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Biosimilars in rheumatology,

Dr. Nidhi Kaeley[1], Dr. Rajesh Kakkar[2]
[1]*Assistant Professor,Internal Medicine,Himalayan Institute Of Medical Sciences*
[2]*Head Of Deparment Of Rheumatology And Internal Medicine,Himalayan Institute Of Medical Sciences*

Abstract: *The use of biologic therapy has revolutionarized treatment of many chronic diseases including several rheumatological disorders. However , biological agents are expensive and unaffordable. The follow-on generic products, also called as biosimilars are about to flood the pharmaceutical market. Biosimilars are not identical to the biological product but are attempted copies of existing biological product. They are different from the generic product in terms of efficacy, safety and immunogenicity. Hence complete awareness about their safety profile and efficacy is essential before prescribing to the patient. In this review , we discuss the usefulness of biosimilars , need for appropriate regulatory guidelines and their current status in rheumatology in India.*

Keywords: *biological agents, efficacy, rheumatological agents*

I. Introduction

The invention of biologics has produced a paradigm shift in the management of many chronic rheumatological disorders .The biologic is defined as therapeutic agent derived from any living material (microbe ,animal or human)which mimic or block the function of naturally occurring proteins, by the US Food and Drug Administration (FDA) centre for biologic evaluation and research.(1) Sucessfully used biologics in various rheumatological disorders are infliximab, rituximab, etarnecept, golimumab, certolizumab and adalimumab. Although , biological agents have been proven to be very effective in various rheumatological diseases where conventional therapies fail .The accessibility of these biologics has always been a matter of debate due to their high cost. Thus, biosimilars -their lesser expensive substitutes have proven to be useful.

Definition Of A Biosimilar

Various agencies like World Health Organization (WHO) ,European Medicine Agency (EMA) and US-Food and Drug Administration (US-FDA) define the term biosimilar as - WHO-A bio-therapeutic product which is similar in terms of quality , safety and efficacy to an already licensed reference bio-therapeutic product.(2) EMA-A biosimilar is a biological medicinal product that contains a version of active substance of an authorized original biological medicinal product (reference medicinal product). A biosimilar demonstrated similarity to the reference product in terms of quality , characteristics , biological activity , safety and efficacy based on a comprehensive comparability exercise.(3) US-FDA-A biological product that is highly similar to a US licensed reference biological product not withstanding minor differences in clinically inactive components and for which there are no clinically meaningful differences between the biological product and the reference product in terms of safety , purity and potency of the product.(4)

Keydifferences Between Biogeneric And Biosimilar

Biosimilars are attempted copies of existing biological medicinal products , although the final product is not identical. The chemical structure of a biogeneric drug is exactly identical to the original reference product. A biosimilar has a very complex three-dimentional structure and thus a complicated mode of action which is never fully reproducible. A chemical drug has one-dimentional structure which is easier to characterize.(5) Small changes in any step of manufacturing process of a biosimilar that is from selection of host cell lines to purification systems ,protein sequencing and post translational modification ,can have an impact on its characteristic structure and function.Thus it is strongly process dependent where as a biogeneric is mainly independent oof production process or site of production. Biosimilars are produced in living systems such as animal or plant cells. Hence any change due to protein folding or post translational modification is liable to alter the final structure. A biogeneric is produced by less complicated chemical synthesis. A biosimilar has 100 -1000 times higher molecular weight as compared to a chemical drug.(6)

Regulatory Pathways Regarding Biosimilars

The first recommendation for biosimilars was established by European Medicine Agency (EMA) issued in 2005 .(7)These guidelines emphasized issued regarding quality, safety and efficacy of the product. The first two biosimilars approved by EMA were omnitrope (biosimilar to gonadotropin)and valtropin (biosimilar to humatrope)in 2006.They were both recombinant growth factor that is somatotropin.(8,9).European Medical

Agency has approved 21 biosimilars by February 2015. Two biosimilars (Filgartim ratiopharm) and valtropin were withdrawn in 2011 and 2012 respectively. Hence there are 19 biosimilars available in the market. European Medicine Agency are widely accepted as gold standard guidelines (9).The World Health Organization (WHO) released guidelines pertaining to safety , efficacy and quality of biosimilars in 2009. India formed its guidelines on similar biologics in 2012 (10) while US-FDA released its first draft of guidelines recently in may,2014. The first biosimilar approved by USFDA was Zarxia (filgastrim –sndz)on march6,2015.

