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Biosimilars: Hope and concern

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Abstract

As patents of the first introduced biologic therapeutics in oncology have begun to expire, competing pharmaceutical companies are allowed to produce and market the same protein as the original agent. These products are called biosimilars. Upon patent expiration, biosimilars would hopefully be a cheaper alternative to the original agent and that is the main reason for their existence. Although the financial aspect is similar to generics, the complex nature of these products generates the need for a distinct regulatory environment. Biosimilars are produced by DNA technology in bacteria, plant cells, or animal cells, while generics are produced by chemical synthesis. Details in the process of synthesis, selection of the microorganism, protein extraction, purification and manufacturing, affect the precise nature of the end product. Monoclonal antibodies are large proteins with four polypeptide chains and interact variably with each other and with the environment. It is important for payors to realize that biosimilars are different from generics; therefore, they need to develop different set of rules for approving, registering, and dispensing biosimilars. Regulators ought to respect the physicians' request for non-interchangeability and facilitate in any possible way of traceability. Such regulations along with a rigorous pharmacovigilance program will satisfy the concerns for true equivalence in activity and long-term safety. This is the only way to accumulate over time reliable safety information for new biosimilars. In conclusion, the wish born by the medical community and the society for a more affordable health system triggers the emergence of biosimilars, which could meet that goal if properly regulated.

Keywords

Biosimilars in oncology, biosimilars, cost savings, biosimilar legislation, regulation, interchangeability

Introduction

Modern therapeutics involves a complex drug discovery and approval process. Historically, pharmacotherapy started as crude natural product administration. In the past century, advances in analytical chemistry enabled the isolation of active ingredients, which eventually could be synthesized in vitro, enabling large-scale production. Subsequently, molecules not existing in nature were developed in vitro, with properties more favorable compared to their natural analogues. This evolution led to a true explosion in therapeutics during the last decades of the 20th century. Despite this progress, synthesis of polypeptides remained virtually impossible so that medicine had to resort to the procurement of such products from animals. For instance, pork insulin or bovine pituitary hormone helped many patients at the expense of extraction complexity, possible viral contamination, and immunogenicity. The demand for a methodology to produce human peptide sequences at an industrial level was answered by the development of genetic recombination techniques, enabling the insertion of heterologous DNA sequences in alien genome. Thus, one could finally produce large quantities of human insulin in non human cells and have it secreted and purified, so that a diabetic patient finally receives the exact lacking human insulin molecule. Such products are collectively termed biologic drugs as they are produced in living organisms. They are polypeptides, often of high molecular weight and complex tertiary and quaternary structure, usually

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undergoing considerable post-transcriptional modifications. Their molecular weight ranges from 4000 Da for non-glycosylated proteins such as hormones, to over 140,000 for monoclonal antibodies.[1] Vaccines, hormones, growth factors, and monoclonal antibodies have been produced and have successfully entered clinical practice. In oncology, commonly used biologics include recombinant hematopoietic growth factors and monoclonal antibodies.[2] Particularly the latter have met with considerable success, resulting in survival benefit. Agents such as trastuzumab and rituximab represent major therapeutic advances that have increased curability of breast cancer and lymphoma.[3] On the other hand, the developmental cost for therapeutic biologics used in oncology is tremendous. This cost is eventually transferred to payors and consequently strains the ever-decreasing financial resources of health care. Biosimilars are intended to alleviate this financial burden. As they are gradually entering the clinic, it is very important for oncologists to comprehend their role without misconceptions.

What is a biosimilar?

