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Review Article

A short review on biosimilars: Future treatment method

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ABSTRACT

In living cells, biosimilars are produced and are usually large, complex proteins that can have a variety of uses. Biologics are used in the field of gastroenterology alone for treating inflammatory bowel diseases, tumors, and endocrine disorders. Biosimilar development is an attempt to reduce the cost of the treatment. Currently, seven biosimilars have been approved by the United States Food and Drug Administration (FDA) for use in Crohn's disease, ulcerative colitis, and colorectal cancer. There are other biologics involved in treating gastroenterologic diseases for which there are no FDA approved biosimilars. The overview of the article explains the use of biosimilars in the treatment of IBD, Oncology, Diabetics, breast cancer.

Keywords: Biosimilars, Treatment, Disease

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INTRODUCTION

A Biosimilar or similar biologics can be defined as a biological product which is formed by genetic engineering techniques and is "similar" in terms of safety, efficacy and quality to a reference biologic. WHO Definition: "A bio therapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference bio therapeutic product." USFDA Definition: A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product. It contains a version of active substance of an already approved biological medicine, which is refered to as 'reference medicine' or 'originator medicine'. Similarity to the reference medicine in terms of quality, structural characteristics, biological activity, safety and efficacy must be established such that they don't have any clinically meaningful differences.

How are Biosimilars Manufactured: The manufacturer of a proposed biosimilar product generates an array of data comparing the proposed product to the FDA-approved reference product in order to demonstrate biosimilarity. The comparative data are generated and evaluated in a stepwise fashion that begins with a foundation of detailed analytical (structural and functional) characterization and comparison of the products, moving on to animal studies if necessary and then to comparative clinical studies. Consequently, rather than generating the same full profile of nonclinical and clinical data as the reference product, a manufacturer that shows its proposed biosimilar product is highly similar to and has no clinically meaningful differences from the FDA-approved reference product may rely in part on FDA's previous determination of safety and effectiveness for the reference product for approval. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients.

Data required for approval of Biosimilar products: A biosimilar product application must include data demonstrating biosimilarity to the reference product. This usually includes data from: Analytical studies demonstrating that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components; Animal studies, including an assessment of toxicity; and A clinical study or studies sufficient to demonstrate safety, purity, and potency of the proposed biosimilar product in one or more of the indications for which the reference product is licensed. This typically includes assessing immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD) and may also include a comparative clinical study.

Advantages of Biosimilars

1. There is huge market needs and growing affordability for Biosimilars in universal and domestic market.
2. Development and manufacturing of Biosimilars are improved by existing manufacturing technology.
3. Due to no investment in phase I-II of clinical trials, Biosimilars are existing at cheaper prices than the reference products, so treatment price with Biosimilars is minor than innovators biological drug.

Disadvantages of Biosimilars

1. Biosimilars are not as much of stable as chemical based pharmaceuticals and thus essential cold chain distribution and have a shorter shelf life. This increases the price and complexity of distribution.
2. The cost of development will be importantly higher than for chemical based generics.
3. The required capital venture in property plant and equipment and the cost of manufacturing will be much greater for Biosimilars than for generic drugs.

Regulatory Pathway for approval of Biosimilars

The leading challenges faced by biosimilar drug developers is proving the equipollence or similar attribute of their biological drug to the reference product because of great variation in properties and even miniature alterations can lead to unacceptable deviations in safety and efficacy.

Various Biosimilar terminologies used by different regulatory bodies

Regulatory Framework in India

Regulatory Guidelines for Biosimilars in India: The regulatory bodies responsible for approval of 'similar biologics' in India are the Department of Biotechnology (DBT), through its Review Committee on Genetic Manipulation (RCGM), and the CDSCO.

Responsible Establishments for the Authorization Process .The competent authorities associated with in the approval process are as follows:

(a) Review Committee on Genetic Manipulation (RCGM)
(b) Genetic Engineering Appraisal Committee (GEAC)
(c) Central Drugs Standard Control Organization (CDSCO)

Regulatory Pathway for Biosimilars in India
INDIA'S FIRST BIOSIMILAR
A vaccine for hepatitis B, was marketed and approved in 2000, according to the global Generics and Biosimilar Initiative (GaBI); more than a decade before the US Food and Drugs Administration (FDA) approved its first biosimilar. Approximately 70 biosimilar products have been approved in India and, according to GaBI's list, more than 25 have been developed in India since 2000.

