(8):917; with permission.

use in the setting of acute rejection with organ transplant patients.[6] Symptoms reported attributed to this type of reaction can include fever, arthralgias, nausea, vomiting, diarrhea, capillary leak syndrome with pulmonary edema, headache, altered mental status, and aseptic meningitis. The most severe cases of cytokine release syndrome were seen with the experimental biologic agent TGN1412.[7] TGN1412 was designed as a humanized superagonist anti-CD28 monoclonal antibody. Six healthy men had been administered the study drug as an intravenous bolus all 10 minutes apart. About 1 hour later, they developed severe headaches, low back pain, nausea, vomiting, diarrhea, and fever. They subsequently were transferred to the intensive care unit after developing hypotension, bilateral infiltrates, and respiratory failure requiring intubation, renal failure, and disseminated intravascular coagulation. Laboratory studies showed evidence of cytokine storm with high levels of cytokines such as tumor necrosis factor-alpha (TNF-alpha) and IFN-gamma. Patients were resuscitated and required intensive cardiopulmonary support (including dialysis), high-dose methylprednisolone, and an anti-IL-2 receptor antagonist antibody. Additional clinical features seen later included desquamation of the skin, digital ischemia in one patient, headaches, myalgias, paresthesias, and issues with concentration.[7] Other monoclonal antibodies have been shown to cause cytokine release syndrome with varying degrees of severity, and they include alemtuzumab, rituximab, and tosituzumab.[8]

Type β: Hypersensitivity

Type β reactions of biologic agents are hypersensitivity reactions that are characterized as either immediate or delayed reactions. Factors affecting these types of reactions include the type of immunoglobulin response elicited, possible presence of complement activation, degree of humanization of the monoclonal antibody, and the presence of adjuvants or excipients.[2]

IgE antibodies directed at non-self peptide sequences are possible and may be a cause of immediate reactions. Overall, IgE-mediated immediate hypersensitivity reactions are thought not to be common causes of immediate reactions because many patients will tolerate the same agent infused at a slower rate and possibly with premedications, including antihistamines and steroids.[5] However, IgE-mediated anaphylaxis has been described with multiple biologic agents, including muromunab (anti-CD3 monoclonal antibody), omalizumab (anti-IgE monoclonal antibody), and cetuximab (chimeric mouse and human monoclonal antibody to epidermal growth factor receptor [EGFR]).[9] IgE-mediated anaphylaxis has also been described with cetuximab, which is a chimeric mouse-human IgG1 monoclonal antibody against the EGFR, typically used in cancer therapy. In this case, studies have shown that IgE-mediated anaphylactic reactions to cetuximab were associated with IgE antibodies against galactose-α-1,3-galactose that were present before treatment with cetuximab.[5,10]

Common acute infusion reactions represent a majority of reactions to monoclonal antibodies. These reactions are predictable, common, and usually mild reactions. They may occur with the first dose. Typical symptoms include fevers, rigors, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, or changes in heart rate and blood pressure.[11] The mechanism is not well understood, but the release of proinflammatory cytokines may have some role in some reactions. Complement activation is also thought to play a role in immediate hypersensitivity reactions because complement cleavage products C3a and C5a may directly stimulate mast cells and lead to IgE-independent mast cell activation.[5]

The degree of humanization of monoclonal antibodies has changed significantly over time. As monoclonal antibodies have evolved from murine-derived monoclonal antibodies to humanized and fully human monoclonal antibodies, their

immunogenicity has decreased due to the decreasing amount of foreign antigens they contain. Although the risk of forming human antimurine antibodies has decreased, even humanized monoclonal antibodies contain non-self peptide sequences that have the potential to lead to human anti-human antibody formation.[2] The consequence of these antibodies is typically delayed with the production of IgG antibodies and involves inactivation of the drug but typically not many symptoms. Complement is also thought to play a role in delayed reactions by immune complex formation and serum sicknesslike reactions.[2] T-cell–mediated hypersensitivity causing delayed maculopapular exanthema has also been suggested in case reports of abciximab where positive intracutaneous tests were shown after 48 hours.[5]

