Biomedical Research and Reviews

Biosimilar Drugs for Therapy of Immune-Mediated Diseases

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Abstract

In recent years, biological therapy has been widely used for the treatment of immune-mediated diseases in rheumatology, hematology, gastroenterology, etc. The indisputable breakthrough in the therapy of certain diseases with immune pathogenesis by biological drugs, as well as their high cost, grounded the prerequisites for the emergence of medicaments similar to the biological drugs, or the so-called biosimilar drugs (biosimilars). The purpose of this review is to compare the biosimilar drugs with their reference biological drugs equivalents, with particular attention being paid to aspects their immunogenicity, safety, and efficacy.

Keywords

Biological therapy; Biologics; Biosimilar drugs; Biosimilars; Immunogenicity; Safety profile; Efficacy

Review

Over the past 30 years, biological therapy has entered into clinical practice. A biological drug is usually a large molecule that is produced by a living cell and which is used to prevent, diagnose or cure a disease, most commonly a tumorous or inflammatory condition [1]. "Biotechnology logical" versions of hormones and enzymes began to be produced in the 1980s, followed by "biological" cytokines, monoclonal antibodies, fusion proteins, etc. Also called "blockbusters", "original" or "referent", the biological drugs already have occupied about 20% of the pharmaceutical industry, comprises of less than 5% of the prescriptions but almost 40% of the cost. The main characteristic of biological medicines is that their production involves a complex series of steps that are subject to strict legal regulations [2].

In the next few years, some of the most commonly used biological products are expected to lose their patents, including Rituxan (Rituximab), Enbrel (Etanercept) and Remicade (Infliximab). This, as well as the enormous success of biological therapy, is a prerequisite impetus for the creation of the so-called biosimilar medications [3].

Biosimilar drugs are also known as "copies", "highly similar" or "interchangeable" medicines. In 2006, the first biosimilar medication was approved in the EU, and in 2009 the definition of a biosimilar drug was given in the US: "very similar to the original drug and without clinically significant differences in terms of safety, purity, toxicity, efficacy of the product and possible side effects, as evidenced by analytical, experimental animal and clinical trials" [4]. The first US biosimilar was approved in 2015.

Biosimilar drugs are large and complex molecules designed to resemble precisely the existing equivalent biological products. Manufacturers of biosimilar drugs must carry out structure analyzses using state-of-the-art technologies to demonstrate that the proposed biosimilar product will have the same primary amino acid sequence as the reference product [4, 5]. Animal toxicity, as well as pharmacokinetics, pharmacodynamics, and immunogenicity, must also be determined in a suitable group of humans. Finally, Production of biosimilar products must undergo serious controls with respect to the stability and quality of the drug, as well as to given impurities [5].

In addition to their structure, biological and biosimilar medicines must also be consistent in functions which are established by use of appropriate in silico or in vitro bioassays. This can be assessed by comparative clinical studies between the biological and the relevant biosimilar drug. To have the interchangeability biosimilarity between biological and biosimilar drugs, there should be accumulated data indicating that both are likely to lead to similar clinical outcomes. It is assumed that biosimilar drugs use the same mechanisms of action; route of. One of the serious differences between biological and conventional drugs is due to the huge complexity of the molecules of biological administration, even doses as of their corresponding biological ones. On the other hand, biosimilar interchangeable drugs should be able to be alternated with the reference medication without creating new risks in terms of side effects or reduced efficacy [6].

One of the serious differences between biological and conventional drugs is due to the huge complexity of the molecules of biological drugs. This is why the biosimilar molecules mimic the effects of biological preparations, but they are never completely identical to them

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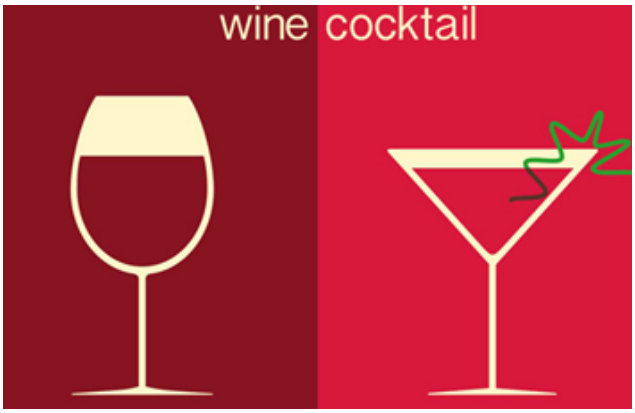

Figure 1: Differences in the reproduction of biological and conventional drugs seen as a reproduction of wine and cocktails

[7]. On the contrary, due to its complex structure and production processes, biosimilar drugs can have unique characteristics.

