Biosimilar: Understanding the Concepts and Developing role in Nephrology.

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Abstract:

Biosimilars are designed to be used interchangeably with biologics and its development is an attempt to reduce the cost of health care. Biologics have variety of uses and are created in living cells. They are typical large complex proteins which can be used in different medical conditions. Biosimilars are a growing drug class and must be nearly identical to their reference biologics in terms of efficacy, side effect profiles and immunogenicity. The low cost of biosimilar is likely to be because it underwent fewer clinical trials. The manufacturing process still involved production in living cells. Erythropoietin biosimilar product is widely used in nephrology practice since 2013. Biosimilars are facing challenges in establishing a significant market share despite of their low cost. This seems to be a reflection of physicians being not confident in switching and patients as well show resistant to switch.

Long term safety and efficacy data is required in addition to increase number of available biosimilar products to improve the confidence of physician and patient. Biosimilar products will require more time to leave significant impact on the market share.

Key words: *Biosimilar, Erythropoietin, Chronic kidney disease, anemia*

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Introduction:

Biologics are therapeutic proteins which are manufactured in a laboratory setting to mimic the structure of naturally produced proteins in the body. They may either antagonize or mimic the function of natural protein . Biological products are indicated in various conditions like growth factors in malignancy, clotting factors for coagulopathies and monoclonal antibodies in inflammatory conditions such as Rheumatoid arthritis, SLE, Inflammatory bowel disease, Multiple sclerosis, Psoriasis. Biologics are also widely used by nephrologists throughout the world in the form of recombinant human erythropoietin (rHuEPO) (1)

A biosimilar is a successor to a biological medicine (known as a reference medicine) for which the patent has expired and exclusivity has been lost. By definition, a biosimilar is required to have same amino acid sequence, same route of administration and the similar strength as of its reference medicine. (2)

Food and drug Administration Authority (FDA) defines biologic medicine as a "pharmaceutical product whose active substance is made by or extracted from living organisms, tissues or cells". (2)

Biosimilar is a biologic that is similar to reference product without any significant differences in terms of safety and potency. These products should meet strict criteria of quality and comparability to their reference biologics. (3) It is a step wise process, **Figure 1**. FDA can approve a biosimilar drug for which the reference product is previously licensed biologic approved. FDA can't approve a biosimilar until 12 years after approval of reference product. The process begins with the structural & functional comparison between the biosimilar and reference product. Animal data is required to determine the toxicity, immunogenicity and pharmacokinetics/pharmacodynamics to assess the safety. Human clinical studies are not strictly required in this case. FDA will give the approval on the basis of "Totality of evidence".

The approval confirms that the biosimilar matches the reference medicine and there are no clinically meaningful differences in terms of safety, efficacy & potency, Figure 1. Since biological products are more complex structure to that of small molecule drugs, they are more expensive to

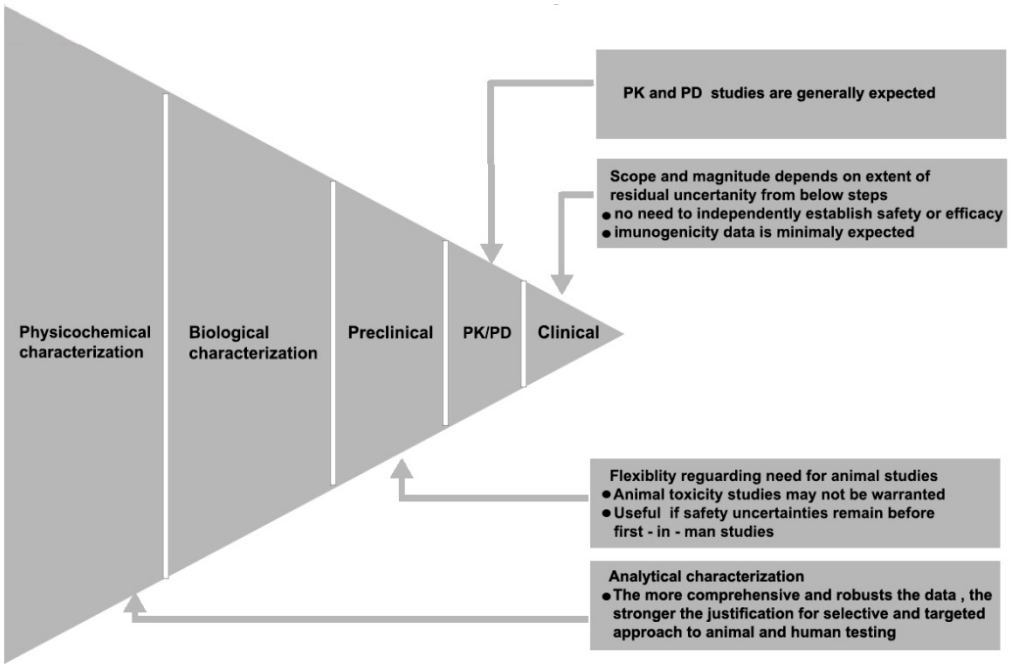

Figure 1: Step wise approach for the manufacturing and establishment of biosimilar product.

develop. By 2020, biologics will constitute approximately 27% of expenditure on global pharmaceutical's, which will lead to enormous financial burden, both on pharmacological industry and patients. (4) Because of high cost of biologics, fewer people may have access to these agents. Patents for these biological medicines are going to expire by 2030 in most of the European countries and USA. This is how the biosimilar demonstrate the cost savings and expansion of the patient access without detrimental impacts on the outcome of patients. They would significantly reduce the costs of biologics and increase their accessibility.