The European Medicine Agency guidelines emphasizes that the biosimilar cannot be simply copied as in the case of a chemical drug. Although it accepts minor differences in the active substance for example in post-translational modification.(7,11). The biosimilar manufacturers should identify a single reference product and conduct tests to establish biophysical similarity. A 'true' biosimilar, as developed along the principles of the EMA guidelines, was recently proposed as a 'copy version of an already authorised biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise'.(12,13,14) European Medicines Agency (EMA) Committee for Medicine Products for Human use (CHMP) gives recommendation for comparability of a biosimilar and its reference product and also regarding naming it as a biosimilar.(15 ,16)The manufacturers should conduct both non clinical and clinical studies to demonstrate such similarity in pharmacodynamics and pharmacokinetics. Non –clinical studies include in vitro and in -vivo pharmacodynamic and toxicological studies. In vitro analysis involves extensive molecular characterization programme to compare the structure and function of a biosimilar. Pre-clinical testing comprises of in- vitro studies(bioassays and receptor binding studies)and animal model studies. In-vivo studies should be performed if in vitro assays are unable to reflect pharmacodynamics. Clinical testing includes phase 1 and phase 111 trials of the drug.

Pharmacovigilance is also an important part of clinical testing . It is done to detect rare side effects of the drug like immune reactions prior to market authorization.(16,17). The phase 11 trial is not required as the objective is not to demonstrate superiority of the product over the reference product. The non –inferiority trials should be conducted. The maximum allowed difference between a biosimilar and its innovator molecule should be 15%(18).Thus head to head characterization studies are required to compare the similar biologic and the reference product. In case the isolation of the drug substance is not possible , comparability can be demonstrated at the drug product level with appropriate scientific justification.(19)

Safety And Immunogenicity

Safety has always been a concern regarding structure ,function and immunogenicity of a biosimilar. Immunogenicity is of utmost concern due to variation in structure and function of a biosimilar and the original reference product. This variability may occur during their manufacturing process as the technology for manufacturing the original biopharmaceutical drug is a closely guarded trade secret.(20)Immunogenicity as the safety issue was highlighted by the increase in number of pure red cell aplasia patients caused by specific formulation of epoietin alfa. Pure red cell aplasia in this case was caused by neutralizing antibodies against endogenous epoietin. It occurred due to a biosimilar called as eprex of epoietin alfa. Polysorbate -80 ,in eprex was believed to be responsible for immunogenicity by triggering the formation of epoietin containing micelles or by interacting with chemicals released by uncoated rubber stoppers of prefilled syringes.(17,18).Recent European Medicine Agency guidelines preclinical trials of some biosimilars may be in sufficient to demonstrate immunogenicity .Hence clinical trials and post marketing surveillance should be done in these cases.(21)

Pharmacovigilance

Robust pharmacovigilance is a must for detection of immunogenicity. The manufacturers should look for rare adverse drug reaction including the type of adverse drug event and drug data which includes proprietary name , international proprietary name (INN) and dosage given.(22).INN is a technical name for mechanical product. Generic adaptation of a chemical drug is given the same name as that of the reference product . Biosimilars should be assigned different INNs for improved pharmacovigilance. Another safety issue with a biosimilar is substitution which is prescribing generic drugs in place of innovator products. This principle should not be applied to the biosimilars as it may confound accurate pharmacivigilance. It may decrease the safety profile of a biosimilar and cause treatment failure.US-FDA allows interchangeability of a biosimilar to that of reference product.(23)

