
Equivalence on efficacy and safety of two formulations of insulin glargine (biosimilar and reference) in the treatment of patients with type 2 diabetes mellitus

Hernandez-Bastida, Antonio¹, Meixueiro-Montes de Oca, Raúl²

¹Nuevo Hospital Obregon, Mexico City, Mexico

²Laboratorios PiSA, Mexico City, Mexico

Email address:

antoniohernandezbastida@hotmail.com (Hernandez-Bastida, A.), jmeixueiro@pisa.com.mx (Meixueiro-Montes de Oca, R.)

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Abstract: Use of biosimilars has allowed the access to biopharmaceuticals to a more patients in the World. Insulin galrgine is an analogue of human insulin to provide consistent level of plasma insulin over a long duration. The aim of this study was compare the safety and efficacy of insulin glargine biosimilar vs reference in individuals with type 2 diabetes. One hundred two type 2 diabetic individuals (64 female and 38 male) were studied in a single center, randomized, comparative study. The patients received during 12 weeks insulin glargine biocomparable or reference at doses of 0.4 to 0.7 IU/kg/day by subcutaneous via. Glycosylated hemoglobin (Hb1Ac), Fasting blood glucose (FBG), and lipid profile were evaluated during the study. Health-related quality of life was evaluated using the 36-item Short Form questionnaire. Hb1Ac, FBG and lipid profile improved significantly from to start to endpoint in both groups. No significant differences were found between both groups. A total of 80.8 and 77.2% of patients had HbA1c < 7.5% and 66.6% and 69.5% achieved the FBG target, for reference and biosimilar insulin glargine, respectively. No significant reductions in body weight were observed between the start and the end of the study. The adverse event more reported was hypoglycemia. There was no apparent association between the levels of cross-reacting antibodies and Hb1Ac, body weight, insulin dose, or hypoglycemic episodes Improvements in both mental and physical health status were found, but no differences significant were found between the groups. We conclude that insulin galrgine biocomparable was similar since the safety and efficacy point of view with insulin glargine of reference in patients with diabetes mellitus 2.

Keywords: Type 2 Diabetes Mellitus, Biosimilar, Insulin Glargine, Efficacy, Safety

1. Introduction

Biologics are medicines made in or isolated from living organisms. These include blood and plasma products, non-recombinant proteins purified from natural sources, recombinant proteins and monoclonal antibodies produced in cell cultured. Follow-on protein products are those manufactured using biotechnology or derived from natural sources that are intended to be sufficiently similar to a biopharmaceutical product already approved by a regulatory agency [1].

Biosimilars are biological products similar, but not identical, to reference products that are submitted to regulatory agencies after patent had just expired of the reference product [2-4]. Biosimilars are not generic versions

of innovator products. Conventional generics are considered to be therapeutically equivalent to reference once pharmaceutical equivalence and bioequivalence (usually a pharmacokinetic and pharmacodynamics studies), have been established and do not require phase III clinical studies. In the case of the biosimilars, they need to be compared with the biodrug reference through a formal clinical efficacy and safety studies, because of physic-chemical characteristics, manufacturing process, etc to establish biopharmaceutical equivalence.

A biosimilar product is defined as a highly similar to the reference product notwithstanding minor differences in clinically inactive components and for which there are no clinically meaningful differences between the biological product and the reference product in terms of safety and potency of the product [5]. Biosimilars are now recognized

around the world as safe and effective medicines and the World Health Organization has also generated guidelines to assist the less highly regulated markets in their consideration of applications from biosimilar sponsors [6].

The need for access to high quality, safe and effective biologics is global, as is the regulatory science, and increasingly the biomanufacturing experiences. Regional regulatory authorities require biosimilar sponsors to compare their biosimilar to the reference product approved in the local region.

Biopharmaceuticals require multifaceted manufacturing and purification processes, and changes to the manufacturing process can result in differences in quality, safety and efficacy [7]. When the manufacturer of a biosimilar establishes its own manufacturing process, this process is unlikely to be 100% the same as the process of the reference biopharmaceutical [8]. Subtle differences arise because biotechnology medicines are derived from living organisms and some process features of the reference biopharmaceutical remain confidential even after patent expiry [9]. Current analytical techniques are not able to detect all potential differences in clinical outcomes between a biosimilar and the reference biopharmaceutical [10]. To substantiate the claim of equivalence between a biosimilar and the reference biopharmaceutical, there is a need for adequately powered equivalence or non-inferiority clinical studies.