The patent protection of a drug including biologics usually expires approximately 20 years after its development.[4] After the expiration of the patent protection, any pharmaceutical company is allowed to produce and market the same therapeutic substance.[5] For small molecule agents, duplicating the production of a drug represents no significant problem as the active ingredient can easily and reliably be synthesized. This has led to wide acceptance of generic drugs that are priced lower, resulting in cost savings. In an analogous fashion, as the patents of the first introduced biologic therapeutics in oncology have begun to expire, competing pharmaceutical companies are allowed to produce and market the same protein as the original agent. These products are called biosimilars. As they are complex macromolecules, they are in fact not identical but variants of the original product, which is the source of concern and perhaps reluctancy from the part of the clinicians.[6] For that reason, they are regulated more stringently as discussed below.[7]

The results of a survey that analyzed the prescribing habits of 470 clinicians in five European countries as far as it concerns the use of biosimilars were as follows: 54% of the clinicians were quite familiarized with the use of biosimilars but only 22% of clinicians had a clear understanding about biosimilars, while 24% was not in position to analyze their views concerning biosimilars, due to lack of knowledge.[8] These findings are consistent with an incomplete understanding of biosimilars, a deficiency that this manuscript attempts to address.

Why is a biosimilar not a generic drug?

Biosimilars are produced by recombinant DNA technology in bacteria, plant cells, or animal cells, while generics are produced by chemical synthesis.[9] The complexity of the production process of a biologic product involves ultrasensitive regulatory mechanisms of microorganisms, not entirely predictable (stochastic) glycosylation processes, and spatial conformation of a large protein affected by multiple and occasionally unforeseen variations of the isolation and purification process. These render the whole endeavor of biosimilar production complicated and fundamentally different from the development of a mere generic. For that reason, they are rightfully considered distinctive from generics, acknowledging the fact that even if the peptide sequence is identical to the original therapeutic agent, the end product is expected to be, and inevitably is, slightly different.

Generic drugs essentially are the same relatively simple chemical structures to the original ones, albeit in a different salt form, or mixed with a different excipient. Thus, simple pharmacokinetic studies suffice for their approval. Such studies satisfy the requirement of bioequivalence between the innovator and the generic product. Generics therefore are deemed identical to the reference products, while biosimilars are qualified as similar but not identical.[9] Importantly, no therapeutic trials of generics are required prior to approval, so that the generic product enters the market easily and without incurring extensive expenses.[10] As a result, generics are in position to reduce pharmaceutical cost and that is exactly the reason for their existence. On the other hand, biosimilars undergo more extensive scrutiny justified by their very nature. A whole new set of regulations had to be developed to assure the community of their validity before they are commercially launched. A new type of therapeutic clinical studies (clinical comparability exercise) had to be invented in order to provide the minimum assurance of their similarity to the innovator, as discussed below.[11] Hence, biosimilars are thought of not as identical but as a very close approximation of the original drug.[10]

Production of biosimilars

Production of biosimilars requires extensive expertise and therefore is usually undertaken by large pharmaceutical corporations. Details in the process of synthesis, selection of the microorganism, extraction, purification, and end product manufacturing affect the exact nature of the end product. Monoclonal antibodies are large proteins with four polypeptide chains and interact variably with each other and with the environment.[2] In addition, such molecules undergo a

complex glycosylation process, which depends on the nature of the microorganisms used and on a number of external factors.[12] In reality, such a biologic product is a mixture of variants of the same polypeptide. As conditions of production may slightly vary in different time periods or among different factories of the same company, different batches of the same commercial product are slightly different. Each batch can be viewed as a distribution probability of closely resembling variants. These slight variations probably have no clinical significance. The probability of difference between production batches obviously increases when another company tries to mimic the innovator without having full knowledge of the patented manufacturing process.

Why are biosimilars needed?

