

Biosimilar Drugs and Pharmacovigilance

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Introduction

In the last 25-30 years, biotherapeutics became main part of the modern medicine and their occurrence in general treatment strategies is increasing day by day. Biotherapeutics are briefly defined by World Health Organization (WHO) as "A biological medicinal product with the indication of treating human diseases". Biotherapeutics are the drugs that are derived from living organisms with complex processes.

Biotherapeutics have greater molecular weight and more complex structure compared to the small molecule drugs synthesized chemically. As their production is based on living organisms, characteristics and quality of the drug is highly affected from manufacturing processes, therefore their regulations are established quite different from conventional drug molecules [1]. Biotechnological drugs are being first-to-market by early 1980s. These biotechnological drugs took place in the market mainly in therapeutic areas of oncology, inflammatory diseases and haematology, and main advantage of these drugs are that they are able to target specific cell types with offering improvement in quality of patients life by revealing less adverse effects.

Successful results obtained in the treatment of life threatening chronic diseases with biotherapeutic drugs. Despite their high cost, there is an increasing demand for using biotherapeutics due to providing successful treatment opportunity. According to statistics it is well known that there is an increasing sales growth in of biotechnological drugs worldwide and dramatically increasing growth is predicted for 2020 as well [2]. Today; patents of many first-generation biotherapeutics have been expired or about to expire and biosimilar products come into question. Biosimilar products are "similar" to the authorised biological product, however they are not identical. European Medicines Agency (EMA) defined biosimilar medicines as "A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use".

It is predicted to reduce healthcare expenditures dramatically by bringing biosimilars to the market. Over the next 10 years, USA estimated up to \$25 billion saving from health costs by using biosimilars [3]. Therefore, there is a huge interest on biosimilar drugs from both regulatory authorities and pharma industry due to their lower cost and predicted market share. EMA provided guidance on approval of biosimilars since 2005 and in 2006 EMA approved Omnitrope (somatotropin) as the first biosimilar drug in EU, however it has been withdrawn in 2012 due to commercial issues. Until today, EMA has approved many biosimilars in the therapeutic areas of haematology, oncology, diabetes, kidney failure, arthritis, Crohn Disease, psoriasis and so on. U.S. Food and Drug Administration also prioritized accelerated approval pathways for biosimilar drugs on 2012 and by 06 March 2015, Zarxio (filgrastim) has been approved as the first biosimilar product in the United States.

Safety Concerns of Biosimilar Drugs

Biotechnological drugs have issues of concern as stability, purity, immunogenicity, bioactivity, drug targeting and delivery

system. Safety, efficacy and quality concepts are very important for biotechnological/biosimilar drug development as well as it is in conventional therapeutics. Safety and efficacy of a biosimilar drug is affected from multistep manufacturing process as well as the host cell.

During the development of a biosimilar drug, main target is to produce a product without any clinically meaningful difference compared with the reference authorised biological drug and it should be intended to be used for the same disease with same doses and treatment regimens. Characterization, non-clinical and clinical studies are required for demonstrating biosimilarity. Due to complex production processes and nature of the living organisms there is a high possibility to not to produce same product in terms of pharmacological specifications, efficacy and safety. By conducting pharmacokinetic, pharmacodynamic, efficacy and safety studies, biosimilar drugs need to be compared with the reference biological drug at recommended doses [4]. Quality approach of a biosimilar drug is vital as it may affect the efficacy and safety of the product. For example protein degradation or impurities occurred during the production may contribute to efficacy and safety of the product. Antibody characterization could be a solution to assess immune responses. Therefore, applying generic approach is not appropriate for biosimilars. These further studies will have a positive impact on developmental costs of new biopharmaceuticals [5]. Extrapolation of indications should be also considered in terms of safety and efficacy. Further specific clinical trial needs should be assessed on the biosimilar basis [6].

Interchangeability and Substitution

In all over the world, substitution and interchangeability decisions are mainly handled at the government level and there are discrepancies between the approaches of different countries. As we have limited data from clinical trials, using a biosimilar interchangeably with its reference medicine is another question for healthcare providers and regulators that need to be answered. EMA evaluations do not include biosimilar interchangeability recommendations. This will be a decision of healthcare providers and regulations on country level [7]. Immunological impact should be taken into account as well while deciding.

Pharmacovigilance Activities for Biosimilar Products

Providing accurate data on safety is relatively limited and difficult due to low incidences at the pre-authorization period. During the post-

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authorization period, it is essential to have a good pharmacovigilance system to assess efficacy and safety of biosimilar drugs.

Effective risk management plans are required for all drugs during post-marketing surveillance, for biosimilar drugs these plans should be revised including special needs derived from the nature of biosimilar product such as extrapolation of indications, potential of immunogenicity. In pharmacovigilance activities of biosimilar drugs; brand names and complete batch information should always be recorded for determining risk of an unexpected variation in the manufacturing which may result in serious consequences. As we have limited ability to predict clinical consequences and there are information gaps, implemented risk management plans will help close monitoring of a drug [8].

Conclusion

Biosimilars have a big potential to reduce our healthcare expenditures and improve patient outcomes especially for chronic diseases. However, in case we don't have good Pharmacovigilance systems and precautions we may face further costs caused by unexpected adverse events. Pre-authorization studies are crucial for safety assessment of a candidate product; however, it is not possible to predict all unintended effects with clinical trials due to the limitations such as narrow population, polymorphic differences, and short duration. Therefore, postmarketing follow up activities are critical

for understanding safety profile of a drug in order to provide rational drug treatments. And also, the authors would like to point out the need of conducting pharmacoeconomic studies in order to clarify the cost effectiveness of biosimilar drugs compared to reference authorised biological drugs. Good pharmacovigilance systems will be a key solution for obtaining reliable data as well as effective and safe use of drugs.

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