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Biosimilar Drugs

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Abstract

Biosimilars are reliable drugs that are similar to the authorized biological products for treatment of various diseases. They have been produced due to the shortage of biological drugs as a result of the great demand. This article reviews the literature on uses of biosimilar drugs in many different ways.

Keywords: Biosimilars; Biologics; Inflammatory bowel Syndrome; Infliximab

Introduction

Biological drugs (Biologics) are large, complex molecules developed in the living organisms including many different substances (i.e., sugar, proteins, nucleic acids, cells and tissues) and are purified in multi-step processes [1]. Biologics are used for treatment of variety of diseases and medical conditions like Crohn's disease, rheumatoid arthritis, ulcerative colitis and many other autoimmune diseases. They also have revolutionized cancer treatment and offered hope for many patients who previously had no effective treatment for their condition[2]. Most biologics have the potential to cause allergic hypersensitivity reactions, a remarkable side effect. Other side effect include injection site reaction, chills, weakness, shortness of breath, peripheral edema etc.[3].

The processes of manufacturing biologics are very complex therefore, unlike generic or small-molecules drugs, they're highly sensitive to any minor changes. A simple, unintended change in any component of the quality system or the manufacturing process may lead to a product drift, evolution, and divergence which can impact the quality, safety, efficacy or interchangeability of biologics[4]. However, the patents of biologics and other periods of exclusivity are near to be expired, which lead to a new way of developing and approving new products, called 'biosimilars', that are similar to authorized biologic products [5].

Biosimilar medications can be recognized from various references with a similar significance; the European prescriptions office characterizes biosimilar as like organic drugs that has just been approved, the supposed reference restorative item. The European Medicines Agency (EMA) definition additionally clears up that a biosimilar shows closeness to the [originator] as far as quality attributes, organic movement, wellbeing, and efficacy based on a comprehensive comparability exercise [6].

A biosimilar product is developing similarly to an original biological medicine with minor changes; due to their complex nature and production methods, so biosimilar medications called follow-on biologics, and considered as the cost-effective alternative to biologics [7]. Biosimilar drugs might present a greater availability than a reference product. Shortage ofbiological drugs as a result of a great demand or absence of active substances can be alley by more production of biosimilars[8].

Express scripts has predicted that the cost of biosimilars will be notably decreased by 20 percent to 30 percent than a reference product, making biosimilar drugs cost much less than biological drugs. However, nowadays the expenses of developing biosimilar drugs have surpassed that of developing generic drugs and there will not be a great difference until the release of more biosimilars to the market [3]. Research and Development (R&D) Corporation has predicted that introducing biosimilars in the USA will decrease the expenses on biologics drugs by $44.2 billion from 2014 to 2024 [9].

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Table 1: Differences between generic and biosimilar[13].

Properties	Generic	Biosimilar
Origin	From genetic material of living cell cultures or DNA technologies	Synthesized in a laboratory or extracted from natural sources
Size	Smaller	Larger by 200 to 1000 times
Weight is relative to size	150 Daltons	150000 Daltons
Manufacturing	Simple and well defined	Complex with potential structural variations
Complexity	Easy to fully characterize	Difficult to characterize
Stability	Relatively stable	Sensitive to storage and handling conditions
Adverse immune reaction	Lower potential	Higher potential, because it originates from living organisms so physician must think twice before using them in immunocompromised patients
Approval requirements	Small clinical trials in healthy volunteers	Large clinical trials in patients

Evaluation of biosimilars helps to approve all biosimilar products are safe and effective. Food and Drug Administration (FDA) experts must confirm that there are no clinically significant differences between biosimilar drugs and its reference product in term of safety, purity and potency [10].

The growth of biosimilars allowed the opportunity to modify more biosimilar drugs into the market. By supporting manufactures to do that, the existence of biosimilars in the market elevated the patient and physician's options to have more access to the latest treatments [11].

As more biosimilars are affirmed and recommended, it is progressively imperative for medical workers to understand more about biosimilars[12]. To address this need, the point of this article is to define biosimilar drugs, understand the importance biosimilar products, and distinguish the difference between biosimilar and generic drugs and to represents clinical examples on the uses of the biosimilar drugs.

