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Review Article

EMERGING BIOSIMILARS IN ONCOLOGY: A REVIEW

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ABSTRACT

Biosimilars are the biological medicinal products that produce the therapeutic effects in the human body similar to that of inner biological molecule. Biopharmaceuticals consist of nucleic acids, amino acids, polysaccharides, or combination of all compounds. In India, the steps have been taken to manufacture biosimilars with the lowest cost and least side effects. Globally, India is one of the major developing countries in manufacturing and marketing of biosimilars. The application of biosimilar was rapidly growing in treating various disorders such as cancer, inflammatory disease, and cardiovascular diseases. For the approval of biosimilars, *in vitro* studies become the necessity for representing comparison to a standard biological in terms of quality for experimental studies indicating similar pharmacokinetics, efficacy, safety, and immunogenicity. Huminsulin was the first DNA-recombinant protein accepted by the US Food and Drug Administration (FDA) in 1982. As currently there are no FDA-approved biosimilars for treating breast cancer, many biologic antibodies are under investigation.

Keywords: Biosimilars, Inner biological molecules, Food and drug aministration, DNA recombinant protein, Oncologist.

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INTRODUCTION

A biosimilar may be a biological medicinal product that is nearly the same copy of an imaginative product which is made by a special company. Biosimilar is additionally referred to as inning biological or subsequent entry biological [1].

Generic medications which are made up of single compounds are totally different from biologically active compounds obtained by applying biotechnology to discover molecules from living systems such as bacteria, yeast, plant, virus, animal, or human cell lines that are biotechnologically modified to provide the drugs. Biosimilars are advanced bio-therapeutically produced drugs consisting of nucleic acids, amino acids, carbohydrates, or combination of these compounds.

Recently, biosimilars are manufactured from the human living system, especially cell lines as the post-translational modification that occurs in the non-human living systems. The safety and therapeutic effect of the final product should not be disturbed by any heterogeneous variations in its quality between different batches [2].

Biosimilars can be manufactured by studying pharmacokinetic and pharmacodynamic studies and compared to that of reference product which takes about 5 years. In pre-clinical studies, the variations in amino acid structure, immunogenicity, Absorption distribution metabolism excretion (ADME) studies, and biological responses will be detected by various investigative tools. This leads to the requirement for pre-clinical studies in developing biosimilars which were analyzed by various regulatory bodies [3]. Biosimilar monoclonal antibody, namely infliximab, was approved by "European Medical Agency" to treat inflammatory bowel disease [4,5]. In spite of the rigorous method made public by many bodies globally for the authorization of biosimilar, some physicians were not willing to use biosimilar, significantly in beneficial indication [5].

In the next upcoming years, subsequent entry biologics will be used to treat rheumatoid arthritis and most of the surveys have been reported stating that it would be appreciated if pharmacists have the rights to alternate the generic drugs with the biosimilars without clinician's consent [6]. In oncology, biosimilars have been developed for the trastuzumab, rituximab, and bevacizumab. ABP 215, BCD-021, PF-06439535, and RPH-001 are the biosimilars for bevacizumab, whereas for the trastuzumab - BCD-022, CT-P6, FTMB/ABP 980, and PF-05280014 are the biosimilars [7].

GUIDANCE ON BIOSIMILAR DEVELOPMENT

For the development of biosimilars, the World Health Organization recommends to conduct categorization and similitude study for its properties, responses, impurities, and its stability additionally to pre-clinical and clinical analysis and therapeutic indications [8-10]. Various applicable regulations and guidelines include Recombinant DNA Safety Guidelines (1990), Guidelines and Handbook for Institutional Biosafety Committees (2011), Guidelines on Similar Biologics: Regulatory Requirements for Marketing authorization in India (2012), Guidelines for Generating Preclinical and Clinical Data for rDNA Vaccines, Diagnostics, and Other Biologicals (1999), and CDSCO guidance for industry (2008). Recently, various researches toward the development of biologically similar products were carried out in the US, Europe, Israel, China, and Brazil [11,12].

vaccine, monoclonal antibodies, recombinant proteins, insulin, erythropoietin, streptokinase, and epidermal growth factor receptor were approved in India as Biosimilars [13-15]. Health Canada and European Medicines Agency (EMA) approve the products that show the resemblance in its biological responses with that of standard which compares the PKs, efficacy, safety, and immunogenicity [16-18]. The developing countries have taken steps to develop the biosimilars with low prices and side effects [9,19]. Several biosimilar products have previously been accepted and sold in Asian nation for diverse types of cancer [20,21].

PHARMACOECONOMIC IMPACT OF BIOSIMILARS

Globally, every year financial status of cancer that has been used for diagnosis and therapy was found to be approximately US$1.16 trillion in 2010 [22,23], and further, it was raised to US$2.5 trillion. In the Asian nation, people have to pay for their personal physical condition and patients are less possible to access individually to valuable cancer treatment [24,25].

Pharmaceutical products are one of the major equipment to prevent, cure, diagnose/modify disease processes so as to reduce diseased condition, disabilities, and death. Upcoming information of various human diseases increased the invention of various targets or proteins toward the disease. The identified proteins create the idea for planning of discovering various pharmaceutical formulations to alter the pharmacological responses and clinical outcomes. Humulin (human insulin) was the first DNA-recombinant protein which was approved by the US Food and Drug Administration (FDA) in 1982 by Genentech and Eli Lilly [26,27]. Hence, there increased the development of a variety of biologics in treating several disorders such as cancer, inflammation, and cardiovascular-metabolic disorders [28,29].