CIPLA
One of the leading pharmaceutical companies announced the launch of first biosimilar etanercept known as etacept in 2013.

RANBAXY
Launched India's first biosimilar of Infliximab
Clinical effectiveness of Infliximab combined with cost effective pricing will enable more number of patients to get access to the treatment in India.

Future Perspectives
- Many companies will have their patent expire in the forthcoming year, which will open the window of opportunity for other biopharmaceutical companies to explore the possibility of development of biosimilar products.
- The global market for the biosimilar is expected to grow by US$10 billion and many companies are anticipated to enter into this lucrative sector.
- Although the biosimilar space is still growing and evolving in the United States, India is a significant player in the world in manufacturing and using of biosimilars . Indian biosimilar market was approximately US$300 million in 2015. The export of biosimilar from India stands at a staggering US$51 million. India has the potential to become a global player in biosimilars.
- According to ASSOCHAM- Sathguru report released in 2016, biosimilar presents a US$240-billion global opportunity to Indian biopharmaceutical industry and the domestic market is expected to grow US$40 billion by 2030. Institute of Medical Sciences' health-care report also envisages a similar opportunity for Indian biopharmaceutical companies associated with manufacturing and marketing of biosimilars.

Biosimilars in Oncology: Currently, the use of biosimilars in oncology practice is constantly evolving as numerous patents on biologic drugs expire. To date, there are only a few approved biosimilars for cancer treatment; however, many more are expected to enter the market soon. Biosimilars to epoetins and filgrastims are used in cancer for treating chemotherapy-induced anemia and for the prevention and treatment of chemotherapy-induced neutropenia. The main concern of clinicians upon switching to biosimilars is immunogenicity, as even small changes in the structure of original biologics may cause loss of efficacy and increase the incidence of adverse events. Immunogenicity may also be triggered by impurities, different routes of administration, storage conditions and patient characteristics. Furthermore, due to their challenging nature, there are a limited number of studies that have investigated the use of biosimilars in oncology. The majority of biosimilarity studies have been performed for rituximab biosimilars in rheumatoid arthritis, however there are concerns whether these findings can be extrapolated in the oncology setting. In order to minimize the associated risks, preclinical studies comparing biosimilars and biologics are required, as well as post-marketing surveillance studies to demonstrate their safety profile in a real world setting and monitor long-term immunogenicity.

Moreover, pharmacovigilance post-marketing and long-term safety data are important to ensure safety and efficacy in the long-term. Monitoring from patients or healthcare professionals includes reporting of any adverse effects, safety concerns or medication errors.

Biosimilars in the treatment of Inflammatory Bowel Disease (IBD)
Biologic therapy, such as those that target tumor necrosis factor (TNF) signaling, has proven to be an efficacious method of treatment for patients with inflammatory bowel disease (IBD) . The impending patent expiry and the relatively high costs of biologics, particularly anti-TNF agents, have paved the way for biosimilar development for IBD. The hope with biosimilars is that their entry into the market will be able to drive competition between pharmaceutical companies to reduce prices like that of the generic market, and that access to appropriate biologic treatments for IBD patients is increased in the long-term. Yet, there are challenging issues such as indication extrapolation and interchangeability that are still being debated in the field of IBD and must be addressed in future issued guidance.

Biosimilars for the treatment of Breast cancer
Human epidermal growth factor receptor 2-positive (HER2+) breast cancer comprises approximately 15%–20% of all breast cancers and is associated with a poor prognosis. The introduction of anti-HER2 therapy has significantly improved clinical outcomes for patients with *HER2+ breast cancer*, and multiple HER2-directed agents

(ie, trastuzumab, pertuzumab, lapatinib and ado-trastuzumabemtansine) are approved for clinical use in various settings.

