REGULATORY CONSIDERATIONS OF BIOSIMILARS AND CLINICAL DILEMA OF THEIR USE

Sonja Genadieva Stavrik[1] Aleksandra Grozdanova[2], Katerina Ancevska Netkovska[2], Magdalena Genadieva Dimitrova[3] , Gligor Dimitrov [4]
[1] University ,,Ss. Ciryl and Methodius,,-Medical Faculty-Skopje, University Hematology Clinic, Macedonia
[2]University ,,Ss. Ciryl and Methodius,,-Faculty of Pharmacy-Skopje, Macedonia
[3]University ,,Ss. Ciryl and Methodius,,-Medical Faculty-Skopje, University Gastroenetrology Clinic, Macedonia
[4]University,,Goce Delcev,,-Medical Faculty-Stip, Macedonia

Majka Tereza, 1000 Skopje, Macedonia

Corresponding authors:
* Sonja Genadieva Stavrik
Tel +389 70 222 031
e-mail adresss: sgenstav@yahoo.com

Potential referees:

Prof dr Alekskandar Stojanovik
University Hematology Department
Vodnjanska 17
1000 Skopje, Macedonia
e-mail: profstojanovic@yahoo.com

Alina Damelia Tanase MD PhD
Head of BMT Unit
Medical Director
Fundrni Clinical Institute
Bucharest, Romania
258 Fundeni str, sector 2
e-mail: alina.tanase@icfundeni.ro
tel: 0040 745 612 055

Charalampia Kyriakou MD PhD
Royal Free Hospital
London, UK

e-mail: rmgvchr@ucl.ac.uk
c.kyriakou@nhs.net
tel: 0044(0) 7900682941
0044(0)7584160255

Abstract

Biomedical products are complex molecules, produced by living cells, molecules that are naturally produced in the human body, like hormones or growth factors, monoclonal antibodies, blood products, immunological medicinal products, sera and vaccines, allergens, and advanced technology products such as gene and cell therapy products. Copies of these drugs, known as biosimilars are comparable but not identical and are not generic version of innovator biological products. Specific regulatory requirements and abbreviated registration process apply in the case of biosimilars, in order to demonstrate efficacy and safety profile and prove that product is similar to the original biomedical product.

Like all medicines, biological medicines work by interacting with the body to produce a therapeutic outcome, but the mechanisms by which they do this may vary from product to product and across indications. Therefore the role of the physicians in treatment of patients with these complex medicinal products is particularly important.

Regulatory issues, manufacturing, safety, physicians have part in develop use of biosimilars as much as generic drugs. Even though, the most important factor for market of biosimilar are commercial factor, still, real clinical dilemma of use are present, so it is necessary to have clear regulatory framework and postmarketing data on the use of biosimilars.

Keywords: biosimilars, innovate product, monoclonal antibodies, regulatory

Introduction

Biomedical products are drugs whose active substance is made by living systems (plant or animal cells, bacteria, viruses and yeast) and biological medicines are used to treat diseases and

genetic disorders in humans. Biological drugs are well established in the treatment of many conditions with increasing use in future years. Many, but not all biological medicines, are made using genetically-modified cells. The global biologic industry has come a long way since its first drug Humulin earnbes US Food and Drug Administartion (FDA) approval in 1982. (Gienentech Inc. Corporate Chronology. 1982) Biological sales now account for about US$92 billion and are expected to worth more than US$176 billion by 2015. (Global Biopharmaceutical Market Report (2010-2015) IMARC) Biosimilars are biological products that are similar, but not identical, to an innovator product that is already on market and its patent has expired. (McKinnon RA. 2009).

Biosimilars is a drug that is designed to be similar to the existing biological reference drug. Due to the complex of biological products and manufacturing process, there will always be small differences in molecular structure, more than reference one. Each manufacturer has its own unique cell lines and develops its own proprietary (unique) manufacturing processes. It is noted that some biological medicines are produced by non-Biotechnology methods and are therefore not necessarily authorized through the centralized procedure. The production of biological medicines involves processes such as fermentation and purification. The manufacturing processes for biological medicines are very sensitive and it is vital that these are precisely controlled in order to obtain consistent results and to guarantee the safety and efficacy of the final product.