γ: Cytokine or Immune Imbalance

Type γ reactions are thought to occur as a function of the biologic agent and its effect on altering the balance maintained by a normally functioning immune system. Type γ reactions may therefore lead to impaired function of a normally functioning immune system leading to infections, autoimmunity, or atopic disease.[2] Examples of agents causing an immune system imbalance resulting in increased infections include an increase in tuberculosis infections in those treated with anti-TNF agents and rituximab-induced hypogammaglobulinemia that has been reported to cause an increase in sinopulmonary infections and report of one death from enteroviral meningitis.[12] IFN-gamma has also been described in inducing autoimmune and autoinflammatory diseases, including lupuslike syndrome, systemic sclerosis, Guillain-Barre syndrome, autoimmune thyroid disease, idiopathic thrombocytopenic purpura, vitiligo, and psoriasis.[2] Finally, anti-TNF agents have also been shown to be associated with the appearance of atopic dermatitis.[2,13,14]

δ: Cross-Reactivity

Type δ reactions occur by virtue of a biologic agent targeting an antigen that is expressed on various tissue cells or by targeting an antigen with a similar structure.[2] The clearest example of this is seen with reports of cetuximab causing acneiform eruptions. Cetuximab targets EGFR, which is strongly expressed in carcinomas of different origin and thought to be associated with tumor progression. EGFR is also expressed on normal skin cells. Cetuximab's binding to EGFR on normal skin cells, therefore, is the likely cause of the associated acneiform eruption.[2,15]

ε: Nonimmunologic Side Effects

Type ε reactions are nonimmunologic side effects that are not predictable and unrelated to a biologic agent's mechanism of action. An example of these types of reactions includes the neuropsychiatric adverse effects, such as acute confusional states or depression seen with IFN-alpha treatment.[2]

MANAGEMENT

Although the classification scheme described above is important in understanding the mechanism of adverse reactions of biologic agents, the management of acute reactions is likely facilitated more so by first differentiating an immediate versus delayed reaction and differentiating immediate reactions as common acute infusion reactions versus hypersensitivity reactions.

Common acute infusion reactions are typically characterized by fevers, rigors, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, or changes in heart rate and blood pressure.[11] The mechanism of these reactions is

not thought to be IgE mediated. In a study of 14 patients treated with infliximab with infusion reactions, none of the patients were found to have increases in either tryptase levels or IgE levels against infliximab.[16] These types of reactions are typically managed with premedication with corticosteroids, antihistamines, analgesics, and/or slower infusion rates.[17]

Hypersensitivity reactions (eg, IgE-mediated reactions) may have overlapping symptoms and be indistinguishable from common acute infusion reactions. With respect to timing, immediate reactions are thought to occur during or within a few hours from either a first or subsequent infusion, whereas delayed reactions are thought to occur up to 14 days following an infusion.[16,17] The prevalence of anaphylactic reactions is thought to be low, for example, occurring in less than 0.2% of patients treated with omalizumab.[18]

Shared symptoms between common acute infusion reactions and hypersensitivity reactions include GI symptoms, dyspnea, flushing, pruritus, and back pain. Symptoms suggestive of hypersensitivity but not standard infusion reactions may include urticaria, wheezing, frequent coughing, or multiorgan anaphylactic symptoms. Hypersensitivity reactions to biologic agents have been shown to be less common than standard infusion reactions.[19] Hypersensitivity reactions have been reported for rituximab (anti-CD20), infliximab (anti-TNF-α), trastuzumab (anti-HER2), omalizumab (anti-IgE), natalizumab (anti-α4-integrin), basiliximab (anti-IL-2Rα), abciximab (GPIIb/IIIa receptor antagonist), and cetuximab (anti-EGFR).[20]

A REVIEW OF ADVERSE REACTIONS TO SPECIFIC AGENTS

Numerous biological agents have been associated with hypersensitivity reactions, including anaphylaxis. Hypersensitivity reactions to most of these agents share similar characteristic clinical features, and the approach to these reactions in regards to diagnosis and management (eg, desensitization) is quite similar. Therefore, this review focuses on biologics with more robust data on hypersensitivity reactions, those with atypical clinical features and those used more commonly by allergy/immunology specialists.