For many decades, the major source of insulin was the pancreas from pigs and cows. After the discovery of the primary structure of the insulin molecule, total chemical synthesis appeared to be the next logical step, however, this process is too complex and expensive at this time. Subsequent to the invention of the biotechnological production of human insulin in the 1990's, using genetically modified bacteria or yeast as production machines, this high-tech approach has been the predominant method for insulin production. In recent years, several biopharmaceuticals, including insulin and insulin analogs, are, or shortly will be off-patent, thereby providing an opportunity to companies to attempt to manufacture biosimilars or biocomparables [11]. In this context is necessary perform efficacy and safety studies on biosimilars to establish a comparability because the efficacy of biosimilar insulin's may be influenced by factors such as physical stability, formulation, or batch-to-batch variability. In other hand, potential immunogenicity is a safety issue largely unique to biopharmaceuticals that may be severe and potentially cause of efficacy loss. The classic immune response to foreign proteins is observed for biopharmaceuticals of bacteria origin [12]. A second mechanism, which is normally directed to self-antigens is based on breaking immune tolerance, which leads to antibody formation to human homologs [13].

In recent years, several companies have started to manufacture biosimilars recombinant human insulin formulations in several countries, introduced into his market with phase III studies to assess the safety and efficacy as backup.

In Latin America, the limited access for biopharmaceutic

drugs, specifically recombinant proteins or monoclonal antibodies, due to cost of treatment constitutes an unmet medical need in these countries. The use of biosimilars drugs has already decreased the cost of treatment in many regions of the world. The approval of generics by regulatory agencies is critical to facilitate patient access to this kind of drugs and will allow governments to afford the cost of these pathologies.

The key to biosimilars development is the demonstration of similarity since the safety and efficacy point of view to achieve commercial viability, represented by a broad product label. The aim of this study was to evaluate the biosimilarity of insulin glargine biosimilar versus insulin glargine reference formulation, in patients with diabetes mellitus 2.

2. Methods

The trial was a 12 weeks open-label, two-arm, randomized, prospective, comparative study conducted in a single center. The study was approved by the Nuevo Hospital Obregon's Research and Ethical Committees. The trial was conducted in accordance with the International Conference on Harmonization guidelines, Declaration of Helsinki and COFEPRIS (Mexican Ministry of Health) guidelines. The trial enrolled 120 patients (49 male and 71 female, aged 32 ± 15.6 years, with diabetes duration 3.6 ± 1.9 years, BMI 28.36 ± 3.8 kg/m²) with type 2 diabetes. The basal characteristics are shown in table 1. None had major complications of diabetes, all were nonsmokers, and all had normal renal and hematological function. All study subjects were taking two or more oral antihyperglycemic drugs (OADs) (metformin, sulfonylurea, pioglitazone) for ≥ 12 months. Exclusion criteria included severe hypoglycemia and significant concomitant disease. All patients had 6 months at least initiation phase to attain Glycosylate Hemoglobin (HbA1c) $\geq 7.5\%$. The HbA1c, glucose, and lipids were measured at baseline and each 2 weeks in the centrally laboratory of the Hospital Obregon.

Eligible patients were randomized to receive insulin glargine biosimilar (Laboratorios PiSA, Guadalajara, Jalisco, Mexico) or reference (Lantus, Aventis Pharma, Mexico). The insulin glargine starting dose was from 0.4 to 0.7 IU/kg/day once a day via subcutaneous injection. Insulin was adjusted to try to achieve HbA1c $\geq 7.5\%$. Concomitant oral hypoglycemics therapy was discretion of the physician. HbA1c measurements were made at start and at 2, 4, 6, 8, 10 and 12 weeks of treatment. Owing to the relatively short duration of the study, the therapeutic target at week 12 for HbA1c, was set at $< 7.5\%$, which was considered clinically important to show improvements in glycaemic control with insulin glargine. Self-monitored plasma glucose concentration was performed every day by the patients using an Accutrend Check (Roche Diagnostics GmbH, Mannheim, Germany) device. Weight, lipid profile and fasting plasma glucose (FPG) changes, were evaluated at 0, 2, 4, 6, 8, 10 and at the end of the study. Adverse events which included

episodes of hypoglycemia and adverse drug reactions were reported by the patients either at each visit or as when they occurred. All the events were recorded by the physician. Insulin antibodies were analyzed by Celerion (Fehraltorf, Switzerland), using a subtraction radioimmunoassay method [14] that was validated according to standard procedures [15]. At the beginning and at the end of the study period, patients were asked to complete the health-related quality of life was evaluated using 36-item Short Form (SF-36) version 2 questionnaire, to investigate how they rated aspects of therapy with insulin glargine (Physical health overall, mental health overall, physical functioning role, body pain, general health, vitality, social functioning role and mental health). Analysis of covariance (ANCOVA) was used to evaluate change from baseline for glycemic, lipid and weight outcomes. Each ANCOVA model included treatment and study as fixed effects and corresponding baseline level as a covariance.