As biologics are the ''ultimate'' medicinal products of the pharmaceutical industry, they come at a very high cost. In addition to the usual considerable expense required for any drug to reach the market, biologicals are inherently burdened with a huge production cost. Therefore, as in the case of generics, payors and society welcome a biosimilar, upon patent expiration, hopefully as a cheaper alternative to the original. Hence, the ''raison d'être'' of a biosimilar is purely of economical nature, similarly to generics. It is hoped that the availability of multiple versions of the same therapeutic macromolecules will result in a reduction of prices through regulated competition. The exact magnitude of cost savings with biosimilar therapeutic antibodies remains to be determined as they are not marketed yet. However, the substitution of erythropoietin and filgrastim use with biosimilars in cancer patients has been estimated to be in the range of 1000–2700 Euros per treatment course, per patient.[13,14] As the price of therapeutic monoclonal antibodies are generally higher than growth factors, considerably more absolute financial gain is expected with biosimilars. Although the financial aspect is similar to generics, the complex nature of these products generates the need for a distinct regulation environment.

Society wishes that competition between manufacturers will indeed compress prices by means of healthy market processes. Governments and regulators ought to protect consumers from market schemes between major pharmaceutical companies because drug affordability would ultimately spare resources that could be used to support further innovation. Having the above in mind, clinicians can better understand why biosimilars inevitably enter the market and why the clinical studies required from the regulatory bodies are different from the usual studies for the development of any new drug.

Legislation and regulations in the European Union

With the introduction of biosimilars, European Union (EU) was the first to create a legislation and regulations agenda. Omnitrope™ (somatropin) was the first biosimilar drug marketed in 2006 on the EU.[15] However, Omnitrope was ''accused'' by the Food and Drug Administration (FDA, the USA regulatory agency) that did not at all differ when compared to the reference product Genotropin, indicating difference of opinions across the Atlantic.[16] Later, on a revision of the guidelines, on the occasion of biosimilar erythropoetins, it was established that non-clinical studies (pharmacodynamic in vitro studies, pharmacodynamics in vivo studies, toxicological studies), clinical studies (pharmacokinetic, pharmacodynamics, clinical efficacy), as well as post-marketing comparative safety data, pharmacovigilance plan, and studies for the extension of indication were required in order to complete the main guideline text for demonstration of comparability.[17] Although each European country has its own regulations concerning biosimilars, the European Medicines Agency (EMA) is the central reviewer by law for all biotechnology-derived medicinal products, including biosimilars and sets the pace for all.[11]

Based on the EU regulation, a medicinal product can be named biosimilar only if it has passed the ''comparability exercise.''[10] Comparability exercises are essential to prove that there is high similarity to the innovator product. Comparability exercises involve analysis and comparison of the production methodology, physicochemical properties, biological properties, immunochemical properties, profile of purities, and impurities.[18] It should be noted that the scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given biological product by the innovator company and for the development of a biosimilar product by another company are the same. Eventually, a clinical study proving equivalent clinical efficacy is required, as discussed below. It is also essential, as it is mandatory by the EMA, that every pharmaceutical company willing to produce biosimilars should provide a risk management plan (EU-RMP).[19] As soon as the review is complete and EMA grants its authorization, the biosimilar product is permitted to be marketed in all EU member states.[11]

Type of clinical studies for approval of biosimilar-extrapolation of indications

Biosimilars, as opposed to generics, are rightfully required by regulators to be subjected to a

non-inferiority comparative clinical trial against the innovator drug. This is the ultimate step before approval and it implies that it has cleared all the previous comparability tests. These types of studies constitute a new paradigm in the field of clinical research as they are not performed with the intention to benefit the patients either by means of improving efficacy or reducing toxicity of a new therapy but purely to demonstrate the inherent variability in consistency. Clinicians and patients involved in such studies may feel that they are part of an impersonal process with the sole purpose to facilitate a drug company market a drug. This fact may raise feelings of alienation and may be seen by clinicians as a deviation from the duty to help any given individual undergoing treatment. However, the need for biosimilars, as dictated by the way the market and societies operate, makes such studies inevitable. Clinicians are called to realize that these comparability studies are very unlikely to harm any patient and may help future patients access more drugs, by means of cost containment.

