

Biologics and biosimilars: what, why and how?



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BIOLOGICS AS PROTEIN THERAPIES

Pharmaceutical products are doctors' major armamentaria for preventing, curing, controlling or modifying disease processes in order to reduce hospitalisations, disabilities and premature death.¹ Increasing knowledge of human diseases, especially after the decoding of the human genome, has accelerated the discovery of disease-related chemicals and/or proteins. These targets form the basis for the design of pharmaceutical compounds to alter biological activities and clinical outcomes. In 1982, the US Food and Drug Administration (FDA) approved human insulin (Humulin) as the first DNA-recombinant protein. Since then, there have been a rapid growth in the number of biologics in many disease areas, notably oncology, inflammation/autoimmunity and cardiovascular-metabolic medicine.²

Structural and functional complexity of biologics

Unlike single molecules which are chemically synthesised with highly predictable structures and functions, biologics are pharmaceutical compounds synthesised or extracted from a biological source often with highly complex structures. They can be broadly divided into monoclonal antibodies, receptor modulators or replacement/modulators of enzymes.² The manufacturing processes of biologics involve living systems (eg, mammalian cell lines, microbial agents, plants, fungus) and complex processes (eg, gene isolation, recombinant DNA engineering, protein purification) which require high technological expertise with precision in order to ensure consistency and quality of the final product.³

These compounds often have additional moieties, such as glycoconjugates, fatty acids and amino acids used to maintain the triple or quadruple structures. These high-molecular weight compounds require special formulations including stabilisers and preservatives for storage, which can influence

their pharmacokinetic and pharmacodynamic properties, as well as their biological activities.³

Immunogenicity and need for surveillance

Because these pharmaceutical products originate from a living system, immunogenicity remains a possibility that can either induce allergic reactions and/or alter the biological activities with clinical consequences. Given these multiple concerns, development of biologics is considerably more expensive and time-consuming than that of small molecules. The latter contain only carbon, oxygen and nitrogen, which are easier to synthesise with low batch-to-batch variabilities.⁴ Thus, immunogenicity against biologics or constituents of the formulation may lead to reduced efficacy or treatment failure. In some rare situations, these induced antibodies may target endogenous proteins resulting in adverse side effects, such as pure red cell aplasia with epoetin.⁵

Using biosimilars to increase access and reduce cost

Despite the high cost of development, due to their targeted nature with high efficacy, biologics are now taking on an increasingly important role in the treatment of common and/or serious diseases such as diabetes, cancer, chronic kidney disease, rheumatoid arthritis, psoriasis, blood disorders, vaccines and inflammatory bowel diseases. In these diseases, proteins such as hormones, growth factors and inflammatory cytokines are disease mediators that form the basis for drug development. In 2016, more than 10 biologics were blockbuster drugs with annual revenue of billions of dollars. With anticipated patent expiry of many of these originator compounds, biosimilars are now given accelerated paths for development in order to increase market access and affordability of these compounds.⁶

In Europe and North America, regulatory agencies such as the European Medicines Association and FDA have developed clear

regulatory guidelines for the evaluation and approval processes of biosimilars regarding their physical, chemical and clinical traits.⁷ To be called a biosimilar, these compounds need to demonstrate structural and functional similarities with comparable pharmacokinetic and pharmacodynamic properties to the originator compounds using sensitive indicators, for example, levels of cytokines, blood glucose or white cell counts. The manufacturer also has to produce evidence regarding the quality control of the processes of synthesis and composition of the formulation.

Once these criteria are fulfilled, these biosimilars are often given similar indications as the originator drugs in order to reduce the development cost and hence the market price.⁸ Once approved, the inherent nature of these complex molecules calls for continuing surveillance to detect allergic reactions or rare events due to immunogenicity or other untoward reactions, which may not be detectable during the development stage. Besides, the batch-to-batch variations may also lead to efficacy and safety issues in the postmarketing phase.⁴

Prescribing, dispensing and administering of biologics

From a prescribing perspective, many doctors were trained to use generic names of the molecules, so-called international non-proprietary names. In many healthcare institutions, automatic substitution using generic drugs is often practised for cost control. Although this practice is widely accepted for single molecules, most regulatory agencies and learnt societies recommend documentation of product identity, brand name, manufacturer name and batch number of biologics. However, these changes in practices and nomenclatures require considerable education of the prescribers. Besides, system support is needed to establish product inventory for tracking and recall purpose, which may not be readily available in small practices and/or institutions, especially in developing countries.⁹

Complex diseases, therapies and care delivery systems

With ageing and modernisation, non-communicable diseases (NCD) such as cancer, diabetes, chronic kidney disease and inflammatory diseases are now the leading causes of death worldwide.¹⁰ Thus, after long disease duration, patients with type 2 diabetes may require insulin analogues with different formulations (long acting, short acting, ultra-short acting, ultra-long acting) to control their diabetes. Some of these patients may go on to develop renal failure and require erythropoietin for treatment of anaemia. Given the close links between diabetes and cancer,¹¹ some of these patients may receive biologics/biosimilars for cancer treatment and drug-induced neutropaenia. On the other hand, anticancer therapies for hormone-sensitive cancers or pancreatectomy for pancreatic cancer may lead to diabetes resulting in complex therapies.¹¹ Similarly, there are close links among chronic inflammatory diseases, autoimmunity and cancer (eg, type 1 diabetes, ulcerative colitis, Crohn's

disease, systematic lupus erythematosus, rheumatoid arthritis) that can further increase the complexity of their biologics treatment.¹²

From diagnosis to treatment to patient advocacy

These examples highlight the new challenges in medical practice where physicians have to diagnose and manage multisystem diseases and use multiple medications in order to control disease processes. Importantly, these patients must be educated about the nature of these interlinking therapies and receive support on how to use these potent medicines properly and effectively, especially for those that require self-administration and dose adjustment, such as insulin.

To achieve these multiple objectives, a multidisciplinary approach with infrastructures and processes is needed to promote adherence, monitor clinical progress and perform regular surveillance. With increasing number of biologics coming off patents, more patients are expected to benefit from these therapies even in low-income to middle-income countries where prevalence and incidence of NCDs are rising rapidly.¹⁰ However, in order to bring out the best of these pharmaceutical compounds, these countries will need to develop regulatory frameworks to ensure the quality, safety and effectiveness of these biologics, including manufacturing processes, distribution networks, automatic substitution, extended indications, postmarketing surveillance and clinical support system.

In the midst of these pharmaceutical advancements, many practising doctors may not be kept fully abreast of the development of biologics and their multiple utilities. It is in this context that clinicians, who stand between science and practice, must equip themselves with these therapeutic trends, understand the interlinking nature of their indications, balance the risk–benefit ratios, monitor their impacts on clinical outcomes and advocate to relevant stakeholders, notably policymakers, payors and industry, to ensure that these patients have access to pharmaceutical products, including but not limited to biologics, with safety, efficacy and quality.⁸

Competing interests None declared.

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