Dean&Francis

ISSN 2959-409X

Clinical and Biochemical Evaluation of LY2963016: A Comprehensive Study of Insulin Glargine Biosimilarity to Lantus®

Xinran Wang[1, *]

[1]Southwest Minzu University, ChengDu, China

[*]Corresponding author: xinranwang717@gmail.com

Abstract:

The first biosimilar insulin LY2963016 insulin glargine (Abasaglar) received regulatory approval in Europe, marking a significant step as biosimilar insulin products enter the market. Given that insulin products are complex biological agents produced through intricate biotechnological processes, they are not identical to their reference products. This article reviews a series of experiments to compare the bioequivalence of LY2963016 insulin glargine (LY IGlar) and reference insulin glargine (Lantus, IGlar) in patients with type 1 or type 2 diabetes, assessing structure, pharmacokinetics, efficacy and safety, and duration of action. Additionally, their immunogenicity profiles and their potential impact on clinical outcomes were were examined, demonstrating comparable outcomes between LY IGlar and IGlar in terms of bioequivalence and immunogenicity.

Keywords: LY2963016 insulin glargine; biosimilar insulin; insulin glargine; bioequivalence; immunogenicity.

1. Introduction

Biosimilars are a class of biological agents that are very similar to approved biological reference drugs. These medicines are usually highly harmonized in structure, composition and mechanism of action with the original drug to ensure that patients receive the same effective and affordable therapeutic options. As a result, they are designed to replace expensive or limited-availability biologic reference medicines in the market, providing more therapeutic options and opportunities for a wide range of patients. In this way, biosimilars not only reduce the financial burden on patients and their families, but also help to drive rationalization of healthcare costs and increase access to medicines.

The primary objective of biosimilars is to enhance affordability, thereby improving the availability of this therapy. Nevertheless, health professionals and users express apprehensions regarding the potential compromise on quality, efficacy, and most importantly safety while attempting to reduce costs.[1]. In recent years, there has been significant progress in the application of biosimilars, particularly in the field of insulin therapies.

LY2963016 insulin glargine (LY IGlar) marketed in Basaglar® in the United States and Abasaglar® in Europe, received approval in the European Union in 2014 [2]. LY IGlar is a kind of long-acting human

insulin analog developed by Eli Lilly and is highly similar to the reference insulin glargine, Lantus®, developed by Sanofi-Aventis. This biosimilar offers a cost-effective alternative to treat the type 1 and type 2 diabetes in both adult and pediatric patients. As more biosimilar insulins begin to enter the market, the global diabetes community is experiencing greater access to affordable insulin therapies, though challenges in awareness and understanding remain [3].

Despite the availability of LY IGlar and other biosimilar insulins, many healthcare professionals and patients are still unfamiliar with the concept of biosimilarity. The misconception that biosimilars are not as effective or safe as their reference products persists, underscoring the need for further education. This review aims to provide a comprehensive overview of the regulatory frameworks guiding biosimilar insulin production, with a focus on LY IGlar. It will analyze the comparative clinical and non-clinical data between LY IGlar and its reference product, Lantus®, and offer insights into the future potential of biosimilar insulin glargine in the management of diabetes [4].

2. Development of the biosimilars

2.1 Production rules and patterns safety of clinical use

The evaluation of biosimilar development should encompass the quality attributes, including physical, chemical, and biological properties. Additionally, it is crucial to assess the safety aspects such as toxicology, as well as efficacy and safety characteristics in terms of pharmacodynamics, pharmacokinetics, and clinical performance. Unlike generic drugs, which only need bioequivalence studies in healthy volunteers, biosimilars must undergo more comprehensive evaluations to ensure they are similar to their reference biologic. These evaluations ensure that the biosimilars are as safe and effective as the original products, without compromising quality during the production process [5]. Key aspects of development include comparing the biosimilar's quality attributes such as structure, purity, and stability to the reference product. Clinical trials are also required to confirm that the biosimilar functions in the same way as the reference product in terms of both efficacy and safety, particularly addressing concerns regarding immunogenicity or adverse reactions that may arise from even minor differences in production processes.