3. Results

Demographic and baseline characteristics of the patients are shown in the table 1. A total of 120 patients were randomized to the study (60 to biosimilar and 60 to reference group). Not all patients completed the study. Four patients did not meet the inclusion criteria, 8 retired his consent to participation and 6 were excluded due to adverse events (3 from reference and 5 from biosimilar group)

Table 1. Baseline characteristics of the two patients group. FPG (fasting plasma glucose); BMI (Body Mass Index), Hb1Ac (Glycosylate hemoglobin).

Variable	Group Insulin Glargine Reference	Group Insulin Glargine Biocomparable
Age (years)	49.72 ± 6.74	51.64 ± 8.43
Male	17	21
Female	35	29
Weight (kg)	75.95 ± 10.87	77.6 ± 9.65
Height (mts)	1.63 ± 3.78	1.62 ± 2.95
BMI (kg/ m2)	28.78 ± 2.09	27.94 ± 1.88
Systolic blood pressure (mmHg)	120.6 ± 5.87	119.35 ± 6.74
Diastolic blood pressure (mmHg)	80.4 ± 4.65	76.1 ± 3.0
Heart rate (beats/min)	73.01 ± 4.16	77.6 ± 5.54
Duration of diabetes (years)	6.67 ± 1.54	7.74 ± 3.02
Hb1Ac (%)	10.1 ± 0.73	10.4 ± 0.51
FPG (mg/dl)	194.4 ± 16.87	187.2 ± 18.59

Due to relatively short duration of the study we decided evaluate patients each two weeks for better control of the studied variables. Concomitant oral hypoglycemic therapy was administered along 12 weeks of the study to discretion of investigators.

Both insulin glargine similar and reference produced a significant ($p < 0.01$) reduction in HbA1c. From basal and endpoint values for insulin glargine reference for Hb1Ac

were 10.1% and 7.39%, respectively (reduction, -26.83%). With respect to time 0 and 12 weeks for insulin glargine biocomparable the values of Hb1Ac were 10.4% and 7.44%, respectively (reduction, -28.46%). However the differences between the values of Hb1Ac of both groups were not significant (Fig.1). Both treatments also yield significant reduction in FPG (insulin glargine reference: adjusted mean ± SE = time 0, 194.4 ± 16.87 mg/dl and time 12 weeks, 127.8 ± 19.54 mg/dl; insulin glargine biocomparable: adjusted mean ± SE = time 0, 187.2 ± 18.59 mg/dl and time 12 weeks, 131.6 ± 13.28 mg/dl).

The improvement in FPG was significantly ($p < 0.05$) in both groups, although the difference was not significant between reference and biocomparable groups (Fig. 2).

There were significant differences between the effects of insulin glargine biocomparable and reference over the levels of total cholesterol, (CT), low-density lipoprotein cholesterol (LDLc) and Triglycerides (Trg) at the end of the study (Table 2). Although In both groups the therapy had favorable effects over lipid profile there were no significant differences between groups.

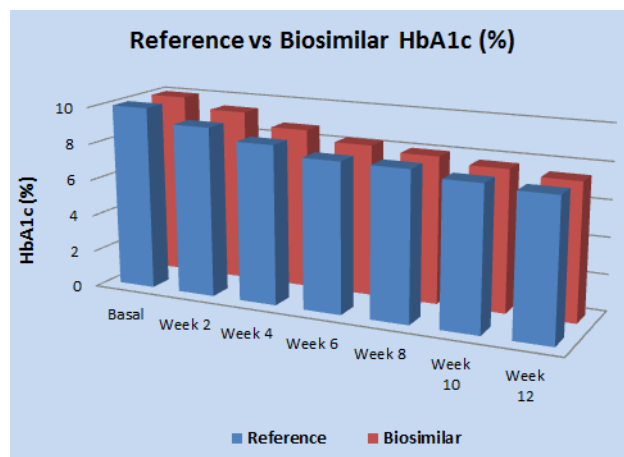


Fig 1. Levels of HbA1 during the 12 weeks of following of both insulins (Reference and Biosimilar). No significant differences were found between both groups.