Comparison between Biosimilar and Generic Drugs

Biosimilars are more complex with possible variations in structure because it comes from living organisms as mentioned above, even though it is from the same species because several factors can be affected such as the quality of soil, use of fertilizers, and other environmental elements, which can cause complexity in the structure of biosimilars. On the other hand, chemicals used in production of generics are measured, simple, and well defined structures. The complexity is easy and full characterized in generic drugs, but its opposite in biosimilars, which are heterogenic because there are no organisms having the same structures. All drugs are tested for stability, to detect if it is exposed to aggregation, degradation, sensitivity to temperature, absorption onto surface, and other factors, which can affect the stability of drugs. The potential of drugs can cause immune reaction and response, so biosimilars have risk to illicit immuneand make reaction rather than generics, because it originates from living organisms so physicians must think twice before using them in immune compromised patients [13-19]. Before using any drugs, it should be approved by FDA. Most biosimilar drugs should undergo clinical trials to determine their effects on patients before being approved and find out the differences between biosimilar and generic drugs [13-19](Table 1).

Innovator Drugs versus Generic Drugs

Innovator “Brand name drugs” is bioequivalent to generic drugs which has the same rate and extent of absorption. Generic and brand name drugs have identical active ingredients and produce the same therapeutic effect [20]. However, the (inactive ingredients) may differ. This is only important in rare cases when a patient has an allergy or sensitivity to one of the excipients [20]. The difference could be also in color, shape, or markings and cost which is the biggest difference between the generic and brand name, generic less expensive than brand named drugs [20].

Health Canada sets different standards for narrow therapeutic range drugs; its bioequivalence requirements are stricter than for other drugs. However, it shows no important clinically differences [20].

Application of Biosimilar Therapies

Biosimilars in inflammatory bowel disease

Tumor necrosis factor-α inhibitors are the main biological agents used to treat Inflammatory Bowel Disease (IBD). Hyams Jet al.[21] evaluated the efficacy and safety of infliximab for inducing and maintaining benefit in children with moderately to severely active Ulcerative Colitis (UC). Infliximab was safe and effective, inducing a response at week 8 in 73.3% of pediatric patients with moderate to severely active UC who did not respond to conventional therapy. The overall remission rate at week 54 for all enrolled patients was 28.6%, assuming the more effective q8w remission rate.IFX appeared to be equally safe and effective in the short-term for patients with active Ulcerative Colitis. Because of their expensive cost in 2013 the first biosimilar monoclonal antibody. Switching of IBD patients from original to biosimilar IFX is effective and safe. Infliximab (IFX), CT-P13 (Remsima®, Inflectra®), was approved in Europe for all indications in which infliximab is approved to be an efficacious method of treatment for patients with Inflammatory Bowel Disease (IBD) with regards to symptom management and mucosal healing [22-24]. In Europe, biosimilar drugs are increasingly regularly prescribed drugs in pediatric IBD. Because of their lower cost, treatment expenses have gone down considerably (up to 30% or more in some countries) and patient access has improved. However, additional well designed studies to investigate long term follow-up of biosimilar drugs in children are still needed [25].

Biosimilars for induction of erythropoiesis

Epoetinalfa (Eprex) is a human erythropoietin produced in cell culture using recombinant DNA technology. It stimulates erythropoiesis and is used to treat anemia, commonly associated with chronic renal failure and cancer chemotherapy.

The first biosimilarepoetinalfa was manufactured by two companies and approved by the EMA. Abseamed®, Binocrit® and

Epoetinalfa HEXAL® are epoetinalfa products and biosimilar versions of the reference product Eprex®. The approval of these biosimilarepoetinalfa products was based on the demonstration of comparability with Eprex® in quality, safety and efficacy by double-blind, randomized, parallel group, multicenter phase III trial involving 479 haemodialysis patients with renal anemia. Biosimilarepoetinalfa was approved for indications in cancer patients and patients planning to undergo surgery (for autologous blood transfusions) *via* data extrapolation - without a full dossier of clinical data for the indication. Two additional biosimilar versions of Eprex®, Retacrit® and Silapo®, although this biosimilarmanufacturer also used Eprex® as a reference product, the International Nonproprietary Name (INN) for these products is epoetin zeta rather than epoetinalfa. The active substance of epoetin zeta was shown to be a representative of the active substance found in Eprex®and the protein structures were comparable. However, differences were noted for the glycosylation profile with respect to glycoforms without an O-glycan chain and variants of sialic acidand a different immunogenicity profile was observed in dogs. The comparability of epoetin zeta to Eprex® was demonstrated in two randomized clinical trials, a correction phase study and a maintenance phase study, involving 922 haemodialysis patients with renal anemia. The correction phase study demonstrated comparability between epoetin zeta and Eprex® for mean hemoglobin levels over the evaluation period. However, comparability was not demonstrated for mean dosage during the evaluation period. Similar results were reported in the maintenance phase study, suggesting a possible difference in the bioactivity of epoetin zeta and Eprex®. Data were also presented from a study involving 261 cancer patients receiving chemotherapy. Biosimilarepoetinalfa, epoetin zeta was approved for indications in renal anemia, chemotherapy-induced anemia, and for pre-donation of blood prior to surgery for autologous transfusion [26].

