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ORIGINAL RESEARCH

Similar Intrapatient Blood Glucose Variability with LY2963016 and Lantus® Insulin Glargine in Patients with Type 1 (T1D) or Type 2 Diabetes, Including a Japanese T1D Subpopulation

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ABSTRACT

Introduction: LY2963016 insulin glargine (LY IGlar) and Lantus® (IGlar), both with identical primary amino acid sequences, were compared in two phase 3 studies for intrapatient blood glucose variability.

Methods: ELEMENT-1 was a 52-week study in patients with type 1 diabetes (T1D), which included Japanese patients, and ELEMENT-2 was a 24-week study in non-Japanese patients with type 2 diabetes (T2D). In ELEMENT-1, 535 patients with T1D were evaluable (268 LY IGlar and 267 IGlar). Of these, 100 were Japanese patients (49 LY IGlar and 51 IGlar). In ELEMENT-2, 756 patients with T2D were evaluable (376 LY IGlar and 380 IGlar). We evaluated and compared intrapatient blood glucose variability of LY IGlar and IGlar in these studies from three different perspectives: intrapatient between-day fasting blood glucose variability, intrapatient between-day daily mean blood glucose variability, and intrapatient within-day blood glucose variability.

Results: Overall, evaluations of all three indices showed that intrapatient blood glucose variability was similar between LY IGlar and IGlar throughout the study periods both in the overall populations of patients with T1D and T2D and also in the subgroup of Japanese patients with T1D.

Conclusion: Intrapatient blood glucose variability between LY IGlar and IGlar was shown to be similar in patients with T1D or T2D.

Abbreviations

ANCOVA	Analysis of covariance
FBG	Fasting blood glucose
IGlar	Lantus insulin glargine
LOCF	Last observation carried forward
LS	Least-squares
LY IGlar	LY2963016 insulin glargine
PD	Pharmacodynamics
PK	Pharmacokinetics
SD	Standard deviation
SMBG	Self-monitored blood glucose
T1D	Type 1 diabetes

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T2D   Type 2 diabetes

INTRODUCTION

LY2963016 insulin glargine (LY IGlar) is the first biosimilar insulin to receive marketing authorization in the European Union [1] and Japan [2] and was authorized as the first follow-on insulin in the USA [3]. LY IGlar has an identical primary amino acid sequence and the same pharmaceutical form and strength as Lantus® insulin glargine (IGlar; recombinant DNA origin; Sanofi-Aventis, Paris, France) [4]. LY IGlar and IGlar have been shown to have similar pharmacokinetic (PK) and pharmacodynamic (PD) properties [5, 6]. Randomized phase 3 clinical trials in patients with type 1 diabetes (T1D; ELEMENT-1) or type 2 diabetes (T2D; ELEMENT-2) further demonstrated that LY IGlar and IGlar have similar efficacy, safety, and immunogenicity profiles [7–9]. In both ELEMENT-1 and ELEMENT-2, the change in glycated hemoglobin (HbA1c) from baseline to the 24-week endpoint was used to demonstrate the equivalence of efficacy between LY IGlar and IGlar [7, 8].

To show similarity of the two products, it is important to make comparisons from both inter- and intrasubject perspectives [10]. For LY IGlar and IGlar, similarity in both inter- and intrasubject PK/PD parameters has been shown in three biopharmaceutical studies conducted in healthy subjects [6]. Reports from ELEMENT-1 and ELEMENT-2 showed similarity of glycemic control between LY IGlar and IGlar based on HbA1c [7, 8], which is a good indicator of interpatient (i.e., population average) glycemic control but is not an appropriate indicator of intrapatient glycemic control [11–13]. Patients with the same HbA1c value may have small or large fluctuations in blood glucose profiles over time, as HbA1c does not reflect daily or between-day variations in blood glucose levels. Therefore, previously reported comparisons of LY IGlar and IGlar based on HbA1c have shown that they are similar in glycemic control from an interpatient perspective, but considering the limitations of HbA1c in reflecting blood glucose variability, the intrapatient perspective needs to be further assessed. Additionally, differences between Asians and Caucasians in, for example, genetic susceptibility to diabetes and underlying pathophysiology, body mass index, diet, insulin dose requirements, and postprandial hyperglycemia, have been suggested/reported [14, 15]. Given these differences, blood glucose variability data in such a subpopulation is of clinical interest not only in Japan but also in other East Asian countries. The ELEMENT-1 study included a Japanese subpopulation as an East Asian subpopulation and thus allowed for a separate analysis. Accordingly, the aim of this study was to evaluate and compare the intrapatient variability of daily blood glucose values in patients treated with LY IGlar and IGlar in the overall population of patients with T1D and in the subgroup of Japanese patients in ELEMENT-1, and in the overall population of patients with T2D in ELEMENT-2.