The blinded randomized phase III comparability trials are usually very carefully planned so that credibility and validity are reassured.[20] Another point of contention is that it is considered sufficient by the regulators for a biosimilar to demonstrate equivalence in one clinical situation only and for one end point. The latter may often be just a complete response rate. Again, clinicians are accustomed to expect more meaningful end points such as progression-free survival or overall survival from a phase III study. One needs to be reminded that these comparability studies are not done for demonstrating clinical benefit of a new drug, but in order to prove to regulators that biosimilars do indeed behave as expected and they do appear to be similar. If the biosimilar has passed all the comparability tests and proves itself to be equivalent to the innovator at least in one clinical end point, then regulators assume the position that it is equivalent in all indications of the innovator drug.

Is this leap of faith justified? As the experience with biosimilar monoclonal antibodies is still limited, a documented answer to the question regarding the validity of extrapolation to other indications is not possible. It is reasonable to expect no significant differences at least in applications involving similar mode of action. As explained previously, the inherent variability, consistency of a biological within the same brand name makes it not perfect. This makes slight differences between biosimilars perhaps less important than the "noise" within the same branded drug. In essence, there is no ideal molecule that others try to duplicate but rather distributions of variantly glycosylated forms of the same polypeptide that are expected to substantially overlap. Given the mechanism of action of the monoclonal antibodies, the non-linear pharmacokinetics and the target saturation dosage employed commonly in practice, efficacy differences are not expected.

It is important to note that based on data extrapolation, epoetin biosimilars were approved for oncology patients with anemia. However, there are still concerns arising with epoetin biosimilars and immunogenicity.[21] Skepticism on behalf of the oncologist is perhaps justified when a new product is administered to potentially curable patients. Typical examples are the use of monoclonal antibodies in the adjuvant treatment of breast cancer and in lymphomas. Long-term toxicity data in addition to efficacy may be required before a switch to a biosimilar is made for such indications. Such special uses of biosimilars in potential curable patients should be the topic of investigation by cooperative groups and clinical researchers in general. It is preferable to leave to the medical societies and the medical communities rather than the regulators or the payors the decision regarding prompt or delayed use of a biosimilar in such cases. All the above reinforce the need for traceability and pharmacovigilance so that possible long-term toxicity is captured.

Immunogenicity

Immunogenicity is determined by different factors such as the manufacturing process of a biologic medicinal product, host factors (age, sex, fitness), the medical history of the patient, and concomitant drugs. Additionally, each pharmaceutical company produces medicinal products using different cell lines and through different manufacturing processes, generating the real possibility of different immunogenicity due to structural variances of the tertiary and quaternary structure and of possible admixtures.[10] Based on the fact that immnunogenicity assays are difficult to interpret in preclinical and clinical studies, regulators require meticulous post-marketing surveillance.[22] Immunogenicity may also affected by the route of administration. For instance, the conversion of intravenous to subcutaneous administration of the same preparation should not be considered as immunologically equivalent, prompting separate evaluation. Recently, the subcutaneous evaluation of trastuzumab has been evaluated: immunogenicity was thoroughly investigated and deemed trivial before approval.[23] Pharmacovigilance is of paramount importance to eliminate the risk of rare, but clinically meaningful to immunogenicity of a biosimilar.

Pharmacovigilance

European legislation (Directive 2010/84/EU) describes the requirements for a biosimilar pharmacovigilance

program as the responsibility of the pharmaceutical company. A qualified person in charge of pharmacovigilance must be identified within the company, responsible for all relevant logistics. According to EU pharmacovigilance legislation, market authorization is provisionally granted, subject to post-authorization safety studies (PASS), as well as post-authorization efficacy studies (PAES).[11] The pharmaceutical industry is thus responsible for supporting an active pharmacovigilance program. Such an effort requires meticulous capturing of data. Summary of the pharmacovigilance reports must be submitted periodically by every marketing pharmaceutical company.[24]

Differences between the biosimilar and the reference product are expected due to the independent manufacturing processes. The case of the subcutaneous administration of a recombinant human erythropoietin biosimilar that caused an increase incidence of pure red cell aplasia is an example of how formulation and packaging may affect safety.[22] Acknowledging the above, it has even been suggested that different international nonproprietary names (INN) and an adapted summary of product characteristics be used, in order to stress the difference between the reference and the biosimilar product, clearly an extreme position. Post-authorization measures are an essential need for biosimilars, so as to add to an ultimate safety and efficacy profile.

