Inertia in Adaptation of Healthcare System to Biologics and Biosimilars

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Abstract

Biologics and biosimilars are underused. Different manufacturing, regulatory and social barriers, and clinical inertia prevent its adequate usage despite indications. Awareness of clinicians, patient education, reduction of costs, regulatory easing, and simplification of manufacturing processes will help in the earlier adaptation of biologics in the healthcare system. Further advancement of technologies will help to generate biologics and biosimilars of greater safety, better efficacy, lesser immunogenicity, and good interchangeability.

Problem Identification

Despite the advent of biologics long back and biosimilars subsequently, they are grossly underused. The intensity of underuse depends on the diseases or the products of biologics. For example, biologics like recombinant human insulin are regularly used in type 1 and 2 diabetes mellitus patients, while biologics like mepolizumab or omalizumab are infrequently used in asthma patients despite indications. Biologics are also underused in rheumatology and oncology patients, though exact values are not known. Awareness is not sufficient regarding biologics therapy. There is inertia in manufacturing sectors and regulatory authorities. The spectrum of problems includes underproduction of biologics, strict rules for approval of biologics by regulatory bodies, high cost of products, limited availability of cheaper biosimilars, concerns regarding safety and efficacy leading to underprescription, gradual loss of efficacy due to antibody production, high risk of hypersensitivity reactions, storage and transport problems, and lack of government support in research related to biologics. Because of different barriers (manufacturing, regulatory, clinical, and social), there is difficulty in the smooth adaptation of biologics in the healthcare system, and there is a need to overcome the inertia with proper strategies.

Definition and Differences of Biologics, Biosimilars, and Generics

Biologics are large molecules with complex structures derived from living sources like human, animal, plant, fungal, or other microbial organisms and are purified in complex, multi-step processes. Biologics have been used for medical purposes for decades. But now, targets have increased exponentially with the advent of new genetic information and a new understanding of subcellular cascades in disease processes. Advanced technologies like microarray, cell culture, recombinant deoxyribonucleic acid (DNA) technology, etc., are being used now for developing biologics. In contrast to small molecule conventional medicines, which are chemically synthesized and of known chemical structure, biological products are of complex structure and are not exactly duplicable. Biosimilars have minor variations in composition, especially of inactive components from reference biologics but have similar efficacy. They are cheaper but are not generics. Biosimilars are named “similar biologics” by Indian regulatory agencies. Interchangeable biosimilars are substitutable for reference biologics without the involvement of the prescriber as per the standard of regulatory approval. Generics are small molecule products containing the same pharmaceutical ingredients as the originally approved reference products.

Different Types and Uses of Biologics and Biosimilars

Some examples of biologics include steroid hormones (e.g., estrogen and testosterone), blood and its components (e.g., platelets), cytokines, growth factors, vaccines, antitoxins, somatic cells, and tissues (e.g., tendons, ligaments used for transplantation), recombinant proteins (e.g., human insulin and erythropoietin), fusion proteins (e.g., etanercept, abatacept), monoclonal antibodies (MAB), and nanobodies (single domain antibodies). Uses of biologics also include gene therapies, stem cell therapies, and other cell therapies (e.g., chimeric antigen receptor T cell therapy used for aggressive B cell lymphomas). MABs are designed to target cytokines and other circulating proteins, drugs (like digoxin), or cell surface molecules. MABs include antitumor necrosis factor inhibitors (e.g., infliximab and adalimumab), anti-interleukins (IL) (e.g., tocilizumab against IL-6 receptor), B cell inhibitors (e.g., rituximab against cluster of differentiation (CD) 20 receptor), anti-integrin inhibitors (e.g., vedolizumab used for inflammatory bowel disorder), osteoporosis inhibitor (e.g., denosumab against receptor activator of nuclear factor-κ ligand), immunoglobulin (Ig) E inhibitor (e.g., omalizumab), and many others. Among the other biologics, T cell costimulation inhibitor abatacept, a fusion protein composed of Fc region of IgG1 fused to the extracellular domain of cytotoxic T lymphocyte antigen-4, CD152 (cytotoxic T-lymphocyte–associated antigen 4), is used for the treatment of rheumatoid arthritis (RA). Anakinra, a recombinant, nonglycosylated form of the human IL-1 receptor antagonist, produced by recombinant DNA technology using an Escherichia coli bacterial expression system, is used to treat RA, cryopyrin-associated periodic syndromes, familial Mediterranean fever, and Still’s disease.