Use of Biosimilars in Nephrology:

Only few Biologics are routinely used in nephrology, this is unlike rheumatology, oncology and gastroenterology but still nephrology has many potential benefits from biosimilar in terms of increasing treatment access while reducing the treatment cost.

Erythropoietin's are most widely used biologics in nephrology. All (rHuEPOs) have same amino acid structure. United States patent on epoetin alpha has expired in 2013 and darbepoetin's patent expired in 2016. There are two epoetin biosimilar which are approved since 2008. (5)They have also undergone extensive clinical trials in USA. *Sandoz* markets the agent in EU under the trade name of Binocrit whereas *Pfizer* markets this agent under the trade name of Retracrit.

Table1

BIOLOGICAL PRODUCTS USED IN NEPHROLOGY				
Agent	**USA Patent Expiration**	**Biosimilar in Development**	**On-label Indication**	**Off-Label Indication**
Epoetin	2013	Pfizer/Hospira; approved by FDA* in 2018	Anemia	
Darbepoetin	2024	Already in use in other parts of the world	Anemia	
Rituximab	2016	Sandoz; filed with FDA* in 2017		Glomerular diseases
Belatacept	2023	None	Kidney Transplant Rejection	
Eculizumab	2021	Amgen and Epirus; expected FDA* filing in 2020	Atypical Hemolytic Uremic Syndrome	Membranoproliferative GN
Basiliximab	Not available	Sorrento/MabTech	Kidney Transplant Rejection	
*FDA:Food and Drug Administration				

Rituximab is a biological product which is indicated in refractory glomerular diseases as well as in the rejection of kidney transplant. United States patent on rituximab expired in 2016 and then *Sandoz* sponsored the biosimilar for rituximab and it was accepted for review by FDA in 2017. (6)

Baciliximab is also used for the prevention of kidney transplant rejection and this biosimilar is under manufacturing in China at the moment. (7) Eculizimab is a biological drug which is indicated for the treatment of atypical hemolytic uremic syndrome (aHUS). Its patent will expire in 2021 and some

pharmaceutical companies are developing its biosimilar and they are anticipating filing for FDA approval in 2020. (8)

Immunogenicity:

As biologics are proteins that can be recognized as "foreign" by body, immunogenicity is always a concern with the use of these agents. This is a particular issue with the use of recombinant erythropoietin's which may lead to the development of antibodies that cross react with native erythropoietin and may result in the development of Pure Red cell aplasia (PRCA). Few cases of PRCA were identified in Europe between 1998 and 2002 after a manufacturing change with reference epoeitin, Eprex. This has led to the suspension of drug in Europe for few years. The problems were solved and they were given license again (9). Two cases of PRCA occurred in Europe when biosimilar epoetin (Binocrit) interacted with tungsten used to synthesize pre- filled syringes (10). These episodes reinforce the fragility of manufacturing, packaging and distribution of a biological agent with regards to immunogenicity, even within strictly regulated markets of EU.

Limitations:

Biosimilar is not a perfect copy of biological drug because of variations in post-translational processes. The major issues regarding biosimilar are long term effects, immunogenicity, efficacy, adverse effects when switching from a biologic to biosimilar. This question is partly addressed by the FDA requiring pharmaceuticals to demonstrate that the production doesn't adversely change the identity, strength, quality or potency of biologic drug. Comparability testing proves the comparability and permits the production without new product development program. Studies have shown that switching is not associated with increased risk of adverse effects and recent clinical trials showed enhanced clinical effectiveness and an appropriate side effect profile. Thus, switching between two proteins that share nearly identical structure should not cause any additional risk. Long term effects still need to be addressed which remains a concern. It is thought that because of structural similarities it is unlikely that there is any substantial difference in long term effects. The other challenging aspect remains the physician preference and patient acceptance for biosimilar products. For the lack of knowledge regarding use of biosimilar in terms of safety and efficacy , the National Kidney Foundation (NKF) conducted a symposium" introduction of biosimilar therapeutics into nephrology practice" in united states in September 2015 (11).

Conclusion:

Biosimilars are a growing drug class and have potential to increase patient acceptance to high level drug therapies while alleviating the financial strain on health care system worldwide. To achieve this, Physicians need to be more comfortable in prescribing biosimilar products instead of their reference biologics. It is also vital that prices of biosimilar should be significantly lower than their reference biologics.

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