CE 1.0 Pharmacology and 1.0 ANCC Contact Hours

Pharmacology Consult
Column Editor: Patricia Anne O'Malley, PhD, RN, CNS

Large Molecule Pharmacotherapy

Biologics in Clinical Nurse Specialist Practice

Patricia Anne O'Malley, PhD, RN, CNS

Few scientists acquainted with the chemistry of biological systems at the molecular level can avoid being inspired.[1]

The development of biologics for the past 20 years has changed the treatment paths for cancer and autoimmune disorders across the life span.[2] Rather than beginning with the disease, biotechnology-based care begins with the identification of genetic variation and uses cell-based therapies to modify the variation. Biologics are directed to specific genotypes or protein receptors. Some of the targets for biologic therapies include anemia, cystic fibrosis, diabetes, hemophilia, hepatitis, genital warts, transplant rejection, cancers, and tissue reconstitution for wounds.[3]

Biologic development is not a new science. Human growth hormone, insulin, and red blood cell–stimulating agents have been on the market for decades. However, with the deepening understanding of genetics and disease, there has been significant expansion in the development of genomics, proteomics, microarray, cell cultures, and monoclonal antibody technologies.[3] The increasing number of biologic development platforms across the pharmacy industry worldwide suggests that this pharmacotherapy will bring even more options for therapy options for the future.[2]

There is no simple definition for biologics. A strict definition of biologics would include only agents produced by living systems consisting of large molecules containing hundreds of amino acids. Another definition would describe a biologic as any substance composed of organic molecules no matter the size. Still, others would include products created in other organisms such estrogen hormone from pregnant mare urine. Finally, biologic can be defined as a product created by a microorganism or mammalian cell, which are large complex molecules, most of which are proteins or polypeptides.[3]

Biologics are described as large complex molecules such as a virus, toxin, antitoxin, therapeutic serum, vaccine, blood product or component, or trivalent organic arsenic compound used for the prevention, treatment, or cure of a disease. The complex molecules and/or mixture are not easily labeled because of construction from bacteria, yeast, insects, plants, other purified natural sources, or mammalian cells.[2] The Table describes the most commonly prescribed biologics, based on these broad definitions. Also included is the biologic type, approval date, Web site address for specific information for use and prescribing, and indications for use.

LARGE VERSUS SMALL MOLECULES

Biopharmaceuticals differ from traditional small molecule drugs related to the size and complexity of the active substance and the complex nature of manufacturing. Even minor changes in the biologic product can result in significant safety and efficacy issues.[4] Biologic activity may be affected by the cell system in which it was produced, the fermentation media, or operating conditions. Because biologics are extremely sensitive to physical conditions and enzyme activity, complex bioassays and stability assessments are required rather than tests for product identity or purity for chemical-based or small molecule drugs. Whereas a small molecule drug may require 40 to 50 critical tests in development, a biologic may require 250 or more. As a result, biologic centers for development and testing are costly, which further explains the high cost of therapy and the global shortage of capacity.[3]

Historically, when the patent of a brand name drug (small molecule) expires, a generic option emerges on the market with the expectation that both products are chemically identical. Approval is the function of meeting established regulatory criteria demonstrating therapeutic equivalence so that small molecule products can be interchanged freely without consideration of patient treatment history.[5]

Author Affiliation: Nurse Researcher, Center of Nursing Excellence, Premier Health, Miami Valley Hospital, Dayton, Ohio.

The author reports no conflicts of interest.

Correspondence: Patricia Anne O'Malley, PhD, RN, CNS, Premier Health, Miami Valley Hospital, 1 Wyoming St, Dayton, OH 45409 (pomalley@premierhealth.com; pomalley5@woh.rr.com).