As many innovator companies are losing their intellectual property rights and patent protection after a stipulated period, the window of opportunities is growing for other companies to manufacture similar products at a lesser cost. As a consequence, many recombinant proteins, MAB, and fusion protein biosimilars are now being generated and available in Indian and international markets. Biologics and biosimilars (especially MABs and fusion proteins) are effective in connective tissue disorders, inflammatory bowel diseases, asthma, demyelinating disorders (e.g., anti-CD20

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MABs like ocrelizumab, ofatumumab, and rituximab used in relapsing multiple sclerosis), hematological disorders and neoplasms. MABs are also useful in migraine (either anti-calcitonin gene-related peptide (CGRP)—antibodies like galcanezumab, epitizeumab, and fremazemab, or anti-CGRP receptor antibodies like erenumab), sickle cell vasoocclusive crisis (e.g., crizanlizumab acting against P-selectin on the surface of platelet and vascular endothelial cells), infectious disorders (e.g., tocilizumab in coronavirus disease 2019), cardiovascular disorders (e.g., abxizimab for percutaneous intervention during angioplasty), chronic rhinosinusitis with nasal polyps (e.g., dupilumab), familial hypercholesterolemia [e.g., proprotein convertase-subtilisin/kinin type 9 MAB to reduce low-density lipoprotein cholesterol level], etc. Biologics are also promising for many diseases currently having no treatment options. Despite their great potential in a vast number of diseases, usage of them is not adequate still now.

**Barriers to Using Biologics**

Barriers to the adaptation of newer biologics and biosimilars are seen at multiple levels. Biologics are highly sensitive to changes in manufacturing conditions leading to product drift, evolution, and divergence, which may impact the safety, efficacy, and immunogenicity of biologics. With the advent of biosimilars and the expiry of patent protection of reference products, similar biologics are being produced by multiple manufacturers (by reverse engineering of the molecule) with different quality systems, which actually can lead to the generation of products with potentially meaningful differences in clinical impact. Along with biosimilars, reference biologics may also have some changes due to minor alterations in manufacturing processes since their approval a few years back. So, a robust pharmacovigilance system is essential to identify the safety, efficacy, immunogenicity, and interchangeability of biologics and biosimilars. As the substitution of newer batches of biologics (after some alterations of the manufacturing process) and biosimilars need tracking of efficacy, side effects, or loss of efficacy due to immunogenicity, physicians’ involvement is essential. The need for such a robust pharmacovigilance system somehow hinders the development, regulatory approval, and marketing of newer biological products.

In contrast to chemically derived drug biologics have difficulty in production, higher cost, questionable safety, and a high potential for immunogenicity (unwanted except for a vaccine). Most biological products are also sensitive to heat and vulnerable to microbial contamination (by bacteria, viruses, and mycoplasma), thus requiring aseptic techniques from the initial stages of manufacturing and needing proper temperature control for storage and transport. Physicians are traditionally familiar with small-molecule drugs but not with biologics. Unstandardized duration of therapy and lack of long-term experience in many biologics are other major concerns. The blood-brain barrier prevents access to large molecule biologics in the central nervous system, so biologics also have doubtful efficacy in neurological disorders. The nomenclature of MABs and their biosimilars is also difficult to memorize. The nonavailability of products, lack of proper distribution, and clinical support systems at the point of care are other important barriers causing underuse. Biologics are available as subcutaneous or intravenous injections but not as an oral therapy, which often hinders their compliance. The use of biologics is rare in many disorders (e.g., asthma) even when they are indicated, in comparison to others like lymphoma and many cancers, hormonal replacements in endocrine disorders, etc. Sico et al., in a workshop, concluded that therapeutic inertia in the usage of biologics is common in severe asthma and is found to be provider, patient, or payer-related. Lack of provider education and health insurance discrepancies are important barriers to biologics usage. Inconsistencies in diagnosis, under-referral of patients, communication gaps among patients and doctors, patient preferences, and transport problems from remote places to referral centers also lead to suboptimal usage of biologics.