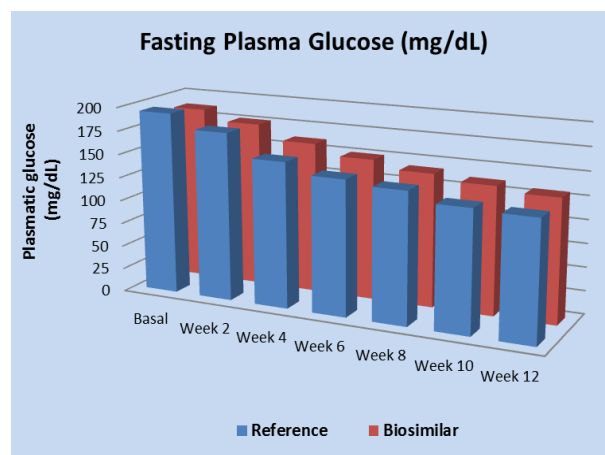


Fig 2. Levels of Fasting Plasma Glucose during 12 weeks of treatment with insulin glargine Reference and Biosimilar. No significant differences were found.

In the full data set, no significant reductions in body weight were observed between start and end of the observational period in both groups.

During the insulin treatment period, no serious adverse side effects were observed in either group. There were no changes in liver and renal function before and after treatment. The most commonly reported adverse events were hypoglycemic episodes. A relative higher prevalence of minor hypoglycemic episodes or classical symptoms of hypoglycemia were observed in the group that received insulin glargine biocomparable (33 episodes) and reference (28 episodes). Mild injection site reactions (erythema, edema, and pain) were observed, but there was no significant difference between the two groups.

For almost all participants, the level of specific antibodies was close to, or below, the limit of detection at screening and remained at the same level after 12 weeks of treatment with both insulin's glargine. Specific antibodies were presented in 30.7% and 34.03% of the patients that received insulin glargine reference and biocomparable, respectively. These patients remained at a low, stable level throughout the study.

No obvious trend was observed in the development of cross-reacting antibodies, since the values were constant in the majority of participants. There was no apparent association between the levels of cross-reacting antibodies and Hb1Ac, body weight, insulin dose, or hypoglycemic episodes

At the end of the trial, the overall component score of Health-related quality of life SF-39 score was significantly higher (improved) with insulin glargine biocomparable and reference. This was largely attributed to a similarity between both insulins glargine. The α coefficients of Cronbach for insulin glargine reference and biocomparable were: for energy and mobility (15 items), $\alpha=0.92$ vs $\alpha=0.95$; diabetes control (12 items), $\alpha=0.83$ vs $\alpha=0.79$; anxiety-preoccupation (4 items), $\alpha=0.80$ vs $\alpha=0.82$; social charge (5 items), $\alpha=0.83$ vs $\alpha=0.87$; sexual function (3 items), $\alpha=0.93$ vs $\alpha=0.90$; and total calcification $\alpha=0.95$ vs $\alpha=0.92$, respectively. All subjects treated of both groups showed a significant improvement in all scores and domains, between baseline and end of trial. These improvements were not significantly different between both groups of treatment.

Table 2. Lipid profile before and after 12 weeks of treatment in patients who received insulin glargine biocomparable or reference. * ($p<0.01$)

	INSULIN GLARGINE BIOCOMPARABLE		INSULINE GLARGINE REFERENCE	
	Basal	12 weeks	Basal	12 weeks
CT mg/dl	198.8 ± 15.3	166.4 ± 17.6	209.9 ± 13.4	172.6 ± 16.5*
LDLc mg/dl	102.7 ± 7.4	94.2 ± 5.9	114.6 ± 9.7	94.4 ± 10.1*
TRG mg/dl	281.6 ± 31.4	162.4 ± 28.6	275.1 ± 24.8	176.7 ± 26.4*

4. Discussion

Biosimilars present a new set of challenges for regulatory authorities when compared with conventional generics. While the demonstration of a pharmacokinetic similarity is sufficient for conventional, small-molecule generic agents, a number of issues will make the approval of biosimilar more complicated. The key question is whether potential differences between biosimilar insulins and their already marketed competitors are of clinical relevance or not. Unfortunately, the answer cannot be determined by even the most state-of-the-art *in vitro* laboratory methods; identifying potential or real difference does require clinical studies with human beings to demonstrate that biosimilar insulin have an equivalent safety and efficacy profile when compared to reference product. Differences between biological proteins products claiming to be similar to approved biopharmaceuticals have been a major concern for the industry and regulatory agencies worldwide. The intrinsic structural and physicochemical heterogeneity of biopharmaceuticals and the complex manufacturing process has the potential to affect safety and efficacy [16-18].

