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Biosimilar insulins: What do you need to know?

June James[1], Robyn K. Pollom[2], Irene Hadjiyianni[3], Gabriele Buchholz[4] and Beverly L. Reed[2]
[1]University Hospital of Leicester NHS Trust, Leicester, UK; [2]Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, USA; [3]Lilly Deutschland GmbH, Bad Homburg, Germany; [4]Diabetesberaterin, Sinsheim, Germany

Biologics are large, complex molecules derived from living organisms and include hormones, such as insulin. Biologics possessing an identical amino acid structure, and similar efficacy and safety to an approved reference product are called biosimilars. The first biosimilar insulin was approved in the European Union in 2014 and more are expected to come to market. Patient education for biosimilar insulins is the same as for other insulins, but additional factors for patients changing their insulin should be considered. This article is a resource for healthcare professionals who treat patients with diabetes and support them in making important treatment decisions.

Keywords: Biosimilar, Diabetes mellitus, Immunogenicity, Insulin, Insulin glargine, Diabetes specialist nurse, Biologics; Devices

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Introduction

Biologics, such as human insulin, insulin analogues[1] and some glucagon-like peptide-1 receptor agonists[2] play an important role in treating people with diabetes. Biosimilars are similar versions of approved biologics that have similar efficacy and safety profiles.[3] The first biosimilar insulin was authorised in the European Union (EU) in 2014[4] followed by another insulin approved in 2016, and other insulins are currently in development (Clinicaltrials.gov, NCT02227875, NCT02273258). Patients and clinicians need to understand what biosimilars are and how to use them in practice. We will review biosimilars and highlight important aspects of treatment with biosimilars that should be considered and discussed with patients.

How biologics and biosimilars differ from nonbiologic drugs and generics

Biologic and nonbiologic drugs (hereafter small-molecule drugs) differ from each other in their size and structure and in how they are made. Small-molecule drugs, such as aspirin and metformin are less complex molecules (Figure 1) and are typically made using chemical methods, which allow for easier analysis, or characterisation, of their molecular structures and properties.[5] Thus, an identical or generic version of the original or reference medicine can be created.[6]

In contrast, biologics, such as insulin, are typically larger, more complex molecules (Figure 1) and are made from living cells or organisms. They are produced using complex, multistep manufacturing processes.[7] Biologic products are more sensitive to minor differences in the manufacturing process, which may change how the drug works.[8] Moreover, biologic manufacturing processes are proprietary and cannot be copied by the manufacturers of biosimilars. As a result, it is not possible to develop a biosimilar that is truly identical to the original biologic, or reference medicinal product (hereafter reference product).[9]

How biosimilars are approved in the EU

Different development and approval processes exist for biosimilar and generic drugs. A generic drug is approved when it is shown to have the same active ingredient with similar pharmacokinetics (PK) (i.e. the way it is absorbed in the blood) and pharmacodynamics (PD) (i.e. how the drug acts in the body) properties to its reference medicine.[6,8,10] However, because biologics are complex, a more comprehensive approach is required compared to that for generics. A biosimilar may be approved when it exhibits no clinically meaningful differences in efficacy and safety compared with its reference product.[7]

Before clinical trials are done in humans, studies are done to compare the quality and mechanism of action of the biosimilar and its reference product.[5,11] In addition, the PK and PD (e.g. onset, peak and duration) of the proposed biosimilar insulin are compared with its reference product.[12,13] Establishing PK and PD similarity is intended to provide reassurance that the biosimilar insulin and the reference product exhibit a similar effect on the blood glucose.[12]

Differences between the manufacturing process of the reference product and the biosimilar insulin can have

Correspondence to: Beverly L. Reed, Clinical, Lilly Diabetes, Eli Lilly and Company, Indianapolis, IN, USA. Email: reed_beverly_l@lilly.com