**Strategies and Solutions**

Dedicated continuous medical education (CME) programs on biologics and more emphasis on them in medical curricula will fill the knowledge gap and create awareness regarding them among physicians. Safety and efficacy issues should be addressed properly in ongoing CMEs. Patients should also be educated and motivated properly for biologics by improving their understanding of disease severity and the benefits and risks of biologics. The fact should be highlighted that the cost is reduced drastically of follow-on biologics and biosimilars and their use should be encouraged both at the patient and physician levels.

Special emphasis should be given to safety issues. Though biologics (like MAB) working on immune cells and cytokines may cause or aggravate infections or malignancy, some of them are of low risk for infections, like anti-integrin inhibitor vedolizumab which inhibits leukocyte trafficking at the gut wall. Infection risk is also low for biologics (MABs) not acting on immune systems. Biologics are target oriented, directed against specific chemicals. Theoretically, they should have fewer side effects and more efficacy in contrast to immunosuppressants like steroids. Metabolic effects of steroids can be avoided by using biologics though they have a risk of some specific infections and other side effects, including immunogenicity. So, awareness regarding the benefits of biologics over risks should be increased without any prejudice among patients and physicians.

The manufacturing sector needs more research for the production of safe and effective biologics at low cost, and it also needs regulatory easing. Minimizing adverse events of biologics is a challenge. Robust research activities are required to identify side effects like immune reactions (like anaphylaxis, serum sickness, and delayed hypersensitivity reactions), generation of autoantibodies against biologics reducing efficacy, target specific side effects (like infections and cancers), and organ-specific side effects (like cardiotoxicity and Kounis hypersensitivity associated acute coronary syndrome). Advanced technologies will help to generate safe biologics with less immunogenicity. However, getting enough volunteers for clinical trials to assess the safety and efficacy of biologics is difficult.

Most of the MABs are either of hybridoma origin or their improvised engineered versions. In hybridoma technology, hybridoma cells are generated via fusion between a short-lived antibody-producing B cell and an immortal myeloma cell. Each hybridoma cell expresses a unique antibody or its improvised engineered versions. The hybridomas are selected for continuous MAB production for a long period. Further research regarding the advancement of hybridoma technology is required focusing on suitable fusion partners, fusion efficiency, and generation of human hybridoma or homohybridoma rather than heterohybridoma, which will help to generate MABs with higher specificity, affinity, and lesser immunogenicity. Research on new promising technologies for generating MABs, like antibody phage display technology and single B cell antibody technology, should also be continued to generate safe, effective, and immunologically acceptable biologics.

The blood-brain barrier issue in the therapy of neurological disorders can be overcome by intranasal delivery of biologics. It is also needle-free, and biologics will bypass first-pass metabolism. Intranasal delivery of biologics
seems to be promising, and research is going on for using highly vascular nasal epithelium as a promising route for biologics. Advanced technologies will help to prepare better formulations for intranasal delivery of high molecular weight biologics using different auxiliary agents, like, permeation enhancing agents, mucolytic agents, mucoadhesive agents, in situ gelling agents, and enzyme inhibiting agents. More research in the field will help to overcome the barrier.

Regulatory issues should be dealt with promptly for approval of biosimilars. However, safety, efficacy, and immunogenicity issues should be kept in high priority, and any compromise may be disastrous. The substitutability of biologics and biosimilars should be assessed by regulatory bodies properly but as promptly as possible. Switching involving physicians will help to detect untoward side effects, efficacy, and immunogenicity. Though a single switch from a reference product to a biosimilar is not intrinsically linked to an increase in immunogenicity, safety, or efficacy issues, further studies are required involving more products with back-and-forth switching, multiple switching, and switching among biosimilars. Regulatory promptness and research support will help in this regard. Patent protection time should be reduced considering the essentiality of products for human suffering, which will reduce the cost of follow-on-biologics and will help to generate more biosimilars at a lesser cost.

Global collaboration with technology sharing, revisiting regulatory guidelines, promoting cheaper follow-on-biologics and biosimilars, and awareness of biologics among physicians and patients’ motivation will help to overcome the inertia of biologics usage.

**References**