The treatment landscape for patients with HER2+ breast cancer is continuing to evolve. While novel agents and therapeutic strategies are emerging, biologic therapies, particularly trastuzumab, are likely to remain a mainstay of treatment. However, access issues create barriers to the use of biologics, and there is evidence for underuse of trastuzumab worldwide.

Biosimilars of trastuzumab are in development and may soon become available. This introduction may improve access to anti-HER2 therapies by providing additional treatment options and lower-cost alternatives. Because HER2-targeted drugs may be administered for extended periods of time and in combination with other systemic therapies, biosimilars have the potential to result in significant savings for healthcare systems.

Biosimilars for the treatment of diabetes

Biosimilar insulins are likely to enter the market of diabetes therapies as patents for major branded insulin products start to expire in the next few years. This would allow providing comparable clinical benefits of the current available insulins at a significantly lower cost, thus increasing the affordability and access of insulin treatment for patients with diabetes. Biosimilars are approved via a stringent regulatory pathway demonstrating quality, safety, and efficacy comparable to the reference product. Additionally, as practitioners' knowledge regarding the differences about pharmacological, clinical, and regulatory aspects between biosimilars and generic small molecules is often suboptimal, specific education on biosimilar prescribing, dispensing, and administering is critical for ensuring patients' benefit and safety. On June 2014, the European Medicines Agency authorized the first biosimilar of insulin glargine, Abasria, 100 Units/ml, for the treatment of diabetes mellitus.

Biosimilars in the treatment of Anemia

Exogenous replacement of erythropoietin (EPO) by recombinant human EPO has been considered a standard of care for the treatment of anemia in patients with chronic kidney disease for more than 20 years. Genetically engineered biologic proteins derived from human, animal, or microorganism sources are a major area of growth in modern medical care, accounting for one-third of new drug approvals in the past decade. Biosimilars , have been available in Europe for more than 10 years with no unusual or unexpected effects compared to their reference biologics whose patents have expired. Given the success of the biosimilar approval pathway pioneered in Europe, it has served as a global reference for other regulatory authorities to establish and implement biosimilar licensure frameworks, including the United States (US), the largest pharmaceutical market in the world. Given 10 of the top 25 drugs sold in 2014 were biologics, and considering the rising costs of healthcare, biosimilars have the potential to become a significant part of the US market.

For the nephrology community, the recent patent expiries for epoetin alfa have created the opportunity to develop biosimilar EPOs. And while no biosimilar in this therapeutic class is approved in the US, there are proposed biosimilars in development.

Treatment Burden

While these treatment methods have provided significant stabilization, and in some cases, improvement, in the visual acuity of patients with neovascular AMD, the financial and frequent visit burden often plays a factor in patient compliance. This is a concern, because various studies have linked undertreatment to a decline in visual acuity.9 In a review of clinical trials published between 2013 to 2018 using bevacizumab, ranibizumab, or aflibercept, initial visual acuity improvements were maintained throughout follow-up so long as the patients were maintained on treatment.9 The most commonly followed trial protocol required monthly injections of bevacizumab and ranibizumab and every-2-month dosing of aflibercept after initial loading doses. The authors reported that visual acuity did correlate with the frequency of injections, and that as-needed treatment was more often correlated with visual decline.

CONCLUSION

Biosimilars are created in living cells and are typically large, complex proteins that may have a variety of uses. Within the field of gastroenterology alone, biologics are used to treat inflammatory bowel diseases, cancers, and endocrine disorders. While biologics have proven to be effective in treating or managing many diseases, patient access is often limited by high costs. The development of biosimilars is an attempt to reduce treatment costs. Although the manufacturing process still involves production within living cells, biosimilars undergo fewer clinical trials than do their reference biologics. This ultimately reduces the cost of production and the cost of the biosimilar drug compared to its reference biologic. Currently, seven biosimilars have been approved by the United States Food and Drug Administration (FDA) for use in Crohn's disease, ulcerative colitis, and colorectal cancer. There are other biologics

involved in treating gastroenterologic diseases for which there are no FDA approved biosimilars. More time will be needed for biosimilars to establish a larger and more consistent market share compared to their reference biologics.

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