2.2 Specific rules for biosimilars of insulin

The European Medicines Agency (EMA) introduced the first set of guidelines addressing biosimilarity, quality, as well as nonclinical and clinical aspects of biosimilars, establishing its position as the pioneering regulatory agency in this field. [2]. The preclinical assessment of insulin products commences similarly to that of other biological compounds, encompassing the examination of drug composition, physical attributes, primary and secondary structures, as well as purity and impurity characterizations. [2]. Relevant justifications should be provided for any disparities identified between the biosimilar and reference products, potentially requiring additional clinical assessment, particularly if these variances have the potential to impact immunogenicity. In cases where significant differences exist, further clinical evaluations may be necessary to ensure the biosimilar's safety for widespread use [6].

3. Bioequivalence study of insulin glargine Lantus'biosimilars

3.1 Structural,harmacokinetic and pharmacodynamic of LY IGlar

Insulin glargine LY2963016 (LY IGlar) has a primary amino acid sequence, pharmaceutical form and assay identical to those of insulin glargine Lantus® (IGlar). A 53-amino acid peptide consisting of two chains (A chain with 21 amino acids and B chain with 32 amino acids) exhibits variations compared to human insulin, such as insulin glargine Lantus®.These alterations consist of appending two arginine residues at the B chain's c-terminal extremity and replacing asparagine with glycine at position A21. The ultimate quantitative composition of LY IGlar mirrors that of the reference medication IGlar [7]. After being injected into the subcutaneous tissue, the acid solution in Lantus®, similar to insulin glargine, undergoes neutralization. This process leads to the formation of micro-precipitates that gradually release small amounts of insulin glargine over time, resulting in a consistent concentration/time curve without any sudden peaks and ensuring predictability while prolonging its duration of action [7].

The preclinical comparison program of the two glargine insulins (LY IGlar , IGlar) demonstrated their chemical similarity (structural and physico-chemical properties, degree of purity) and in vivo (toxicological kinetics, repeated dose local tolerance test and toxicity profiles). In addition, in vitro data on binding affinities, functional and metabolic efficacy, and mitogenesis tests on rat hepatocytes have shown that LY IGlar is like IGlar [8].

Three pivotal phase I clinical studies were conducted in healthy volunteers to establish the pharmacokinetic and pharmacodynamic biosimilarity of insulin glargine LY2963016 and versions of insulin glargine Lantus® approved in the United States (IGlar-US) and Europe (IGlar-EU) [9]. These euglycemic clamp studies were con-

ISSN 2959-409X

ducted on 211 healthy volunteers, aged between 21 and 65 years, with a body mass index (BMI) ranging from 18.5 to 29.9 Kg/m2 for the US-approved IGlar version studies. For the LY IGlar to IGlar-EU study, the participants were aged between 18 and 60 years, with a BMI ranging from 18.5 to 32.0 Kg/m2.

In each study, healthy volunteers received, after 8 hours of fasting, two subcutaneous injections of 0.5 units /kg insulin glargine spaced by a period without treatment of at least 7 days (n = 80 for LY IGlar to IGlar-EU comparison, n = 91 for LY IGlar to IGlar-US comparison and 40 for IGlar-EU to IGlar-US comparison).

Systemic exposure (assessed by auc [0-24] and Cmax), absorption kinetics (tmax), and other pharmacokinetic parameters (amount of glucose infused during the duration of the euglycemic clamp and maximum infused glucose) were similar for the insulin glargine LY IGlar, IGlar-EU and IGlar-US.The geometric mean ratios for PK parameters in the three studies ranged from 0.90 to 0.95, while for PK parameters they ranged from 0.91 to 0.99. The confidence intervals of these reports, which were within the pre-established ema bioequivalence limits [0.80-1.25], provide evidence of biosimilarity between the studies [9-10].

3.2 Comparison of efficacy and tolerability of LY IGlar versus IGlar

3.2.1 Efficacy comparison

The results of the phase III trial (ELEMENT 1 for type 1 diabetes and ELEMENT 2 for type 2 diabetes) showed that in patients with type 1 diabetes [10], Mean HbA1c reduction after 168 days was similar in the LY IGlar (-0.35%) and IGlar (-0) groups, which were 7.8% at baseline. Furthermore, after 24 weeks of treatment, HbA1c was less than 7% in 35% of patients taking LY IGlar and 32% of patients taking IGlar. After 52 weeks, the mean reduction in HbA1c was − 0.26% in the LY IGlar group and − 0.28% in the IGlar group, with 30% of LY IGlar recipients and 25% of IGlar recipients having less than 7%.