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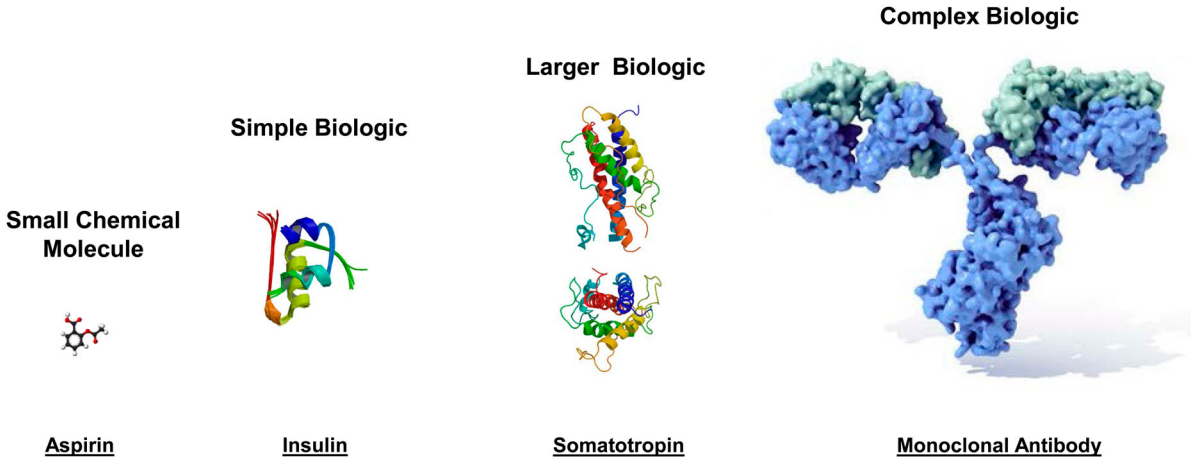

Figure 1 Comparison of nonbiologic small molecule and biopharmaceuticals. Images are used under a Creative Commons licence. The Aspirin structure: 'Aspirin-3D-balls' image created by Ben Mills (benjah-bmm27). This image is in the public domain. Source: http://commons.wikimedia.org/wiki/File:Aspirin-3D-balls.png. White background added to the original image. Insulin image created by Wojciech Bocian and Lech Kozerski. This image is in the public domain. Source: http://www.rcsb.org/pdb/explore.do?structureId=2jv1. Somatotropin image: This image is in the public domain. Source: https://commons.wikimedia.org/wiki/File:Somatotropin_1HGU.png. Monoclonal antibody: 3D model of immunoglobulin molecule by National Library of Medicine. This image is in the public domain. Source: http://commons.wikimedia.org/wiki/File:Inmunoglobulina.png.

profound effects on the final product and may affect how patients respond.[9,14] Therefore, studies that compare the safety outcomes of the biosimilar insulin with its reference product in people with diabetes are required.[12] These studies evaluate the type and frequency of adverse events, including hypoglycaemic events, allergic reactions and injection site reactions. In addition, efficacy may be assessed to demonstrate similar clinical outcomes (i.e. glucose-lowering effect, HbA1c improvement and dose) between the biosimilar and its reference product.[13,15]

Given their large, complex structure, biologics (including biosimilars) may trigger an immune response, because the body may react to them as if they were foreign substances.[5] When antibodies are developed, they may not always result in negative clinical consequences;[5,16] nevertheless, in some instances, these antibodies may affect efficacy or result in adverse events.[7] Therefore, the evaluation of immune responses is required as part of a biosimilar safety assessment. Like all biologics, once a biosimilar is approved, it is important to continue to monitor patients for safety issues or concerns, including those related to immunogenicity.[1,7]

Prescribing considerations

Cost of biosimilars The development of biosimilars does not require as many clinical studies as those for new biologic medicines, so they tend to be less expensive than their corresponding reference products, with an estimated cost savings of approximately 11–40% in the EU.[17,18] However, the cost of developing and manufacturing biosimilars is higher than that for generics, so they cannot be expected to have as large of a price reduction as generic drugs.[18]

Practical considerations when using a biosimilar

When a biosimilar receives marketing authorisation, it does not automatically receive approval for all therapeutic indications[19] or specific patient populations[20] as its corresponding reference product. However, if certain regulatory criteria are met, along with scientific justifications, then the biosimilar may be used for other approved indications of the reference product.[11,21] The Summary of Product Characteristics (SPC) provides detailed information for healthcare professionals on approved indications and populations that allow the biosimilar to be used safely and effectively.