Biosimilars in rheumatology

CT-P13 is a biosimilar of the drug of infliximab (which is a human-murine monoclonal antibody against the pro-inflammatory cytokine tumor necrosis factor-α). CT-P13 was approved by EMA for the treatment of rheumatoid arthritis, ankylosing spondylitis, crohn's disease, ulcerative colitis, psoriatic arthritis and psoriasis. The CT-P13 infliximab formulation is the same as infliximab and it has similar physiochemical characteristics. The approval of CT-P13 was based on the results of an exercise done in two well-designed clinical trials and showed that CT-P13 was equivalent to infliximab in terms of pharmacokinetic characters in patients with ankylosing spondylitis, and in terms of efficacy in patients with rheumatoid arthritis. In both studies, CT-P13 was well tolerated with a similar tolerability profile to that of reference infliximab. Immunogenicity evaluations demonstrated that the proportion of patients that are developing anti-drug antibodies was similar with each agent. Preliminary data from trial extensions showed that in patients who changed from reference infliximab to CT-P13, efficacy was preserved and similar to those who were treated with CT-P13 and it has the benefit to reduce treatment costs subsequently, significant money saving compared to infliximab [27].

Compared to CT-P13 and infliximab in patients with active ankylosing spondylitis and rheumatoid arthritis respectively equivalence in efficacy and safety was demonstrated in the phase 3 PLANETRA trial. Two phase 1 trials comparing etanerceptbiosimilar candidatesTuNEX and HD203 in healthy volunteers showed a high degree of similarity.

The last included trial referred to GP2013, a rituximab biosimilar candidate, which demonstrated PK and PD bioequivalence to reference product in three different dosing regimens in cynomolgus monkeys.

So Infliximab, etanercept and rituximab biosimilar candidates have demonstrated PK bioequivalence in the trials [28].

Biosimilar pegfilgrastim

Pegfilgrastim is a long-acting pegylated form of filgrastim, which requires only once-per-cycle administration for the management of cancer chemotherapy-induced neutropenia [29]. Recombinant human Granulocyte-Colony Stimulating Factor (G-CSF) e.g. filgrastim is used primarily to reduce incidence and duration of severe neutropenia and its associated complications in cancer patients that have received a chemotherapy regimen, by stimulating the bone marrow to produce granulocyte and stem cells into bloodstream [30].

Neulasta is the originator product which is currently the only pegfilgrastim product available on the US market, the first step towards establishing biosimilarity of this pegfilgrastim molecule to Neulasta, namely demonstration of analytical similarity, appears to have been met [31]. Pegfilgrastim is administrated subcutaneously and its elimination is mostly mediated by neutrophil and the mechanism of that involves binding of the growth factor to the G-CSF receptor on the cell resulting in degradation of the growth factor-receptor complexes inside the cell [32]. During chemotherapy-induced neutropenia, the clearance of pegfilgrastim is significantly reduced and the concentration of pegfilgrastim is sustained until onset of neutrophil recovery [32]. Because of the highly efficient regulation of pegfilgrastim clearance *via* neutrophils and neutrophil precursors, a single fixed dose of pegfilgrastim can be given once per chemotherapy cycle in conjunction with a variety of myelosuppressive chemotherapy regimens [32].

Conclusion

Biosimilar drugs have no clinically significant difference between them and its reference product. Biosimilar drugs are expected to be an essential component in reducing health care costs and enhancing patient access to important, often life-saving medication. Biosimilars are highly similar, comparable, version of an approved biologic medicine; the challenge with biosimilarsis to know the differences which matter clinically, so before they can be used by patient the specific product given should be clearly identified.

Recommendation

According to the huge expectations and benefits of biosimilar drugs, scientists are advised to do more researches and experiments, in order to assure the expectations, and lowering the health care costs. The biosimilar drugs are known to be highly similar to their reference products, we demand to approve that there are no differences between them, and highlight the instructions should be followed while using them and determined the contraindications if present, as it might have valuable impact on the patient life. Therefore, further researches and clinical trials are advised to be done with clear description of the above demand.

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