Current Status Of Biosimilars In India

The first comprehensive guidelines for the approval of similar biologics in India , came in effect in june 2012 after the approval of Department of Biotechnology under the Ministry of Science and Technology.(19) . Although before these guidelines , many biosimilars were being used in India under ad-hoc abbreviated pathway.Table1 summarizes the list of various biosimilars used in rheumatology along with their cost . Indian market has witnessed nearly 20% annual growth for the year ending November 2011 in the

segment of biosimilars. Top pharmaceutical companies are involved in this segment like Biocon ,Dr Reddys ,Lupin and Cadila health care. In april 2007,Dr reddy marketed Reditux, abiosimilar of rituximab in India.(24) The other biologics in India are Mabtas (by intas biopharmaceutical) and by zenotech lab. Cipla pharmaceutical company launched its first biosimilar of etarnacept called as Etacept on April 17,2013 .(25,26). India first biosimilar to infliximab called as Infimab , also approved by Drug Controller General of India was produced by Ranbaxy in December 2014.(27,28) .Infimab has been proven to have similar efficacy,safety and immunogenicity to thar of original product that is infliximab as demonstrated by a phase III trial including 183 rheumatoid arthritis patients.(29).Other similar biologic approved in India are Exemptia,commercial name of biosimilar to adalimumab while while HD203, an etanercept biosimilar, was approved in South Korea.(30)
Although the cost savings offered by similar biologics compared to originator biological is their major advantage for not only for the patients ,physician and insurance providers , the issue regarding their safety, efficacy and quality of these products is the matter of concern . This is mainly due to the lack of stringent evaluation guidelines from the Indian drug regulatory system.

This issue has been highlighted by the fact that noticeable differences in potency have been found between several Indian similar biologics compared to their reference biologicals. A study carried out by Boehringer Ingelheim revealed that the India-registered Elaxim (tenecteplase; Emcure) was not a similar biologic to Metalyse (tenecteplase; Boehringer Ingelheim). The study also concluded that differences in the manufacturing process had introduced impurities that affected the potency and efficacy of the similar biologic. Similarly, Roche conducted studies comparing their originator biological Rituxan (rituximab) with Reditux (rituximab; Dr Reddy's) and highlighted numerous differences including a much higher level of remaining host cell proteins in Reditux compared to Rituxan, as well as differences in glycosylation. Thus it has been noted that the similar biologics approved in India have not been processed by strict regulatory process approved by EMA(European Medicines Agency).(31)

Summary

The biosimilars are considered to be equivalent to biologics but are not exactly identical to the original product. Hence, the treating physician should be aware of not only their safety , efficacy and quality but also their differences from original product. This can prevent unwanted side effects of the drug .Biosimilars represent new innovational molecules which have potential to offer benefit to large number of patients at half the cost as compared to the original product. But their safety remains the primary concern. Hence , consistent pharmacovigilance is required for clinicians for their confident use.

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Table I Summary of trade names and approximate price of common biosimilars used in rheumatological diseases available in India

Original Product	**Expiry Date Of Patent**	**Indian Brands Available**	**Cost Of Biosimilar**
Rituximab(Rituxan/Mab Thera)Rs 80,000for 500mg.Ristova Costs Rs 37500 For 500mg.	2013(Eu),2016 (Usa)	Reditux(Dr Reddys) Mabtas(Intas) Rituximab Biosimilar From Zenotech Labs	Rs 39,996 For 500 Mg Rs 64000 For 1 Gram Rs 27500 For 500 Mg
Etarnecept (Embrel) Rs 8700 For 25 Mg	2015(Eu) 2018(Usa)	Etacept(Cipla)	Rs 6150for 25 Mg
Infliximab(Remicade)Rs 41000 For 100mg	2015(Eu) 2028-29(Usa)	Infimab(Bowo15) F Rom Ranbaxy	50% Lower Cost