When all intellectual property protection and marketing exclusivity for the references drugs have expired, copying can be offered by other biotech company. The patent expire of many biological drugs will open the door for numbers of biosimilars to enter the market. Marketing approval legal regulation is much more complex issue than generic equivalents of reference drugs.

In order to innovator product to enter the clinical use, clinicans should be aware of use biosimilars of some of the issues that have emerged during the development and approval of these products.(Ledford H.2010) The aim of this article is to intoduce and describe specific issue related to the regulatory considerations of biosimilars and clinical dilema by using of health care workers.

Clinical dilemma of use

From clinical point of view it is always interesting to share you experience with other clinicians and pharmaceuticals because there is no universal rule still.

Monoclonal antibody was one of the biggest advancement in the treatment of hematologic malignant diseases. In November, 1999 in Journal of Clinical Oncology Ronald Levy published Karnofsky lecture: Immunotherapy of Lymphoma. He claimed "Monoclonal antibodies are the first example of the payoff for cancer treatment that comes from our knowledge of the immune system. Monoclonal antibodies were the product of a fundamental discovery and they are now changing the a paradigm of how disease are diagnosed and treated." (Levy, 1999)

The goal of CD 20 targeted therapy is to kill B lymphocytes by the use of monoclonal antibodies (MoAbs) against the B cell specific human CD 20 molecule. As a clinicians we are aware that rituximab is a human-to-mouse chimeric monoclonal antiCD20 antibody. Rituximab act through three different mechanisms: complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), induction of apoptosis and complexity of interaction between these mechanisms. Today, rituximab is a mainstay in the therapy of a broad variety of b cell malignanacies, but we still do not understand the mechanism of action responsible for rituximab anti-tumor effects. (Van Meerte T et al, 2010)

In 1997 the first MoAb called rituximab was approved by US Food and Drug Administration, specifically for the treatment of patients with relapsed/refractory CD20 positive low-grade/follicular lymphoma. (Sousou T et al, 2010). Today, nearly over a two decades later, rituximab has become a benchmark of a target therapy and one of the biggest treatment success in B cell lymphoid malignances. So, today the standard of care for a vast majority of B cell lymphoid malignant hematologic disease include rituximab as single agent or in combination with chemotherapy. Rituximab has greatly enhanced the outcome of patients with B cell hematologic malignancies and has become a part of a therapy for newly diagnosed

patients with B cell Non-Hodgkin lymphoma at diagnosis as well as for relapsed patients. The improvement in response rate, progression free survival and overall survival in patients treated with immunochemotherapy makes rituximab the standard of care for patients with indolent B cell lymphoma as well as for the B cell high grade lymphoma. Rituximab has greatly changed the manner in which B cell NHL are treated. (Zwick C et al, 2010). After long term follow up data had been available to be analyzed and introduction of rituximab combined with chemotherapy translated into improved survival in patients with B cell indolent and aggressive lymphoma. A combination of rituximab and an antracyline-based chemotherapy has been accepted as the standard of treatment for patients with any stage diffusse large B cell lymphoma. Patients with follicular B cell lymphoma, as most frequent low-grade lymphoma, after induction therapy, should be treated with maintenance program after immunochemotherapy for two years with rituximab as a single agent.

So, there is no dough, that a huge cohort of patients have been successfully treated with rituximab. Rituximab has been recognized as well-tolerated, relatively safe and very important often less invasive alternative in comparison with traditional mostly chemotherapy based therapies for those conditions. We must emphasized that those conclusions are based on a results from the multicenter randomized studies and the measuring of the efficacy of rituximab has been estimated through response rate, progression free survival and overall survival. (Hert JM et al, 2005).

From clinical point of view, doctors can asses response rate of the treatment very early but there is a high risk of relapse, so response rate is not firm surrogate for estimating the therapeutically results. Progression free survival may not correlate to overall survival. So, overall survival is hardiest to be achieved but is safest for estimation the effect of treatment for the patients. Sometimes we need follow up of the lymphoma patients treated with rituximab for a long period of time, even a decade to clearly estimate the benefit of treatment. Every clinician will agree that only survival data will safely demonstrate equivalence. (Hirsh BR et al, 2014).