Based on the above, pharmacovigilance systems should differentiate between innovator products or other biosimilars. Every pharmacovigilance program should be able to identify the biosimilar medicinal product prescribed.[10] Therefore all three, the INN, the brand name of the biosimilar product, and the batch number, should be retained in the long term at the dispensing pharmacy. This will enable the association of any possible toxicity not only with the particular company but also with the particular factory and batch, as slight difference between batches may occur. It is important, therefore, that doctors who are prescribing biosimilars, to add the brand name to the INN on the prescription. Only based on team effort, the side effects of biosimilar medicines will be correctly captured.

Interchangeability

Related to the above is the issue of the interchangeability. Since the medical community cares primarily about the safety of the patients, medical systems ought to enable physicians to continue the same brand biosimilar for every individual patient. Substitution by the doctor or automatic substitution by the pharmacy must be discouraged. This is the only way to accumulate reliable safety information for new biosimilars. It is very important for payors and central pharmacists to realize that biosimilars are different from generics in that aspect and to develop different set of rules for procurement, registering, and dispensing biosimilars. In a survey conducted by the European Association for bioindustries and the Alliance for safe biologic medicines, it was concluded that clinicians believe that the authority they have on prescribing the treatment should be respected by their colleagues, including the pharmacists.[8] Proper education of the involved professionals will help elucidate the peculiarities of biosimilars and the rationale for the concepts mentioned above.

Where the regulator and the oncologist meet?

Understanding not only biosimilars but also the complex nature of biologic medications is essential for developing rational regulations and patterns of practice. Regulatory bodies should understand the concerns of clinicians and respect their primary goal to serve the individual patient in their clinic. On the other hand, clinicians should realize the financial reason for the development of biosimilars and to not adhere to a purist's rejection view which is inconsistent with the inherent variability of biologic systems and products. The concern about a very small, if any, probability of harming the patient should be appeased by an eager and well-organized post-marketing monitoring process.

Physicians should be kept updated with all late documents related to a marketed biosimilar product. For Europe, the European public assessment report (EPAR) contains all the relevant news apart from documentation on interchangeability and substitution.[11] Relevant information on biologics and biosimilars before prescribing them to the patients is publicly available and, as the issue acquires greater importance, it is expected to become a popular topic in meetings and conferences. A responsible pharmaceutical industry should be at the physicians' side to inform on the updates concerning the newly marketed authorized medicinal products.

Regulators ought to respect the physicians' request for non-interchangeability and facilitate in any possible way traceability. Such regulations along with a rigorous pharmacovigilance program will satisfy the concerns for long-term safety. Regulators may want to propose the use of a particular biosimilar for financial reasons, but they should respect at all times a justified insistence of a physician to prescribe the innovator product. The physician's prerogative is relevant in cases related to extrapolation of uses, continuity of biosimilar use in patients already on treatment, and toxicity. In exchange, physicians should acknowledge the

incorporation of biosimilars as a means to reduce pharmaceutical cost and accept their use as per payor's suggestion, provided there is no medical contraindication. The concept of yielding a portion of the decision process to payors, although unpalatable, has already been introduced due to managed care. There has been an increasing influence of health systems and regulations on prescribing any drug, not only biosimilars. This has been reluctantly accepted at least when it is not harmful to patients.

In conclusion, the collective effort born by the medical community and the society for a more affordable health system triggers the emergence of biosimilars. Full understanding of their attributes, caution when needed, good organization, and dialogue with good faith among all parties involved in patient care will lead to their productive incorporation in current medicinal practice, ultimately aiming at better health care for all.

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