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A REVIEW ARTICLE ON USE OF BIOSIMILARS IN THE TREATMENT/ MANAGEMENT OF VARIOUS AILMENTS

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ABSTRACT

Biosimilar is a biological product almost similar to an existing approved product obtained from natural sources and having a complex structure. Biosimilars differ in development, evaluation and regulatory approval from the reference product. Biosimilars are being utilized in the treatment of various diseases like inflammatory bowel diseases (IBD), rheumatoid arthritis, renal conditions, oncologic conditions, etc. And its use in various other diseases is under research and progress.

Keywords: Biosimilar, IBD, Rheumatoid arthritis, oncologic, reference product

INTRODUCTION

Biosimilar is a biological product produced by following a special stepwise procedure, such that it demonstrates similarity towards the reference product in terms of quality attributes, safety, efficacy, potency, immunogenicity based on comprehensive comparability exercises. There should be no clinically significant difference between the biological product and the reference product **[1, 2, 6]**.

A reference product is an existing approved product, which is structurally complex and is isolated from natural sources (proteins, amino acids, or combination of these, or living entities such as cells and tissues) **[3, 4]**.

Biosimilars are not to be considered as generic equivalents as they differ in development and regulatory approval. The analysis and clinical trials for potential biosimilars compare the physicochemical properties, biological properties, efficacy & safety. They do not re-establish mechanism of action, determine optimum dosing, or demonstrate patients benefit, because they are already established by the originator **[1, 2, 5]**.

Due to various specific and unique considerations regarding regulatory approval of biosimilars, specific guidelines have been developed by the EMA (European Medicines Agency), FDA (Food & Drug Administration) & WHO (World Health Organization) **[1, 2, 6]**. Development and evaluation of biosimilars involves processes and studies which are extensively analytical and functional in nature.

A biosimilar may be designated as 'interchangeable', which means the biological product may be substituted for the reference product and can be expected to produce same clinical results as the reference product in any given patient. **[7]** Only FDA has the authority to approve a biosimilar as interchangeable with the reference product **[8, 9]**.

The term 'biosimilar' is newer to almost all sectors of pharmaceutical industries. It is often confused and inappropriately associated with terms like generic, bio better and bio superior. The reason might be the lack in providing a unison definition for the respective term by the regulatory agencies.

Though, currently biosimilars represent very small portion of biopharmaceutical market. But with the allure of significant saving in the whole development procedure, shorter regulatory timeline, the biosimilars market is certainly expected to expand. Another assured reason for the pharmaceutical companies to show interest in development and production of biosimilars is the reduced potential business risk. As biosimilars are almost copies of the originator product which has already established its mechanism of action, side effects, adverse effects, drug interactions and other pharmacological aspects and also have ensured its safety and efficacy, hence making biosimilar development a less risky business.

To achieve this projected growth in the area of biosimilars development, a quality management system (QMS) is necessary. Using a balanced QMS, the development cost can be reduced and regulatory barriers to innovation can be curbed. A competent QMS will provide control for documents,

equipment, learning, process development and change management **[46]**.

Use of biosimilars in treatment/ management of various ailments

JR-131 as a biosimilar to a long-acting erythropoiesis – stimulating agent darbepoetin alfa in treatment of renal anemia

Renal anemia is a characteristic complication that occurs in people with chronic kidney disease (CKD). In CKD, kidneys are unable to produce enough erythropoietin (EPO) – which is a glycoprotein hormone produced by interstitial fibroblasts in kidney & is responsible for induction of red blood cell production. This deficiency of EPO causes RBC count to drop and leads to anemic conditions which might grow worse to absolute kidney failure and related consequences **[10-12]**.

Earlier in 1980s, this condition was corrected by blood transfusion. Few years later, first recombinant human erythropoietin (rhEPO) was introduced internationally which treated renal anemia with high effectiveness. However, receiving the drug two-three times a week at clinic was felt quite burdensome by the patients **[13-15]**. This point of view led to the development and approval of a longer-acting erythropoiesis stimulating agent (ESA) darbepoetin alfa.

Darbepoetin alfa is a modified rhEPO varying in carbohydrate chain structure (replacement of five amino acid residues of the native rhEPO).