Switching, substitution and interchangeability

Additional prescribing considerations for biosimilars may include switching and substitution. Switching occurs when a healthcare professional decides to prescribe a biosimilar in place of its reference product.[5] In contrast, automatic substitution occurs when a pharmacist decides to dispense a biosimilar instead of the prescribed reference product without obtaining the prescriber's consent.[9] As of this writing, no universal guidelines or EU substitution policies exist. Each Member State decides its own substitution policy.[3,7,13] Many EU countries prohibit or oppose automatic substitution.[22–24]

Switching or alternating treatments between the biosimilar insulin and its reference product raises the issue of interchangeability. Interchangeability occurs when one medication is switched with another identical medication that is expected to produce the same therapeutic effect.[5,25] Although the European Medicines Agency (EMA) does not assess interchangeability, the decision is left to EU Member States.[13] Because a biosimilar is not identical to its reference biologic, we believe that

additional scientific evidence will be needed to demonstrate interchangeability, such as evaluating the safety and efficacy of switching or repeatedly alternating between the biosimilar insulin and its reference product.[26] It is important for the healthcare professional to be informed and consulted when a patient switches from one insulin to another.[27] As an example, in the UK, changing from one insulin to a biosimilar insulin should not be done unless there is a clinical justification and the patient and healthcare professional have discussed the pros and cons of changing treatment.[23]

Biosimilar names

In the EU, the biosimilar and its reference biologic may have identical International Nonproprietary Names (INNs).[28] For example, insulin glargine is the INN for Lantus® (Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany),[29] which is the reference product, Abasaglar® (Eli Lilly and Company, Indianapolis, IN, USA)[30] and Lusduna® (Merck Sharp & Dohme Limited, Hoddesdon, UK) which are the biosimilars. Hence, the prescribing healthcare professional should specifically identify the brand name (e.g. Lantus®, Abasaglar® or Lusduna®) of what is intended to be dispensed and should be consulted before a biosimilar is substituted for the reference product. Knowing the specific medication being dispensed is important when reporting adverse events and determining whether they may be related to the specified medication.

Delivery devices and storage

Insulin delivery devices, such as insulin pens, are typically unique to each manufacturer and their product. When using a reusable pen, the cartridges containing biosimilar insulin may not be compatible with the reference product pen.[13,15] Furthermore, prefilled insulin pens from different manufacturers are unique. Thus, in the event a new insulin is prescribed, it will be necessary to provide the appropriate insulin pen device and the accompanying 'Instructions For Use'. Although the insulin pens may be similar, they are not the same, and patients should be made aware of a change in their device. Likewise, the stability and shelf life conditions for the biosimilar insulin may be different from the reference product.[31] Therefore, when educating patients, consult the SPC and general information for device use and storage instructions (e.g. temperature and expiration).

Key considerations

- Changing from one insulin to another should be done under the supervision and consent of the prescribing healthcare professional in consultation with the patient.
- It is essential that insulin is prescribed by the brand name and that the device is specified. This information should be included in patient documentation (e.g. insulin safety card/patient insulin passport).
- Patients can expect to see a similar blood glucose-lowering effect and safety profile as the reference product.
- The stability, shelf life and storage of the biosimilar insulin may differ from its reference product; therefore, the SPC should always be checked.
- The insulin pen delivery device may be unique to the biosimilar insulin. Patients will need to be instructed on the correct use of the biosimilar pen device.

Conclusion

Nurses and other healthcare professionals who provide care and education for individuals living with diabetes have become accustomed to increasing numbers of therapeutic options. The introduction of biosimilar insulins is unique, because they do not represent a class of medication with a new mechanism of action. According to the regulatory requirements to demonstrate similarity, these molecules have no clinically meaningful differences with their reference product. Because of this similarity, diabetes specialists and healthcare professionals must not assume that there are no additional messages to convey regarding the use of biosimilar insulins. Enhanced knowledge of biosimilars provides the opportunity and necessary information to make wise treatment decisions. Using this knowledge to provide effective patient education ensures patients have the information they need to initiate or transition confidently and safely to biosimilar insulins when they are clinically indicated.

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Contributors

J.J. has served as a consultant for an advisory board for Eli Lilly. R.K.P., I.H. and B.L.R. are employees of and hold stock in Eli Lilly. G.B. has served as a consultant for an advisory board for Eli Lilly.

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