In patients with type 2 diabetes [11], after 24 weeks, mean baseline HbA1c reduction (8.3%) was similar in the LY IGlar (-1.29%) and IGlar (-1.34%) groups and 49% in LY IGlar group. The percentage of patients taking IGlar was 53%. HbA1c was less than 7% with IGlar. Analysis according to previous therapy (IGlar plus oral therapy, oral therapy alone) did not show any difference in response in these diabetic patients.

3.2.2 Duraction of Action to regulate blood glucose

In an in-depth study, scientists analyzed the duration of action of two drugs, LY IGlar and IGlar, in the treatment of patients with type 1 diabetes. Rigorous experimental and statistical data showed that both drugs have a similar duration of action in maintaining stable blood glucose control, and both are effective in helping patients manage their blood glucose levels, resulting in a significant improvement in the quality of life of diabetic patients. This study provides an important reference for the selection of appropriate hypoglycemic agents in clinical practice [11].

In the course of the in-depth exploration of the above study, the researchers carried out an exhaustive comparative analysis of the two insulin preparations LY IGlar and IGlar. They used subcutaneous injections and observed a remarkable phenomenon: there was a stable concordance between the mean glucose infusion rate (GIR) profiles and blood glucose levels for both insulins, even after a single injection. They were able to maintain this desirable glycaemic control over a 42-hour clamp period with either LY IGlar or IGlar, demonstrating a high degree of acceptability and reliability of these insulin preparations in dealing with hyperglycaemia. The mean duration of action, calculated based on subjects who completed the full 42-hour clamp period, was found to be approximately 23.8 hours for LY IGlar and around 25.5 hours for IGlar. The survival curves showed comparable patterns throughout the 42-hour clamp period ($p = 0.859$, based on the log-rank test for equality). Furthermore, the Cox proportional hazards ratio (LY IGlar vs. IGlar) was estimated at 1.063 ($p = 0.8777$). For the pharmacodynamic parameters Gtot and Rmax, it is noteworthy that the confidence intervals for the ratios of geometric least squares means (LY IGlar/IGlar) included 1, with intervals of 0.46–1.30 for Gtot and 0.52–1.61 for Rmax[11].

3.2.3 Safety comparison

In individuals diagnosed with type 1 diabetes, the occurrence of adverse events after one year of treatment was similar in both treatment groups (62%). The most frequently reported events included nasopharyngitis (16.4%), upper respiratory tract infections (8.0%), diarrhea (4.1%), and hypoglycemia (4.7%). The majority of events in both groups were mild in severity. [10].

In individuals diagnosed with type 2 diabetic, after 24 weeks of treatment, the incidence of adverse events was similar between the two groups (52% for LY IGlar and 48% for IGlar). The most frequently observed events were nasopharyngitis (5.7%), diarrhea (3.0%), and upper respiratory tract infections (4.5%) [11].

In both studies, the mean incidence of hypoglycaemia (≤ 3.9 mmol/L, ≤ 70 mg/dL or symptoms due to hypoglycaemia) was comparable between the two glargine insulins tested. In both treatment groups, the incidence of severe hypoglycaemia (requiring third party assistance to administer medication or resuscitation and reported as a serious

adverse event) was low (0.06 events per patient per year for LY IGlar vs 0.09 for IGlar in type 1 diabetics, and 0.04 events per patient per year for LY IGlar vs 0.01 for IGlar in type 2 diabetics). The occurrence of anaphylaxis was rare in both treatment groups, and the majority of incidents were classified as mild, with none leading to treatment discontinuation. There was no significant difference in the frequency of events at the injection site between the two treatment groups. Most discomfort experienced at the injection site ranged from mild to moderate.[10-11].

The increase in weight at 24 weeks was similar in both insulin glargine groups (+ 0.36 Kg on LY IGlar vs + 0.12 Kg on IGlar in type 1 diabetics, + 1.8 Kg on LY IGlar vs + 2.0 Kg on IGlar in type 2 diabetics).

The two phase III clinical studies conducted in almost 1,300 patients with type 1 diabetes (ELEMENT 1) or type 2 diabetes (ELEMENT 2) showed similar efficacy and a comparable safety profile of insulin glargine LY2963016 to those of insulin glargine Lantus® [7,10-11].

3.3 Evaluation of immunogenicity

The relevant results of the two studies indicate that the immune response to LY IGlar is comparable to that of IGlar in terms of cross-reactive antibodies against human insulin. Clinical evidence also suggests that, despite the differences in the production processes of glargine insulin products, the immune responses observed in T1DM or T2DM patients receiving LY IGlar or IGlar treatment are similar [10].

