Biological Therapies of Immunologic Diseases

Strategies for Immunologic Interventions

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KEYWORDS

• Biotherapy • Biotherapeutic • Immunomodulatory • Monoclonal antibody

KEY POINTS

- To understand at a basic level the general classes of biological therapies.
- To understand the targets of biotherapeutics in asthma, allergies, and other immune-mediated disorders.
- To take note of up-to-date and future therapies for immune-mediated disorders.

INTRODUCTION

The immune system is a highly complex and ever-evolving network of signaling molecules and target cells, with several potential targets for therapeutic modification. Throughout the past few decades, numerous methods of immunomodulatory biological therapy have been proposed and extensively studied, yet only some have demonstrated success. The ability to concurrently alter a component of the immune system, account for several downstream effects, reduce adverse drug events, and minimize the risk of consequent autoimmunity and/or malignancy has proven extensively difficult. Nonetheless, several strategies for immunologic intervention have been successfully applied to the practice of medicine (**Table 1**). This article covers currently available biotherapeutic agent classes as well as potential direction for future therapy.

MONOCLONAL ANTIBODIES

Monoclonal antibodies (mAbs) have received considerable attention since their conception more than 40 years ago. By definition, mAbs are antibodies created

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Table 1
Description of biotherapeutic agent classes

Biotherapeutic Class	Description	Examples of FDA-Licensed Products
Monoclonal antibodies	Antibodies created from a single clonal line designed to target a specific epitope	*Chimeric*: infliximab (anti-TNF) *Humanized*: omalizumab (anti-IgE), mepolizumab (anti-IL5) *Human*: adalimumab (anti-TNF), canakinumab (anti-IL1B), ustekinumab (anti-IL23/13)
Cytokines	Small secreted proteins involved in cell–cell signaling, used either in natural form or via recombinant DNA technology to serve as competitive inhibitors	*Natural*: interferons (α, β, γ) *Recombinant*: anakinra (recombinant IL-1RA)
Fc fusion proteins	Proteins consisting of the Fc domain of IgG (generally IgG1) fused to a ligand or peptide antigen, produced by recombinant genetic engineering	*Competitive inhibition*: Etanercept, rilonacept *Direct receptor stimulation*: Alefacept, romiplostin
RNA		
siRNA	Small double-stranded RNA product designed to bind, cleave, and silence a target mRNA	None
Antisense oligonucleotides	Synthesized single-stranded antisense segments designed to directly regulate mRNA expression via binding through specific Watson-Crick hybridization	Fomiversen, mipomersen, pegaptanib
Kinase inhibitors	Specific inhibitors of kinases (phosphorylating enzymes), typically acting via occupation of an active binding site	Imatinib (anti Bcr-Abl, CD117, PDGFR), nintedanib (anti-FGFR), tofacitinib (anti-JAK)
Antichemokine drugs	Small molecule inhibitors designed to target chemokine receptors	None

Abbreviations: FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; Ig, immunoglobulin; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; mRNA, messenger RNA; PDGFR, platelet-derived growth factor receptor; siRNA, short interfering RNA; TNF, tumor necrosis factor.

from a single B lymphocyte clone that bind a specific antigenic epitope.[1] The first mAbs were formed by Kohler and Milstein in 1975 via the hybridoma technique,[2] involving fusion (either chemically or virally) of immortalized myeloma cells with splenic B cells of an animal specifically inoculated with the target epitope. Cells are then grown in selective hypoxanthine-aminopterin-thymidine medium, whereby only hybridoma cells can survive. Because unfused myeloma cells lack the ability to produce hypoxanthine guanine phosphoribosyltransferase (HGPRT), they are rendered unable to replicate their own genetic material within the medium owing