Various candidate biosimilars to darbepoetin alfa are under development. JR-131 is a recombinant human protein produced using Chinese hamster ovary cells as a host cell line, developed by JCR pharmaceuticals & Kissei pharmaceuticals. Physicochemical and biological evaluation of JR-131 have demonstrated its similarity to the reference medical product i.e., darbepoetin alfa **[16-18]**.

A biosimilar of infliximab (IFX) in management of Inflammatory Bowel Disease (IBD) & rheumatoid arthritis

Inflammatory Bowel Disease (Crohn's disease & ulcerative colitis) are idiopathic inflammatory diseases affecting the lining of various parts of digestive tract, causing abdominal pain, weight loss, fatigue, severe diarrhea and similar symptoms.

IFX (anti-TNF agent) is a full length, bivalent IgG monoclonal antibody, which blocks TNF (tumor necrosis factor) by two different mechanism of action: blockade of TNF receptor-mediated mechanism and induction of transmembrane TNF – mediated mechanism **[19, 20]**.

Both soluble (sTNF) & transmembrane (tmTNF) ligands interact with either of two different receptors- TNFR1 & TNFR2. In rheumatoid arthritis, IFX is thought to act predominantly by neutralization of sTNF & tmTNF **[21, 22]**.

Celltrion's biosimilar of IFX (CT-P13, Remsima^{TM}) manufactured & marketed in South Korea was approved for all indications of reference product, including all rheumatological conditions & IBD **[23, 26, 27]**.

Clinical trials prove that Remsina TM & other biosimilar of IFX – Inflectra TM have equivalent efficacy and safety as the reference product **[24, 25, 28, 29]**.

Rituximab biosimilars in the treatment of non – hodgkin's lymphoma and different oncologic conditions

Rituximab was the first monoclonal antibody to be approved for the treatment in oncological conditions and still is a fundamental component in the treatment of non – Hodgkin's lymphomas. Inspite of recent advanced options for the treatment of lymphomas, Rituximab in combination with other agents remains a useful option. **[30]**

Rixathon & Truxima were the first Rituximab biosimilars developed by Sandoz, Holzkirchen, Germany & Celltrion, Incheon metropolitan city, South Korea. The approval was based on the satisfactory result derived from the comprehensive comparability studies with the reference product (MabThera/Rituxan, Roche, Basel, Switzerland/Genentech, CA, USA). **[31-34]** This comparability study included extensive physicochemical evaluation, structural evaluation, data from clinical & pre- clinical pharmacokinetic, pharmacodynamic & immunogenicity assessment. The final step in the development of both the biosimilars was the confirmatory phase III clinical trial in patients with advanced follicular lymphoma **[35-41]**. Similarities demonstrated in these trials along with some other tests, provides an extensive evidence to allow extrapolation of this data with reference product to the biosimilar in other nontested indications **[42]**. Biosimilars can be allowed to produce affordably compared to the reference product, by this way of development involving reduced requirements for clinical testing, patronized by health authorities all over the world.

Data collected from office based oncologic practices in Germany (July 2017-June2019) reported that Rituximab biosimilars were used across all indications, including extrapolated indications. This real-world data of non-Hodgkin's lymphoma (NHL) & chronic lymphocytic leukemia (CLL)

depicted the increased use of Rituximab biosimilar in multiple treatment protocols.

With a doubtless prospective, biosimilars can provide cost effectiveness in cancer treatment making it more accessible to the patients, hence supporting sustainability of cancer care.

CONCLUSION

This review gives a brief introduction about biosimilars and draws light on the utility of biosimilars in the treatment of various ailments. Biosimilars have provided a valuable and efficient option among the medications used for management and treatment of various diseases, pathological conditions and even extrapolated indications. The above review also shows the advancements that are being made in this field (production, evaluation, regulatory approval, and marketing) and the increasing usage as well as acceptance of biosimilars among medical personals and patients.

Strict and compliant parameters had been set for the regulatory approval of a biosimilar. Physicochemical, biological, clinical, pre-clinical & immunogenicity assessments are made precisely, and the data obtained from these assessments are analyzed critically to avoid any sort of error or complication in any step of biosimilar processing.

Biosimilars of medications used in psoriasis, different oncologic conditions and rheumatic diseases, ankylosing spondylitis, etc. are under critical analysis for development. Ongoing clinical trials and research are at verge of making breakthrough progress in this field.

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