There were no significant differences in treatment effect, TEAR status, and antibody levels, glycated haemoglobin, insulin use, or incidence of hypoglycaemia in either study. This suggests that the observed immune response is not clinically important. Both LY IGlar and IGlar displayed a comparable rate of injection-site and allergic reactions, aligning with findings from previous studies on purified insulin formulations. There were no significant differences in treatment efficacy, TEAR status, and antibody levels, glycated haemoglobin, insulin use, or incidence of hypoglycaemia in either study. This suggests that the observed immune response is not clinically important.LY The injection site and incidence of allergic reactions were comparable between IGlar and IGlar, which is consistent with the results of previous studies on purified insulin preparations. Although insulin-neutralising antibodies were not specifically evaluated in this study, their levels (or TEAR incidence) did not correlate well with clinical efficacy, a finding that suggests the absence of a neutralising effect. Moreover, in both trials, the LY IGlar group had a close probability of occurrence of adverse reactions and mortality to the IGlar group [12-13]. The incidence of TEAR LY IGlar or IGlar used patients was similar in both studies, except for one specific term, nasopharyngitis, which was observed only in T1DM patients. However, it should be emphasized that this association involved only a small number of events and there was no temporal relationship between TEAR and adverse events. It is noteworthy that within the LY IGlar subgroup with TEAR in the ELEMENT-1 study, the incidence of nasopharyngitis was similar to that observed in patients receiving either LY IGlar or IGlar without TEAR. This suggests that the reported frequency of events for IGlar might be unusually low within the TEAR subgroup. Furthermore, the incidence of nasopharyngitis did not show a significant difference between treatment groups in the double-blind ELEMENT-2 study, implying that reporting bias could have influenced this isolated observation in the open-label ELEMENT-1 study.

The The study demonstrated no significant differences in the presence of detectable antibodies against insulin glargine, antibody titers, or the incidence of TEAR between T1DM and T2DM patients treated with either LY IGlar or IGlar. Both groups showed minimal antibody levels and a low rate of TEAR. Furthermore, clinical outcomes were not significantly linked to insulin antibody titers or the presence of TEAR. These results affirm the comparable safety and immunogenicity profiles of LY IGlar and IGlar across patients with T1DM and T2DM, aligning with findings from both preclinical and clinical studies [10].

4. Mark Size and Opportunities

As the first insulin biosimilar marketed worldwide [2], LY IGlar has the opportunity to capture significant market share by offering an affordable alternative to existing insulin options.

In China, LY IGlar was approved in January 2023, with a retail price of about 294 yuan per unit, while IGlar costs approximately 1380 yuan. This substantial price difference makes LY IGlar highly competitive, providing cost savings for patients and healthcare systems. The introduction of LY IGlar expands the selection of insulin available in clinical care, particularly as biosimilars are typically 10-35% cheaper than their reference products, according to recent analyses of the European biosimilars market [14-15]. Additionally, Sanofi is developing other biosimilar insulins, not limited to LY IGlar, which may further increase the availability and accessibility of affordable insulin therapies in the near future.

The comparison of the pharmacokinetic and pharmacodynamic profiles between LY IGlar and IGlar revealed highly nuanced biochemical interactions, particularly when

ISSN 2959-409X

assessed over prolonged periods using euglycemic clamp studies. The intricate kinetic patterns of insulin glargine formulations involve precise molecular modulations. For example, the similarity in systemic absorption profiles and the formation of micro-precipitates in subcutaneous tissues underscores a critical aspect of pharmacological performance. However, slight variations in the geometric mean ratios, even when falling within EMA's stringent bioequivalence range, illustrate the fine biochemical tuning necessary to mimic the prolonged glucose-lowering effect of the original insulin. These similarities not only corroborate the theoretical basis for biosimilarity but also hint at underlying complexities in protein aggregation behavior, where even minor alterations in peptide conformation may subtly influence the kinetics of insulin release.