Biologics for Asthma

Omalizumab

Omalizumab is a humanized monoclonal antibody that binds IgE. In 2007, a joint task force was formed between the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology Executive Committees to examine Genentech's Xolair (omalizumab) clinical trials and postmarketing surveillance data on anaphylactic reactions. In this report, the anaphylaxis reporting rate was found to be 0.09% (35 patients reported to have anaphylaxis out of 39,510 patients receiving omalizumab over an approximate 2.5-year period).[21] With respect to timing of reactions, they found that many reactions, especially reactions occurring after the first to third doses, occurred greater than 1 hour after injection. This report led to recommendations for a 2-hour observation period for the first to third doses of omalizumab and 30-minute observation periods for subsequent doses.[21] A follow-up report published in 2011 showed that most reactions occurred during these recommended waiting times ($\sim$77%).[22] Additional recommendations for patients being treated with omalizumab from this task force report included education regarding signs and symptoms of anaphylaxis and the prescription of epinephrine autoinjectors to all patients.[21,22]

The mechanism for omalizumab anaphylaxis is not well understood. Because omalizumab is composed of 5% mouse polypeptide, it is possible that IgE-mediated reactions may occur against the murine sequences. However, the unusual delayed nature of these reactions and infrequent skin test positivity suggest that this is not the primary mechanism. Excipients have also been proposed to be a cause of anaphylactic reactions to omalizumab. Price and Hamilton[23] reported 2 patients who developed anaphylaxis after more than a year of successful omalizumab administration. Both of these cases were thought to be anaphylactoid in nature and possibly due to an excipient, polysorbate, which has also been found to cause similar allergic reactions since the 1970s.[24] Whether this is the cause of most anaphylactic reactions to omalizumab remains unproven.

Diagnostic testing for IgE-mediated hypersensitivity reactions can involve skin prick and intradermal testing, but it is critical to determine nonirritating concentrations for drug testing. Omalizumab is the only biologic agent in which nonirritating concentrations were determined in a systematic fashion. Different dilutions of omalizumab for both skin prick and intradermal testing were studied in 2010 to establish safety and determine interpretable results for likely IgE-mediated immediate hypersensitivity reactions. Dilutions in sterile water were found to cause irritant reactions, so dilutions with saline were subsequently used. The investigators established a nonirritating concentration of a dilution with saline of 1:100,000 (concentration of 1.25 μg/mL).[25] However, the utility of omalizumab skin testing and further data about the positive and negative predictive values are still unknown.

Desensitization with biologic agents has emerged as an option to manage hypersensitivity reactions; however, results have been mixed with omalizumab. In 2006, a case of a 32-year-old woman was reported who had developed generalized erythema and itching 5 minutes after her first dose of omalizumab 300 mg in the treatment of her asthma and idiopathic chronic urticaria and angioedema.[26] She was treated with epinephrine and additional nonsedating antihistamines. As the patient had seen clinical benefit over the subsequent few weeks in the control of both her asthma and her chronic urticaria, the risks and benefits of further doses were discussed, and she elected to pursue options to receive additional doses. Subsequent doses were given per a desensitization protocol as follows: 7.5 mg, 15 mg, 30 mg, 60 mg, 45 mg (remaining dose) every 30 minutes. During the subsequent doses, she experienced marked generalized erythema and pruritus beginning with the last 3 injections and persisting for several hours. She also was noted to have fever and hypertension suggesting a systemic component to these reactions. With subsequent infusions, she was premedicated with ibuprofen 600 mg and did not develop any further signs of hypersensitivity. However, despite premedication before the seventh dose, she developed a petechial rash 1 to 2 days after the dose that was thought to represent a possible serum sicknesslike reaction, and no further doses were given.[26]

