Adverse Reactions to Biologic Therapy

Sheenal V. Patel, MD*, David A. Khan, MD

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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Division of Allergy and Immunology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, F4.206, Dallas, TX 75390-8859, USA
* Corresponding author.
E-mail address: sheenal.patel@outlook.com

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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.