Rituximab biosimilars are at an advanced stage of development and pharmakokinetic data seem

identical. Having in mind that every monoclonal antibody is unique means that only small structural changes can have significant consequences in terms of efficacy, safety and immunogenicity. Moreover, much of the development and clinical experience that is gained from the generation and optimization of antibody clearly emphasized that assays might not be able to discriminate differences and safety may differ with impurity profile, so efficacy might not be transferable. (Jahn EM et al, 2009).

Many questions have been waiting to be answered. Do we have firm evidence or we still need robust clinical trials to ensure comfort among hematologist who treat malignant hematologic diseases. Based on the definition that biosimilars are agents that are similar but not identical to the reference biopharmaceutical monoclonal antibody-biosimilar have been introduced and described as products with well established manufacture and structural characterization, with available potency assays, well established function, well known safety profile and well established efficacy profile. (Simoens S, 2011).

From practice points of view legislative battles are still going on, so clinicians need to be active participants in such a debate. At the present moment there are no dilemmas that clinicians have huge clinical experience but in some points still a limited understanding of the biosimilars, having in mind it is quite distinct from traditional generics. Clinical potential of monoclonal antibodies have to be increased by improving existing properties as a key strength of antibodies as therapeutic and it is still unmet need. A clinical imperative is to achieve a better outcome for patients is target malignant cell with more potent and effective monoclonal antibody.

Regulatory considerations of biosimilars

A generic drug is a less expensive copy of an innovator drug product. Generic can be produced when the patent on a drug has expired, for drugs which have never held patent, in countries where patent is not in force, so generic company can certify that the branded company patent is invalid or unenforceable. Generic drug applications are generally not required to include preclinical and clinical data to prove safety and effectiveness. The generic manufacture demonstrate only

pharmaceutical equivalence and bioequivalence between generic and innovator products.

This approach cannot be applied to biosimilars, however, because the active substance of a biological products is a collection of large protein isoforms and not a single molecular entity, as is generally true for conventional small- molecule drugs. Thus the active substances in two products are highly unlikely to be identical and, therefore, unlike generics, biosimilars are only similar and not identical to the innovator products. These differences imply that biosimilars should not be approved and regulated in the same way as conventional generic drugs.

The regulatory process for approval of biosimilars is more complex than for the generic innovator product because the design of a scientifically valid study to demonstrate the similarity of a highly process-dependent product is not easy. Further, the analytical tests currently available are not sophisticated enough to detect the slight but important structural differences between innovator and biosimilar products. Modest differences may have clinical implications and pose a significant risk to patient safety. Therefore, it is considered necessary that biosimilars must be assessed for clinical efficacy and safety by valid preclinical and clinical studies before marketing approval[1234](Crommelin DJ et al 2005; Roger SD, 2006; Roger SD, 2007; Schellekens H, 2005)

1. The European Union (EU) has established a regulatory framework for the marketing authorization of biosimilars, based on comparative quality and clinical pharmacokinetic studies, nonclinical studies, clinical pharmacodynamic studies, and limited toxicology studies, as well as comparative clinical efficacy and tolerability studies. In the USA, a regulatory framework was established in 2010 (Mellstedt H, 2010). The market accessibility of biosimilars may reduce costs to patients and social security systems. In general, the literature expects biosimilar medicines to be around 15% to 30% cheaper (For instance, a European analysis observed that in 2009, the percentage price difference between reference biopharmaceuticals and biosimilar medicines amounted to 14% for

somatropin, 17% for erythropoietin, and 35% for filgrastim.The market accessibility of biosimilars is also motivated by key government objectives related to, for instance, building manufacturing capabilities within a country) than reference biopharmaceutical medicines (Long M et al, 2009). In this respect, some European countries have implemented industrial policies to encourage the development of biological products (Danzon PM et al, 2006).

Conclusion

The first generation of biomedical products manufactured using recombinant technologies was in the 1980s, and they are now on the way to patent expiration. As a result research based and generic pharmaceutical companies are making effort to develop substitutes for original biologics, referred as biosimilars. Never the less, introducing a biosimilar to an innovator product is far more complex than introducing a generic equivalent to innovator product based on a new chemical entity. Biomedical products are produced by cells in culture which are more variable than chemical synthesis methods. However, for generic pharmaceuticals, it is impossible to generate the same or identical copy of an innovator product. The field of biosimilars presents more challenges such as: verification of similarity, compatibility of biosimilars and innovator, unique naming to various products, regulatory framework, marketing, intellectual property rights, and safety.

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