DOI: 10.1097/NUR.0000000000000297

Table. Commonly Prescribed Biologic Agents: Indications, Prescribing Information, and Resources

Biologic	Indications	Manufacturer
Actemra (tocilizumab), 2010, https://www.actemrahcp.com/ Interleukin-6 receptor antagonist Injection	Moderately to severely active rheumatoid arthritis (RA) with an inadequate response to 1 or more disease-modifying antirheumatic drugs Patients 2 years and older with active polyarticular juvenile idiopathic arthritis (JIA) Patients 2 years of age and older with active systemic JIA	Genentech USA, Inc, and Biogen, a member of the Roche Group, San Francisco, California
Avastin (bevacizumab), 2004, https://www.avastin-hcp.com/ Vascular endothelial growth factor–specific angiogenesis Inhibitor Infusion	Platinum-resistant ovarian cancer, breast, colorectal, kidney, non–small-cell lung cancers, recurrent glioblastoma	Genentech USA, Inc, and Biogen, a member of the Roche Group, San Francisco, California
Avonex (interferon β-1a), 1996, https://www.avonex.com/ Interferon β Injection	Relapsing multiple sclerosis and in persons with a first attack with lesions on MRI consistent with MS diagnosis	Biogen Idec Research, Triangle Park, North Carolina
Cimzia (certolizumab pegol), 2008, https://www.cimzia.com/ Tumor necrosis factor (TNF) blocker Injection	Crohn disease and maintaining clinical response in adult patients with moderately to severely active disease with an inadequate response to conventional therapy Moderately to severely active RA, active psoriatic arthritis, active ankylosing spondylitis	UCB Group, Smyrna, Georgia
Enbrel (etanercept), 1998, https://www.enbrel.com/ Tumor necrosis factor blocker, fusion protein Injection	RA, psoriatic arthritis, plaque psoriasis, moderate to severe polyarticular JIA, ankylosing spondylitis	Amgen, Thousand Oaks, California
Humira (adalimumab), 2002, https://www.humira.com/ Tumor necrosis factor blocker Injection	RA; ulcerative colitis; psoriatic arthritis; ankylosing spondylitis; Crohn disease; plaque psoriasis; hidradenitis suppurativa; noninfectious intermediate, posterior, and pan uveitis; polyarticular JIA	AbbVie, North Chicago, Illinois
Kineret (anakinra), 2001, http://www.kineretrx.com/ Interleukin-1 receptor antagonist Injection	Moderately to severely active RA in people 18 y and older when 1 or more other drugs for RA have not worked Cryopyrin-associated periodic syndrome called neonatal-onset multisystem inflammatory disease Not for children with juvenile RA	SOBI, Stockholm, Sweden
Lantus (insulin glargine [rDNA origin] injection), 2000, https://www.lantus.com/ Long-acting human insulin analog Injection	Diabetes: long-acting insulin for adults with type 2 diabetes and adults/pediatric patients (aged >6 y) with type 1 diabetes	Sanofi, Bridgewater, New Jersey
Lucentis (ranibizumab), 2006, http://www.lucentis.com/ Vascular endothelial growth factor inhibitor Injection	Wet age-related macular degeneration, macular edema after retinal vein occlusion, and diabetic macular edema	Genentech USA, Inc, and Biogen, a member of the Roche Group, San Francisco, California
Neulasta (pegfilgrastim), 2002, https://www.neulasta.com/ Leukocyte growth factor Injection	Neutropenia	Amgen, Thousand Oaks, California
Orencia (abatacept), 2005, http://www.orenciahcp.com/ Selective T-cell costimulation modulator anti-CD28 Injection	Rapidly progressing adult RA, moderately to severely active polyarticular JIA in pediatric patients older than 6 y	Bristol-Myers Squibb, New York, New York

Continued

Table. Commonly Prescribed Biologic Agents: Indications, Prescribing Information, and Resources, Continued