Further cases were published in patients with mild to moderate reactions in 2011. A case series of 3 patients included those with mild to moderate reactions with symptoms of cough/dyspnea, urticaria, and angioedema. Two of the 3 patients were noted to also have vocal cord dysfunction. The investigators utilized a desensitization protocol that started with 0.0625 mg with doubling doses every 30 minutes up to 40 to 55 mg maximum doses with a cumulative dose of 113 to 190 mg. All 3 patients had mild to moderate reactions during the protocol, but 2 of the 3 patients were able to receive weekly omalizumab doses thereafter.[27] This case series contrasts with the experience of an attempt at desensitization in a patient who had an anaphylactic reaction (dyspnea, nausea, hypotension) 1 hour after the second dose of omalizumab

150 mg. Desensitization in this case was then performed after negative skin prick testing, but after the fourth dose (31 mg), the patient was again noted to have an anaphylactic reaction with nausea, chest tightness, and a significant drop in forced expiratory volume in 1 second.[28]

Mepolizumab

Mepolizumab is a humanized monoclonal antibody that binds to and inactivates IL-5, which is a cytokine that is thought to play a role in eosinophil recruitment, persistence, and activation.[29] Mepolizumab has been shown to decrease the frequency of asthma exacerbations in patients with severe persistent eosinophilic asthma and decrease maintenance oral glucocorticoids in severe persistent eosinophilic asthma patients as well.[29] The most common adverse reactions observed with mepolizumab include headache, injection site reactions, back pain, fatigue, nasopharyngitis, rash, and pruritus. Injection site reactions have been reported to occur in as much as 8% of patients treated with mepolizumab. An increased incidence of herpes zoster was also seen compared with placebo in some trials.[30]

Reslizumab

Reslizumab is also a monoclonal antibody against IL-5 that is indicated for add-on maintenance treatment of patients with severe persistent eosinophilic asthma. Anaphylaxis was observed to occur with reslizumab infusion in 0.3% of patients in placebo-controlled trials. Anaphylaxis was seen as soon as the second dose and either during the infusion or within 20 minutes of completion of the infusion. Therefore, patients should be observed for symptoms and signs of anaphylaxis after administration of reslizumab. The most common adverse reaction observed was oropharyngeal pain.[31] In addition, some trial data also showed an increase in the rate of malignancies reported within less than 6 months of exposure to reslizumab (0.6% reported in patients receiving reslizumab vs 0.3% reported in patients receiving placebo). There was no specific type of malignancy that was found to be most common. Increases in creatine phosphokinase, myalgias, and other musculoskeletal complaints were also seen more frequently in patients receiving reslizumab compared with placebo.[31,32]

Benralizumab

Benralizumab is a humanized monoclonal antibody designed to target the IL-5 receptor α chain and block the effects of IL-5 on eosinophils. Unlike mepolizumab and reslizumab, it is not yet FDA approved for the treatment of severe eosinophilic asthma and is continuing in investigational trials. To date, the most common adverse reactions seen with benralizumab include headaches, nasopharyngitis, and nausea. Injection site reactions have also been reported.[33,34]

Other Biologics Notable for Specific Adverse Drug Reactions

Rituximab

Two main categories of adverse reactions to rituximab include immunodeficiency and hypersensitivity. Rituximab is a chimeric monoclonal antibody that binds to CD20. It is used to treat B-cell lymphomas and many autoimmune diseases. It causes rapid depletion of CD20 expressing B-cell precursors and mature B cells, which remain low for 6 to 9 months.[35]

Because of its peripheral B-cell–depleting effects, many studies have sought to determine immune-mediated consequences in those treated with rituximab. In 2013, a large retrospective study was published to determine the long-term safety of rituximab in rheumatoid arthritis patients. They included 3194 patients including