In the present study, we compared the efficacy and safety of insulin glargine biosimilar versus insulin glargine reference in a population of type 2 diabetic patients. After 12 weeks of short-treatment, insulin therapy the 66.6% and 69.5% of the patients that received insulin glargine reference

and biosimilar, respectively, achieving glycemic control target. The average of the patients with Hb1Ac < 7.5% who reached the target were 80.8% and 77.2%, for insulin glargine reference and biosimilar, respectively, with no significant differences between the two groups. Similar results were found by other studies in which the administration of long-acting basal insulin improves glucose-induced insulin secretion in hyperglycemic patients with type 2 diabetes [19-21]. Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion. Insulin therapy is thus frequently required during the course of the disease to maintain glycemic control and prevent diabetes complications. In this case, we initiated insulin glargine when alternative antihyperglycemic agents have failed when symptomatic or marked hyperglycemia was presented. In this study both insulin glargine caused less nocturnal hypoglycemia, with comparable Hb1Ac reductions. Insulin remains the most potent antihyperglycemic agent available for uncontrolled type 2 diabetes. It can significantly improve diabetes control when added to other antihyperglycemic oral agents, given as once-daily basal insulin. Insulin initiation is indicated as in this study when fasting plasma glucose levels are frequently above 250 mg/dl or HbA1c is above 10% [22].

The primary safety concern for biosimilar agents is their potential immunogenicity. There may be no clinical consequence for developing an immune response to a biopharmaceutical. The patient may develop binding

antibodies that not significantly affect the activity of the biosimilar. For almost all participants, the level of specific antibodies was close to, or below, the limit of detection at screening and remained at the same level after 12 weeks of treatment with both insulin's glargine. Specific antibodies were presented in 30.7% and 34.03% of the patients that received insulin glargine reference and biosimilar, respectively. These patients remained at a low, stable level throughout the study. No obvious trend was observed in the development of cross-reacting antibodies, since the values were constant in the majority of participants. There was no apparent association between the levels of cross-reacting antibodies and Hb1Ac, body weight, insulin dose, or hypoglycemic episodes. Similar results have been reported for other authors in whom the presence of antibodies has not apparent effects over efficacy or safety of insulin glargine [23-25].

Our study with insulin glargine biosimilar and reference compared the quality of life through the SF-36 questionnaire and the results shown a benefit to treatment satisfaction: investigators have suggested that this may be linked with the lower variability in plasma glucose concentrations and reduced risk of hypoglycemia associated with insulin glargine. Although there have been clinical trials evaluating health related quality of life with insulin long-term or analogues [26-28], our study is one of the first to directly assess health-related quality of life of an insulin biosimilar. Both insulin's in the same way, evidence a beneficial health-related quality of life effect at the end of the study in all the items of the SF-36 questionnaire. At endpoint, the overall physical and mental health components score were significantly higher than basal score in patients with diabetes mellitus type 2 under treatment with insulin glargine, never mind if they received reference or biosimilar insulin.

The approval of biosimilars is critical to facilitate patient access to high-quality biologic medicines and will allow society afford the truly innovative molecules currently in the global biopharmaceutical industry's pipeline. A biosimilar will be considered interchangeable with a reference product if the developer demonstrates that it can be expected to produce the same clinical results in any given patient and the risk associated with alternating or switching between the two products is not greater than that involved in continuing to use the reference product. In Mexico, as in many other countries, have developed and implement of stringent guidelines for evaluation of biosimilars and for allow substitution. Finally clinicians need comprehensive information on biosimilars, and biopharmaceuticals in general, to make informed treatment decisions.

It is important to recognize that the COFEPRIS provides a rigorous and balanced approach to the approval process. The national regulations are attempting to meet the demands of the healthcare market while ensuring the quality and safety of biosimilars.

Our conclusion is if the effect of basal insulin glargine biosimilar, was similar to that insulin glargine reference, might be a reasonable alternative to glargine reference for initial or substitution insulin therapy in patients with type 2

diabetes mellitus.

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