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PERSPECTIVE

Biosimilars for Healthcare Professionals

Biosimilars for prescribers

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Biosimilars are copies of original biological medicines. Biosimilarity is a new concept in drug development. Physicians prescribing biologicals need more neutral information on the quality, safety and efficacy of biosimilars.

Keywords: Biosimilars, comparability, interchangeability, prescribers, regulators

Introduction

The European Union (EU) was the first highly regulated area to create a legal and regulatory framework for copies of original innovative biological medicines, similar biological medicinal products (biosimilars). There are currently 19 biosimilars with a valid marketing authorization in the EU. These products represent different levels of structural complexity and are used in several therapeutic areas. In contrast to the pharmaceutical community, where biosimilars have been intensively debated, the interest among physicians has been very modest.

Do physicians understand the concept of biosimilarity?

Dolinar and Reilly [1] published a survey of 470 prescribers in France, Germany, Italy, Spain and UK. Respondents were all specialists who prescribe biologicals, including nephrologists, rheumatologists, dermatologists, neurologists, endocrinologists and oncologists. Only 22% of the specialists claimed to be well informed about biosimilars, even if most responders were affiliated with a hospital or an academic medical centre. Only 19% used the European public assessment reports (EPARs) as a regular source of information. Instead, 47% of responders had acquired their information during seminars and conferences. Thus, regulators and prescribers seem to be disconnected.

An interview-based survey among Finnish specialists [2] reported that several specialists felt that the interchangeability of biosimilars is difficult to evaluate because biosimilars are 'similar but not the same'. In addition, quality and immunogenicity issues were also of concern to some interviewees. A fraction of specialists had problems in understanding extrapolation of indications, i.e. extrapolation of therapeutic similarity tested in one indication to other indications of the reference medicinal product. In general, specialists requested additional information on biosimilars to decrease the prevailing uncertainty.

Aapro [3] described the concerns of oncologists. Their main concerns come down to the slogans 'Similar but not the same' and 'The product is the process', i.e. small differences could lead to differences in safety, efficacy and immunogenicity.

There are major differences in the uptake of biosimilars in the EU Member States [4]. These differences may be partly explained by the level of information available to prescribers.

Educating prescribers

The main point in many articles dealing with biosimilars has been that biosimilars are not generics and, therefore, the extrapolation and interchangeability are questioned [5, 6]. Another factor that has muddled the biosimilar waters is the use of the term 'biosimilar' for any copy of the biological product including those that have been licensed outside the highly regulated regions [6].

Basics

It is essential that the prescriber can distinguish EU biosimilars from 'biosimilars' in other regions [7]. The definition of the biosimilar in the Committee for Medicinal Products for Human Use 'Guideline on similar biological medicinal products' [8] is very helpful as a starting point for discussion of biosimilars.

'A biosimilar is a biological medicinal product that contains **a version** of the active substance of an already authorized original biological medicinal product (reference medicinal product) in the EEA [European Economic Area]. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy needs to be established based on a comprehensive **comparability** exercise'.

This definition contains at least two very important messages. First, the biosimilar contains a new version of the active substance of the reference product. The definition helps to explain that a biosimilar is a very close copy as compared to biobetters, unrelated products targeting the same receptor, line extensions, etc. The second point is that the comparability exercise is the way to demonstrate that different versions of a biological substance have similar efficacy and safety.

Product is the process

Clinicians tend to focus on clinical data only. However, biosimilars should be judged on the basis of the totality of evidence [9]. The development of a biosimilar is based on an extensive comparability exercise where the biosimilar is compared to its reference by physicochemical and structural analyses as well as by *in vitro* functional tests [10]. Human pharmacokinetic studies will ensure a comparable exposure and a confirmatory clinical trial in at least one therapeutic indication will be conducted. The slogan 'The product is the process' cannot be used as an argument against the development of biosimilars. The current biosimilars have proven that a biological product can be copied.

Similar but not the same – comparability

There is extensive experience in comparability studies that control the safety and efficacy of biologicals after manufacturing changes. Current methods to analyse physicochemical and structural differences are extremely sensitive. Analysis of manufacturing batches of the originator (reference) products has revealed differences after a change in the manufacturing process between the pre- and post-change batches [11]. In these cases, no clinical studies were performed. These differences were similar to those that have raised a lot of concerns when observed between a biosimilar and its reference product. Thus, the slogan 'Similar but not the same' applies to originator products at the time of licensing and today!

Extrapolation and mechanism of action

Several learned societies have published recommendations and position papers advising prescribers to refrain from using biosimilars

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in therapeutic indications that have not been studied in clinical trials [12]. The fear of extrapolation is surprising considering the experience from the manufacturing changes of the reference products and line extensions of the reference products [12]. For biosimilars, the extrapolation has to be justified for each therapeutic indication considering the mode of action of the active substance and the characteristics of the target patient populations. If the mechanism of action of the active substance is different in different therapeutic indications, additional data need to be delivered. An illustrative example is the extrapolation of the indications in the case of biosimilar infliximab [13] where additional data were requested to support extrapolation. No problems have been encountered with the extrapolated therapeutic indications of the current biosimilars in the EU.