627 patients who were followed for greater than 5 years. They showed that the most common adverse events were common acute infusion-related reactions that mostly occurred with the first dose and were categorized as mild or moderate based on common terminology criteria for adverse events. With respect to immune-related adverse events, they demonstrated hypogammaglobulinemia at the following rates: low IgM, 22.4%; low IgG, 3.5%; and low IgA, 1.1%. Their data showed that hypogammaglobulinemia was not associated with increased infections.[36] However, another study in 2014 reported 19 cases of symptomatic, persistent hypogammaglobulinemia after rituximab with most of these cases seen in hematologic malignancies.[12] The mean interval since last rituximab dose was about 3 years, and 18 of the 19 patients were treated with gammaglobulin replacement because prophylactic antibiotics were not helpful in decreasing risk of infectious illness in this group of patients. Most these patients had sinopulmonary infections, and one died from enteroviral meningoencephalitis.[36] Therefore, it is important to consider that rituximab-induced hypogammaglobulinemia may persist for years after rituximab infusion and is not always associated with symptoms. However, in those patients who have increased infections, consideration for gammaglobulin replacement should be made on a case-by-case basis.

As mentioned above, common acute infusion-related reactions are the most common adverse effect seen with rituximab use. Up to 77% of patients will have infusion-related symptoms with the first dose. Also, up to 80% of fatal reactions occur with the first dose.[37] Premedication with acetaminophen, antihistamines, and corticosteroids is typically recommended. Delayed reactions have also been observed with rituximab with reports of serum sicknesslike reactions occurring in patients with a mean of 7 days following infusion. Most of the patients reported in a systematic review had reactions following their first cycle and most commonly had symptoms of fever (79%), arthralgia (73%), and rash (70%). Most patients were treated with corticosteroids with good response. Attempts at premedication for 4 patients were mixed, because they reported 2 patients tolerated repeat doses, whereas one had recurrent serum sickness and one had angioedema.[38]

Etanercept/adalimumab injection site reactions

Etanercept and adalimumab are both subcutaneously administered TNF blockers used in a variety of inflammatory joint and bowel diseases. One of the most common adverse reactions with their use is an injection site reaction. Zeltser and colleagues[39] retrospectively reviewed etanercept use in patients receiving therapy for various inflammatory arthritic conditions or inflammatory bowel disease and found injection site reactions were reported in 20% of patients. They found that all occurred within the first 2 months of therapy, typically occurred 1 to 2 days after the last injection and resolved within a few days, and were observed to wane with time. They performed skin biopsies in patients who experienced these injection site reactions and showed they had inflammatory infiltrates composed of mostly lymphoid cells and some eosinophils, in a perivascular cuffing pattern, without evidence of leukocytoclastic vasculitis. Further analysis of the lymphoid cells showed that most of them were cytotoxic CD8+ T cells. They suggested the mechanism of these reactions may be a delayed-type hypersensitivity reaction that is T-cell mediated, which wanes over time due to induction of tolerance. Immediate hypersensitivity reactions including anaphylaxis have also been reported with etanercept and adalimumab.[40]

Bavbek and colleagues[41] examined the role for subcutaneous desensitization protocols for both etanercept and adalimumab in the setting of injection site

reactions or immediate type hypersensitivity reactions. For etanercept, they included 6 patients who had injection site reactions to etanercept 10 minutes to 24 hours after subsequent injections and one patient who had experienced urticaria, angioedema, wheezing, vomiting, and hypotension 5 hours after the fifth injection. All the patients had negative prick tests, positive intradermal tests at 15 minutes, and negative readings from intradermals at 24, 48, and 72 hours. All 7 patients underwent subcutaneous desensitization protocols and were able to tolerate subsequent etanercept doses with only mild local erythema when premedicated with cetirizine. For adalimumab, they included 4 patients with injection site reactions 1 to 6 hours after subsequent doses and one patient who had urticaria 2 to 3 hours after the third injection. Prick testing was positive in 4 patients; intradermal testing was positive in one patient, and delayed intradermals were negative in all the patients at 24, 48, and 72 hours. All 5 patients underwent successful subcutaneous desensitization; however, they all experienced local erythema that was smaller than the initial reactions. They were all able to tolerate subsequent adalimumab doses with premedication and tolerated spacing of their adalimumab doses to every other week.