Biologic	Indications	Manufacturer
Remicade (infliximab), 1998, https://www.remicade.com/ Tumor necrosis factor blocker Infusion	RA, ulcerative colitis, psoriatic arthritis, ankylosing spondylitis, Crohn disease, plaque psoriasis	Janssen (pharmaceutical company of Johnson & Johnson), Titusville, New Jersey
Rituxan (rituximab), 1997, http://www.rituxan.com/ CD20-directed cytolytic antibody, anti–B cell Infusion	Non-Hodgkin lymphoma, RA, chronic lymphocytic leukemia RA with another prescription of methotrexate, after ineffective treatment with TNF Granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis with glucocorticoids	Genentech USA, Inc, and Biogen, a member of the Roche Group, San Francisco, California
Simponi, Simponi Aria (golimumab), 2009, https://www.simponiaria.com/what-is-simponi-aria Tumor necrosis factor blocker Injection	Adults with moderate to severe RA, taken with methotrexate	Janssen Biotech, Inc, Horsham, Pennsylvania
Xeljanz (tofacitinib), 2012, http://ra.xeljanz.com/ Inhibitor of Janus kinases Tablets	Moderately to severely active RA in which methotrexate was not effective Unknown if Xeljanz/Xeljanz XR is safe and effective in people with hepatitis B or C or if safe and effective in children	Pfizer Labs, New York, New York

This is not so for biologics. Biologic agents are large complex proteins, difficult to manufacture, and sensitive to environmental conditions. Quantification of the biosimilar compared with the brand name biologic requires an in-depth analysis of manufacturing requirements, as well as structural, immunological, pharmacodynamic, pharmacokinetic, and clinical outcomes. Because of the complexity of biologic structures, biosimilar products are expected to demonstrate similarity to the brand name biologic but not identical clinical effects.[5] Biosimilars could be described as genetically engineered copies that are similar rather than identical to a referenced biological agent with claims of similar safety, quality, and efficacy to the referenced drug. However, a biosimilar product is not the same as a generic product in the small molecule world. Although similar to biologic, the risk of acute or chronic immune responses exists, and although the therapeutic effects may be the same, adverse effects may be different.[4]

Therefore, in practice, substitution or interchangeability of a biologic and biosimilar is not as automatic as with generic small molecule drugs. Careful patient reevaluation and assessment are required, and a new prescription is often the path if a biologic is changed to a biosimilar agent.[4,5]

The Food and Drug Administration (FDA) approves biosimilars.[4,5] The introduction of biosimilars requires a specific pharmacovigilance plan because adverse events may appear only after the biosimilar drug has been used for a long period with greater numbers of patients.[4]

Oral dosing of biologics generally does not provide bioavailability related to the molecule size, polarity, and enzymatic destruction in the gastrointestinal tract.[2,3] Because of the large size of the molecules, biologics are absorbed slowly and take a longer period to reach peak concentration. Whereas small molecule drugs are usually cleared via hepatic or renal and biliary excretion, biologic clearance is a much more complex systemic event with multiple complex processes beyond the scope of this article.[2]

Crucial differences between small and large molecule agents are first the risk for immunogenicity with biologics, which is influenced by dose, duration of therapy, and drug reintroduction. Immunogenicity may also decrease the therapeutic effects of the biologic. Second, although fixed dosing is the usual standard for adults when prescribing small molecule drugs, a biologic is dosed based on body size, as well as pharmacokinetics, pharmacodynamics, and the therapeutic window. Although biologic drug-drug interactions have been reported, they are usually mild in nature and less common than what occurs in small molecule drugs related to differences in how the agents are cleared.[2]

EVIDENCE AND IMPLICATIONS FOR PRACTICE

Efficacy for the use of biologics is recognized. With regard to risk, an element of uncertainty remains as the research agenda moves forward. Results from a meta-analysis of 160 randomized controlled trials with 48 676 participants and 46 extension studies with 11 954 participants revealed that these biologics as a group (Orencia, Humira, Kineret, Cimzia, Enbrel, Simponi, Remicade, Rituxan, and Actemra) compared with controls were associated with statistically significant higher rates of adverse events, withdrawals due to adverse events, serious infections, and tuberculosis reactivation. The rate of serious adverse events, lymphoma, and congestive heart failure were not significantly different when biologic and control groups were compared.[6]