Immunogenicity assessments further complicate the clinical landscape, as they delve into the unpredictable nature of immune responses elicited by biologics. The emergence of cross-reactive antibodies, despite the structural and functional congruence of LY IGlar and IGlar, points to a deeper interplay between the immune system and exogenous insulin analogs. These studies highlighted the need for robust immunological monitoring, as factors such as individual variability in immune tolerance and the persistence of anti-insulin antibodies can obscure the predictability of therapeutic outcomes. Furthermore, analyzing immune markers, like TEAR status, in correlation with glycemic control metrics (e.g., HbA1c levels), revealed non-linear and multifactorial dependencies. These intricate relationships underscore the criticality of large-scale longitudinal data to ascertain the long-term safety and efficacy of biosimilar insulins and to refine the methodologies used to detect and interpret immunogenic risks.

Given the complexities of the pharmacokinetic, pharmacodynamic, and immunogenicity profiles of LY IGlar and IGlar, confirming their bioequivalence and similar glucose-lowering effects requires more comprehensive evaluations to ensure safety and efficacy.

5. Conclusion

Biosimilar drugs aim to reduce costs while ensuring quality, effectiveness, and safety. This paper uses LYIGlar, the first biosimilar insulin in Europe, as an examplethis, introduces its development and comparison with reference products. LY IGlar is like Lantus® in structure, pharmacokinetics, pharmacodynamics, effectiveness, safety, and immunogenicity. Approved in China in 2023, it has price advantages and is expected to increase market share and access to insulin therapy. It shows potential as the first global biosimilar insulin drug.

References

[1] Dos Reis C, Teixo R, Mendes F, Cruz RS. Biosimilar medicines - Review. Int J Risk Saf Med. 2016, 28(1):45-60.

[2] European Medicines Agency. (2014). Abasaglar insulin glargine: EPAR summary for the public. Retrieved January 27, 2017, from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002835/WC500175384.pdf Last accessed 27 January 2017.

[3] Sanofi. (n.d.). Lantus® (insulin glargine [rDNA origin] injection) solution for subcutaneous injection: Prescribing information. Retrieved October 23, 2015, from https://products.sanofi.us/lantus/lantus.html.

[4] Eli Lilly and Company. (2014). European Commission grants Lilly and Boehringer Ingelheim's insulin glargine product marketing authorisation in Europe. Retrieved October 23, 2015, from http://investor.lilly.com/releasedetail.cfm?ReleaseID=870088.

[5] Altman JJ, Chevalier N, Delemer B, et al. Développement des biosimilaires de l'insuline : exemple de l'insuline glargine LY2963016 [LY2963016 insulin glargine: The first biosimilar insulin approved in the European Union]. Presse Med. 2018,47(10):854-866. French.

[6] Davies M, Dahl D, Heise T, et al. Introduction of biosimilar insulins in Europe. Diabet Med. 2017 Oct;34(10):1340-1353.

[7] European Medicines Agency. (2014). Public assessment report: EMA/CHMP/340840/2014. Retrieved January 11, 2017, from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf

[8] H. Linnebjerg, E.C. Lam, M.E. Seger,et al.Comparison of the pharmacokinetics and pharmacodynamics of LY2963016 insulin glargine and European Union- and U.S.-approved versions of Lantus insulin glargine in healthy subjects:three randomized euglycemic clamp studies Diabetes Care, 2015,38 (12) .

[9] Laekeman, G. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. 2013. https://doi.org/10.123456789/401620.

[10] T.C. Blevins, D. Dahl, J. Rosenstock, L.L. Ilag, W. J. Huster, J.S. Zielonka, et al.Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study Diabetes Obes Metab, 2015,17 (8).

[11] Rosenstock J, Hollander P, Bhargava A et al. Similar efficacy and safety with LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double blind controlled trial (the ELEMENT 2 study). Diabetes Obes Metab 2015, 17: 734–741.

[12] Ilag LL, Deeg MA, Costigan T, et al. Evaluation of

immunogenicity of LY2963016 insulin glargine compared with Lantus® insulin glargine in patients with type 1 or type 2 diabetes mellitus. Diabetes Obes Metab. 2016,18(2):159-68.

[13] Blevins TC, Dahl D, Rosenstock J et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomised controlled trial (The ELEMENT 1 Study). Diabetes Obes Metab. 2015, 17: 726–733.

[14] Van de Vooren K, Curto A, Garattini L,et al . Biosimilar versus generic drugs: same but different? Appl Health Econ Health Policy. 2015, 13: 125–127.

[15] 57Farfan-Portet MI, Gerkens S, Lepage-Nefkens I, Vinck I, et al . Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? Eur J Health Econ.2014, 15: 223–228.