DIAGNOSTIC EVALUATION OF BIOLOGICAL HYPERSENSITIVITY REACTIONS, GENERAL PRINCIPLES

Beyond a careful history, various diagnostic testing modalities are used in the evaluation of immediate hypersensitivity reactions and include skin prick testing, intradermal testing, in vitro testing, and drug challenges. The experience with respect to skin prick and intradermal testing for monoclonal antibodies is increasing rapidly. In a study published in 2009, Brennan and colleagues[20] described their center's experience with desensitizations to monoclonal antibodies, including rituximab, infliximab, and trastuzumab. They performed intradermal skin tests using 1:100 and 1:10 dilutions in patients before rapid desensitizations; however, no controls were tested to determine nonirritating concentrations. They had positive intradermal tests in 4/6 patients for infliximab, 6/9 patients for rituximab, and 2/2 patients for trastuzumab and suggested their reactions may be due to immediate hypersensitivity. In cases of positive skin test results, desensitizations were recommended. In the largest desensitization study published to date by Sloane and colleagues,[42] they included 32 patients with hypersensitivity reactions to biologic agents and performed skin prick and intradermal testing. Their skin test results were as follows: rituximab 9/15 positive tests, infliximab 4/9 positive tests, trastuzumab 3/3 positive tests, bevacizumab 2/2 positive tests, tocilizumab 1/1 positive test, and cetuximab 1/1 positive test.

With respect to in vitro testing, the experience is rather limited. Chung and colleagues[10] reported that in patients with cetuximab anaphylaxis, they were able to detect IgE antibodies directed toward cetuximab using the ImmunoCAP assay in 17 of 25 patients who had anaphylaxis.

In addition, elevated tryptase levels may confirm mast cell activation in cases of immediate hypersensitivity, but normal serum tryptase levels in the setting of a reaction should not be interpreted as reassuring. Basophil activation tests have not been evaluated in large studies, and their accuracy in evaluating immediate hypersensitivity with monoclonal antibodies is not known. Finally, drug challenge may be considered in patients with milder reactions with features not suggestive of IgE-mediated reactions, but there are no clear data on the safety of this approach for more moderate-severe allergic reactions.

Overall, the data regarding various testing modalities typically used to evaluate immediate hypersensitivity reactions are limited but expanding. Skin testing has been performed, but nonirritating concentrations for most agents are not well established and predictive values (negative or positive) are not known. For moderate to severe reactions, the lack of sufficient methods to evaluate for immediate hypersensitivity often leads to empiric desensitization, if there is no other feasible alternative.

RAPID DRUG DESENSITIZATIONS TO BIOLOGICAL AGENTS

Rapid drug desensitizations to biologic agents should only be performed when the agent is needed as first-line therapy. Delayed reactions are contraindicated and include Stephens-Johnsons syndrome, toxic epidermal necrolysis, drug rash with eosinophilia with systemic symptoms, acute generalized erythematous pustulosis, erythema multiforme, serum sickness, and so forth. Successful desensitizations have been reported to multiple agents, including rituximab (anti-CD20), trastuzumab (anti-HER2), infliximab (anti-TNFα), cetuximab (anti-EGFR), bevacizumab (anti-VEGF-A), tocilizumab (anti-IL-6R), ofatumumab (anti-CD20), brentuximab (anti-CD30), alemtuzumab (anti-CD52), etanercept (fusion protein against TNF-αRII), and adalimumab (anti-TNFα).[19] Premedications are important for desensitizations and include the use of antihistamines, corticosteroids; and acetominophen may also be considered to reduce fever. Aspirin has been used to prevent flushing and montelukast to prevent bronchospasm in chemotherapy desensitizations. Because of infrequent administrations of most of biologic agents, repeat desensitizations are then typically required as well. Sloane and colleagues[42] showed that when patients are chosen carefully with respect to type of reactions and stratified according to risk, desensitizations are a safe and feasible alternative to allow patients to remain on first-line therapies they have previously had immediate hypersensitivity reactions to. They performed a total of 120 rituximab desensitizations and had no reactions with 86 desensitizations (72%), mild reactions with 23 desensitizations (19%), and moderate or severe reactions in 11 patients (9%). One patient required epinephrine. No deaths were associated with these desensitizations. Overall, most reactions to monoclonal antibodies occurred at the twelfth step and were mostly cutaneous reactions. Based on their overall experience including both chemotherapeutics and monoclonal antibodies, they provided prognostic information and determined patients with an initial grade 1 or 2 hypersensitivity reaction have a 91% to 92% chance of having no (grade 0) or minimal (grade 1) symptoms during their first rapid drug desensitization. They also reported that patients with an initial severe (grade 3) hypersensitivity reaction have an 86% chance of having no or a minimal hypersensitivity reaction during their first desensitization, but continue to have a 9% chance of having a severe hypersensitivity reaction during the first desensitization.