Although these results were statistically significant, clinical significance should be considered. For persons who received any biologic, 137 of 1000 dropped out because of adverse effects compared with 98 of 1000 who received placebo. As for serious infection, 35 of 1000 experienced serious infections compared with 26 of 1000 who received placebo. Twenty of 10 000 had tuberculosis compared with 4 or 10 000 who received placebo. Finally, for all adverse effects, for persons who received any biologic, 770 of 1000 had adverse effects compared with 724 of 1000 who received placebo.[6]

What is the role of the clinical nurse specialist (CNS) with regard to biologic therapies? The CNS can make a powerful difference in the care and outcome for patients receiving biologic therapy through assessment, education, and careful monitoring. Screening, reviewing risks and benefits with treatment options, and monitoring for allergic reactions and/or sensitivities can drive favorable outcomes. A crucial aspect of care is careful surveillance for current, recurrent, or latent infections, particularly tuberculosis. Infection screening also requires the assessment of risks related to piercings, tattoos, and foreign travel. Do not forget to evaluate cardiac risk factors, comorbidities, liver function, and reproductive health before and during therapy. Clinical nurse specialist management of biologic therapy can drive safe and cost-effective complex treatment. The CNS can also provide precious support for the patient who fails therapy or has exhausted options for biologic therapy.[7]

RESOURCES FOR THE CNS

The Center for Biologics Evaluation and Research (CBER) is within the FDA, an agency within the US Government's Department of Health and Human Services. The CBER's mission is to protect and enhance the public health through the regulation of biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies and approves biological products based on authority from the Public Health Service Act and in specific sections of the Food Drug and Cosmetic Act.[8]

The Center for Drug Evaluation and Research is a division of the US FDA and monitors most drugs as defined in the Food, Drug, and Cosmetic Act. Some biological products are also legally considered drugs, but they are covered by the CBER.[8]

For additional information regarding biologic approval, product and manufacturer information, reports, and related resources, check out the FDA Web site: http://www.fda.gov/BiologicsBloodVaccines/ucm121134.htm.

THE FUTURE

For the past 20 years, biologic manufacturing has provided multiple options for therapy that was not possible with small molecule therapies. However, improvements of bioavailability and delivery systems are needed. New delivery systems could further drive product development, as well as patient compliance with therapy. Promising routes for biologic delivery include intranasal, pulmonary, and transdermal routes, as well as the use of nanotechnologies.[9]

References

1. Cram DJ. *From Design to Discovery (Profiles, Pathways, and Dreams)*. Washington, DC; American Chemical Society; 1990.
2. Zhao L, Ren TH, Wang DD. Clinical pharmacology considerations in biologics development. *Acta Pharmacol Sin*. 2012;33(11):1339–1347.
3. Morrow T, Felcone LH. Defining the difference: what makes biologics unique. *Biotechnol Healthc*. 2004;1(4):24–29.
4. Kumar R, Singh J. Biosimilar drugs: current status. *Int J Appl Basic Med Res*. 2014;4(2):63–66.
5. Tothfalusi L, Endrenyi L, Chow S. Statistical and regulatory considerations in assessments of Interchangeability of biological drug products. *Eur J Health Econ*. 2014;15(suppl 1):S5–S11.
6. Somgj JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview (review). *Cochrane Database Syst Rev*. 2011;(2):CD008794.
7. Oliver SM. The role of the clinical nurse specialist in the assessment and management of biologic therapies. *Musculoskeletal Care*. 2011;9(1):54–62.
8. US Food and Drug Administration; US Department of Health and Human Services. About CBER. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm123340.htm. Accessed February 13, 2017.
9. Skalko-Basnet N. Biologics: the role of delivery systems in improved therapy. *Biologics*. 2014;8:107–114.