To imagine clearly the differences between conventional and biological drugs, we can talk a little about drinks. To copy the cocktail from the local bar, you just have to mix the ingredients listed in the barman's recipe in the specified proportions - and ready, the same drink you have tasted. Thus, conventional drugs are produced completely the same. But when we talk about biological therapy, it can be compared to the incredible wine you were admired a few years ago on your vacation. If you want to copy this wine, you should consider not only the grape variety, the area in which it is grown but also the unique process of fermentation, aging, etc. (Figure 1).

Wine production is much more complicated than mixing the ingredients for a cocktail. Reproducing the biological therapy is likewise complicated. Their molecules are too large and complex, thus it is difficult for these molecules to be reproduced and the copies are called "similar." Moreover, single-branded biological drugs may vary slightly between themselves in different batches of the manufacturing process [8].

In order for physicians to be confident that the biosimilar substance used is essentially the referent product, the comparative efficacy trials are conducted as placebo-controlled trials for each new drug. In addition to follow-up until the 3rd and 6th month and 1st year in clinical studies, it is important to monitor the efficacy and safety of the drug over the long term by use of standard pharmacovigilance. Currently, most studies reported no significant differences in the incidence of adverse events in both biological and biosimilar drug (including reactivation of latent tuberculosis) [3].

The potential possibility of a biosimilar drug to elicit an immune response, or so-called immunogenicity is a serious problem but hypothetical concern. Most often immunogenicity presents in the formation of antibodies to the respective drug. Most anti-drug immunogenicity has not clinical relevance, but is possible that the anti-drugs immunogenicity responses may make the biological drug, making it ineffective. The currently available modern technologies allow evaluation of the molecule changes after its production, known to cause immunogenicity [9]. For example, a biological drug can be analogous to a biosimilar one, but the latter can possess further attached carbohydrate to their structure. Thus, the patient's immune system can recognize both structures differently and form antibodies to only one of them. Unfortunately, most of the immunogenicity factors remain unknown. For this reason, only clinical trials will be able to recognize the potential immunogenicity of biosimilar product and to establish the best method of administration, dosage, appropriate for the certain patient (i.e., genetic predisposition, etc.) [9].

For example, the high similarity of a reference biologic to its reference biologic also extends to immunogenicity, if the patient has antibodies to reference biologic version is Infliximab and is attempting treatment with a biosimilar infliximab drug, it is likely that antibodies will form and its efficacy will be reduced [6].

The biosimilar drugs are prescribed for the same diseases as biological ones their reference biologics and it can be assumed that both drugs will act on the same mechanism for the certain diseases to the degree that the mechanism of action is known. If it comes to a time when the insurance company or insurance institution will choose which drug to use for therapy, it is usually the cheapest medicine in the so-called "non-medical change of treatment". However, this risks because of the fact that it is not yet known how the patient will respond to the change with the new drug [9].

Economic analysis shows that one of the major differences between biological and biosimilar drugs is their price - the latter are usually 30% lower. Economists predict that in the next 10 years, over $ 1 trillion will be saved in treating by use of biosimilar products for the same diseases treated so far with biological therapy. Most researchers believe that this will be more beneficial to society as a whole because more patients will be able to receive treatment but less beneficial for the individual patient unless the efficacy and safety profiles are the same for both types of treatment [10].

Moreover, many resources are currently being used to develop biosimilar drugs that, with their innovative structure, do not simply duplicate and even exceed the benefits of the reference medicine, so they are called 'bio-betters' or 'bio-superiors' [7].

Most manufacturers of biological therapy, as well as 90% of practitioners in dermatology, endocrinology, oncology, nephrology, neurology, and rheumatology, would like the labeling to be different; biosimilar preparations should be explicitly marked as such because otherwise, this may cause confusion that the application will be the same as for the biological agent. Indeed, 61% of European doctors believe that identical preparations have identical indications. In fact, all of this has to be proven in further studies. 82% of the clinicians would like the package leaflet to include analytical and clinical data on efficacy and safety compared to the referent product [9]. The poll also shows that 34% of doctors who regularly prescribe generics would prescribe their respective biosimilars. Around a quarter of doctors, however, are still unable to give a definition of biosimilar medicines or have not heard of them. Very useful in this case will be "Purple book", which will list all approved biosimilars with information and their reference products. This book will be like the "cousin" of the Orange book, which describes generic biological drugs [11,12].

Conclusion

The decision about what medication to prescribe for the particular patient should be taken by the treating medical practitioner, his or her knowledge, and the patient's individual characteristics

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