Because reactions to desensitizations for biologics occurs in approximately one-third of patients, steps to reduce these reactions for subsequent desensitizations are important. In addition to adding premedications as discussed above, adding additional steps to the desensitization protocol may also be helpful. Although some investigators suggest adding an additional more dilute bag with an extra 4 steps to the beginning of the protocol, the authors have found that adding additional steps to the last bag (when most reactions occur) is more helpful. An example of this is shown in **Table 3** for a patient who reacted to rituximab during his initial desensitization, but with modifications to the protocol subsequently, tolerated 3 desensitizations without reaction.

Table 3
Modification to rapid desensitization protocol for rituximab

Original rituximab desensitization protocol						
Step	Solution (10 mg/250 mL) Conc. = 0.04 mg/mL	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with step (mg)	Cumulative dose (mg)
1	1	2	15	0.5	0.02	0.02
2	1	5	15	1.25	0.05	0.07
3	1	10	15	2.5	0.1	0.17
4	1	20	15	5	0.2	0.37
	Solution (100 mg/ 250 mL) Conc. = 0.4 mg/mL					
5	2	5	15	1.25	0.5	0.87
6	2	10	15	2.5	1	1.87
7	2	20	15	5	2	3.87
8	2	40	15	10	4	7.87
	Solution (992 mg/ 250 mL) Conc. = 3.968 mg/mL					
9	3	10	30	5	19.84	27.71
10	3	20	30	10	39.68	67.39
11	3	32.5	30	16.25	64.48	131.87
12	3	45	30	22.5	89.28	221.15
13	3	57.5	30	28.75	114.08	335.23
14	3	70	30	35	138.88	474.11
15	3	82.5	30	41.25	163.68	637.79
16	3	95	30	47.5	188.48	826.27
17	3	100.5	26	43.75	172.8	999.07

Modification to rituximab desensitization protocol						
	Solution (10 mg/250 mL) Conc. = 0.04 mg/mL					
1	1	5	10	0.83	0.033	0.033
2	1	10	10	1.66	0.066	0.099
3	1	20	10	3.33	1.33	1.462
	Solution (100 mg/ 250 mL); Conc. = 0.4 mg/mL					
4	2	5	10	0.83	0.33	1.792
5	2	10	10	1.66	0.66	2.452
6	2	20	15	5	2	4.452
7	2	40	15	10	4	8.452
	Solution (492 mg/ 125 mL); Conc. = 3.936 mg/mL					
8	3	10	15	2.5	9.84	18.292
9	3	20	15	5	19.68	37.972
10	3	25	15	6.25	24.6	62.572
11	3	30	15	7.5	29.52	92.092
12	3	35	15	8.75	34.44	126.532
13	3	40	15	10	39.36	165.892
14	3	45	15	11.25	44.28	210.172
15	3	50	15	12.5	49.2	259.372
16	3	55	15	13.75	54.12	313.492
17	3	60	15	15	59.04	372.532
18	3	65	15	16.25	63.96	436.492
19	3	70	14	16.33	64.27	500.762

SUMMARY

Biologic therapies are emerging as a significant therapeutic option for many with debilitating inflammatory and autoimmune conditions. As expansion in the number of FDA-approved agents continues to be seen, more unanticipated adverse reactions are likely to occur. At the current time, the diagnostic tools including skin testing and in vitro testing to evaluate for immediate hypersensitivity reactions are insufficient. Desensitizations can be considered for reactions suggestive of IgE-mediated mechanisms, but allergists/immunologists should be involved in managing these patients.

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