COMPLICATION OF BIOSIMILARS IN STRUCTURE AND FUNCTIONS

Biologics are pharmaceutical preparations that are produced or extracted from biological sources with extremely complicated structures. Hence, biologics was different from chemically synthesized generic molecule which has conventional structures and functions. They are classified into organism antibodies, receptor modulators, or enzyme modulators. Biologics are manufactured from various systems and process such as heterogeneous mammalian cell lines, microorganisms, natural sources, recombinant DNA technology, and gene coding isolation [30]. To retain the triple or quadruple structures, the biosimilar products contain extra groups such as polypeptides, fatty acid, and amino acid sequences. It is necessary to include various additives to store it and also to influence the structure. These higher molecular weight preparations also need formulations including stabilizing and preservative agents for storage, which might have effect to increase their pharmacokinetic and pharmacodynamic properties.

IMMUNOLOGY

As these pharmaceutical products originate from a mammalian cell, immunogenicity remains a clear stage that it may provoke sensitivity or alter the responses with clinical effects. By focusing on these numerous issues, manufacturing of biosimilars is significantly difficult and takes longer when compared to generic molecules. It is easy to manufacture the generic drugs from batch to batch differences as it contains only carbon, oxygen, and nitrogen, which are easier to synthesize with low batch-to-batch variabilities [31]. Thus, immunogenicity against biological product or constituents of the preparation could result in decreased effectiveness or therapy negligence. Rarely, these elicited immunoglobulins could aim for the intracellular mediators leading to undesirable reactions like Diamond-Blackfan anemia with epoetin [32].

BIOPHARMACEUTICALS IN BREAST CANCER

While there are currently no FDA-approved biosimilars of drugs that treat breast cancer, many biologic antibodies are under investigation. Trastuzumab, a monoclonal antibody that targets human epidermal growth factor receptor 2 (HER2), was shown to hinder the breast cancer cell proliferation that overexpresses HER2. In 2001, it was shown to improve the overall pharmacological response and its duration along with survival rate in combination with chemotherapy compared with chemotherapy alone. This led to the approval of trastuzumab in treating HER2-positive metastatic breast cancer in 2006. Since then, trastuzumab approval has expanded to cover additional settings, treatment regimens, and cancer types. In 2008, about more than 420,000 women with HER2-positive breast cancer had received trastuzumab treatment which is considered as standard. The US patent for trastuzumab is set to expire in June 2019; it expired in July 2014 in Europe. The success of trastuzumab, in combination with its expired patent, has prompted the investment into competing biosimilars [33-36].

Although 19 biosimilars for trastuzumab are currently being investigated, MYL-1401O has shown the most success toward the patients with HER2-positive metastatic breast cancer [37,38]. As progression-free survival or overall survival may be insufficient to demonstrate biosimilarity between reference products and their biosimilars, bodies such as the EMA have recommended using an activity-measuring clinical endpoint such as partial complete response or oxygen reduction reaction (ORR) as the primary endpoint [39]. The primary outcome measure of this study was a comparison of the best ORR at week 24 between the combination of biosimilar trastuzumab (MYL-1401O) with taxane and reference trastuzumab with taxane. The study showed that patients receiving reference trastuzumab plus a taxane had an ORR of 64.0% at 24 weeks and patients receiving biosimilar trastuzumab plus a taxane had an ORR of 69.6%, a rate within pre-defined equivalence boundaries. Progression-free survival at 48 weeks was 44.7% and 44.3% for reference and biosimilar trastuzumab, respectively; overall survival was 85.1% and 89.1%, respectively; adverse events affected 94.7% and 98.6% of patients, respectively [40,41]. PF-05280014, another biosimilar of trastuzumab, was reported as having demonstrated equivalence in its primary endpoint in November of the past year; data from this study have not yet been presented [42]. Finally, biosimilar trastuzumab has been investigated only as a single agent, while trastuzumab plus pertuzumab is considered the standard of care. The development and testing of biosimilar drugs may continue to change the ways doctors to treat their patients. Increased understanding of the approval and testing process, as well as potential benefits and risks of the use of biosimilars, are essential for practicing oncologists. Biologic pharmaceutical options remain costly, and incorporation of biosimilars may lead to health-care savings of 30% or more, with market entry costs, pricing reactions, and many other factors establishing the ultimate level of cost reduction that may be seen [43].

CONCLUSION

Biologics or biopharmaceuticals or biotechnologically produced drugs are key growth enhancers in the pharmaceutical market [44]. Development of biosimilars provides the opportunity for drug manufactures to employ a comparator official outside the European Economy Area throughout the clinical study of biosimilars products. For the last three decades, the biosimilars are products which are growing rapidly in the market and mainly intended in the treatment of various incurable diseases. Biosimilar products are obtained from the living cells with high molecular weight and complex than chemical drugs. The EMA WHO and US FDA guidelines are some of the reference standard for many countries. 16 countries adopted these guidelines and 3 countries filled the drafts as the basis of their own regulations.

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