No formal switch studies – so what?

For the time being, there is no EU regulatory guidance on interchangeability. Nevertheless, there are both theoretical and clinical arguments to support interchangeability of the EU biosimilars. For many reasons, clinical interchangeability studies may not be feasible [14, 15].

In terms of efficacy, it is unlikely that products containing different **versions of the same active substance** and being comparable at the population level would act differently in an individual patient. Theoretically, differences might occur if the formulations of the biosimilar and the reference product would be very different causing inter-patient variability. This possibility can be clarified by reviewing EPARs of the biosimilars available on the EMA (European Medicines Agency) website.

Currently, the main concern of switching patients from a reference product to its biosimilar is immunogenicity. There is no theoretical basis or clinical evidence suggesting that a **switch itself** would cause immunogenicity. The known examples of switch-related immunogenicity have occurred after a manufacturing process change of an innovator product resulting in an inferior version of the product.

An inferior immunogenicity profile of a biosimilar cannot be completely ruled out but it is unlikely for two reasons. First, the anti-drug antibody (B-cell) responses of biosimilars are always investigated before marketing authorization [16]. An inferior immunogenicity profile is not compatible with biosimilarity. Second, the active substance of a biosimilar has the same amino acid sequence as the reference product and, thus, shares the linear T-cell epitopes. A strong immune response would require a new T-cell epitope. In addition, the levels of immunogenic impurities and aggregates are tightly controlled. Finally, the knowledge of serious immunological complications of the innovator product, such as pure red cell aplasia triggered by epoetin alfa, will help the biosimilars developer to be prepared for the potential problem and to prevent the entry of an inferior product to the market [17].

Ebbers et al. [18] looked for evidence of switch-related adverse effects from three sources: the EudraVigilance database for serious adverse effects of biosimilars; prospective switch studies of two versions of the same product, including biosimilars; and retrospective studies that involved sequential use of biologicals. They found no signal of switch-related adverse effects. This is reassuring for a prescriber who will consider a switch from the reference to its biosimilar version.

Carrots and sticks to prescribers

Switching to a biosimilar seems not to offer any benefit for an individual patient or prescriber. The motivation has to come from a wider understanding of the role of biosimilars to support sustainable pharmacotherapy. Many prescribers are already facing rationing of biological therapies because of their high costs [3]. Considering the increasing role of biologicals in pharmacotherapy, this problem will escalate rapidly. Thus, a prescriber must weigh the inconvenience and potential risk of switching, on one hand, and patient access to biologicals, on the other. Prescribers could be given an easier access to new medicines provided that they use biosimilars.

The relationship of prescribers to biosimilars is somewhat similar to attitudes towards generics in the past. Experience with generics suggests that the payers will not tolerate a very slow uptake of biosimilars. France has already taken the first step by introducing the possibility of substituting reference products for their biosimilars in first-time users of biologicals [19].

Conclusions

Currently, many physicians hesitate to use biosimilars and would like to have more information. It is important that regulators in the EU Member States distribute information that is already available. Otherwise, prescribers are left with information that is influenced by commercial interests. The problems encountered in the EU are probably shared by other regions as well.

The key messages that need to be conveyed to prescribers are:

- A biological product can be copied by an extensive comparability programme and reverse engineering of the manufacturing process of the biosimilar
- The current biosimilars in the EU have proven to be of high quality and as efficacious and safe as their reference products
- There are always some differences between the reference and biosimilar products. However, the same type of differences is seen after manufacturing changes of the reference products between the pre- and post-change versions
- Extrapolation of therapeutic indications is based on scientifically valid criteria. Thus far, no problems have been encountered with the 'extrapolated' indications of biosimilars
- Available data suggest that the current EU biosimilars are interchangeable with their reference products

For patients

Most therapeutic proteins are produced by a biotechnological manufacturing process, i.e. by living cells. Products that are derived from living cells are always heterogeneous. Therefore, there is some variation between production batches, especially if the manufacturing process is changed. The manufacturers have to do comparability studies to demonstrate that the safety and efficacy of the product has not changed after the change in the manufacturing process. Biosimilars are new versions of original biological medicines. Biosimilars are shown to be comparable to the original medicine by extensive comparability studies. This approach to drug development is not well known to physicians who prescribe biological medicines. Therefore, physicians have been reluctant to prescribe biosimilars. The purpose of this manuscript is to summarize the information that is essential for the prescriber to become confident in the quality, safety and efficacy of biosimilars.

Biosimilars have been shown to reduce the costs of biologicals and, in this way, to improve patients' access to important medicines.

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