METHODS

Study Design

In this report, data from ELEMENT-1 and ELEMENT-2 were analyzed. Detailed study methods and results for the primary endpoints for both studies have been reported [7, 8] as well as those for the subgroup analysis of Japanese patients in ELEMENT-1 [16]. ELEMENT-1 was a 52-week open-label study of patients with T1D being treated with basal and bolus insulin; it included a 24-week treatment period and a 28-week extension period [7]. ELEMENT-2 was a 24-week double-blind study of patients with T2D who were insulin-naive or previously treated with IGlar [8]. In both studies, patients were randomized to LY IGlar or IGlar treatment. The initial dose was equivalent to their prestudy insulin dose, except that patients with T2D who were insulin-naive started with 10 units of LY IGlar or IGlar. The LY IGlar or IGlar dose was titrated on the basis of daily blood glucose levels [7, 8]. Both of these studies were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki [17],

and all patients provided written informed consent [7, 8]. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Outcomes

Intrapatient blood glucose variability with LY IGlar and IGlar was assessed and compared using three measures of variability derived from 7-point self-monitored blood glucose (SMBG) profiles (premeal for each meal, postmeal for breakfast and lunch, bedtime, and 03:00 h), which were collected three times in the 2-week period before each clinic visit. Patients visited the clinic at weeks 0 (baseline), 2, 6, 12, 18, 24, 30, 36, 44, and 52 in ELEMENT-1 and at weeks 0 (baseline), 2, 12, and 24 in ELEMENT-2.

The three measures of variability analyzed were intrapatient between-day FBG variability, intrapatient between-day daily mean blood glucose variability, and intrapatient within-day blood glucose variability. Intrapatient between-day FBG variability for each visit was calculated as the standard deviation (SD) of the three morning premeal blood glucose values. Intrapatient between-day daily mean blood glucose variability for each visit was calculated as the SD of the three daily means of the 7-point SMBG profiles. Intrapatient within-day blood glucose variability for each visit was calculated as the mean of the three SDs of the 7-point SMBG profiles.

Statistical Analysis

The analysis population was comprised of all randomized patients who took at least one dose of study drug. If the measurement for a visit was missing, the previous non-missing measurement was analyzed using last observation carried forward (LOCF) methodology. HbA1c is shown in the NGSP value as recommended by the Japan Diabetes Society [18]. Each measurement was analyzed using an analysis of covariance model with country, time of basal insulin injection (daytime, evening/bedtime), and treatment as fixed effects, and baseline HbA1c

as covariate. The analyses described in this manuscript were prespecified in the study protocol and/or statistical analysis plan.

RESULTS

In ELEMENT-1, 535 patients with T1D were included in the analysis (268 LY IGlar and 267 IGlar). Of these, 100 were Japanese patients (49 LY IGlar and 51 IGlar). In ELEMENT-2, 756 patients with T2D were included in the analysis (376 LY IGlar and 380 IGlar). No Japanese patients were included in ELEMENT-2.

Least-squares (LS) means of intrapatient between-day FBG variability in both treatment groups ranged from 36.3 to 46.7 mg/dL in the overall population of patients with T1D, and from 33.2 to 56.3 mg/dL in the subgroup of Japanese patients. There were no statistically significant differences at any visit or at endpoint (LOCF) in patients with T1D, except for two visits (weeks 6 and 52) in the overall population, where the values were significantly lower in the LY IGlar group compared with the IGlar group (Fig. 1a, b). In the population with T2D, LS means of intrapatient between-day FBG variability in both treatment groups ranged from 13.7 to 18.4 mg/dL, and no statistically significant differences were observed at any visit or at endpoint (LOCF) (Fig. 1c).

LS means of intrapatient between-day daily mean blood glucose variability in both treatment groups ranged from 15.6 to 21.5 mg/dL in the overall population with T1D and from 22.1 to 30.8 mg/dL in the subgroup of Japanese patients. There were no statistically significant differences between treatment groups at any visit or at endpoint (LOCF) in patients with T1D (Fig. 2a, b). In the population with T2D, LS means of intrapatient between-day daily mean blood glucose variability in both treatment groups ranged from 9.8 to 14.0 mg/dL, and no statistically significant differences were observed at any visit or at endpoint (LOCF) (Fig. 2c).

LS means of intrapatient within-day blood glucose variability in both treatment groups ranged from 44.1 to 56.7 mg/dL in the overall population with T1D and from 49.1 to 64.8 mg/
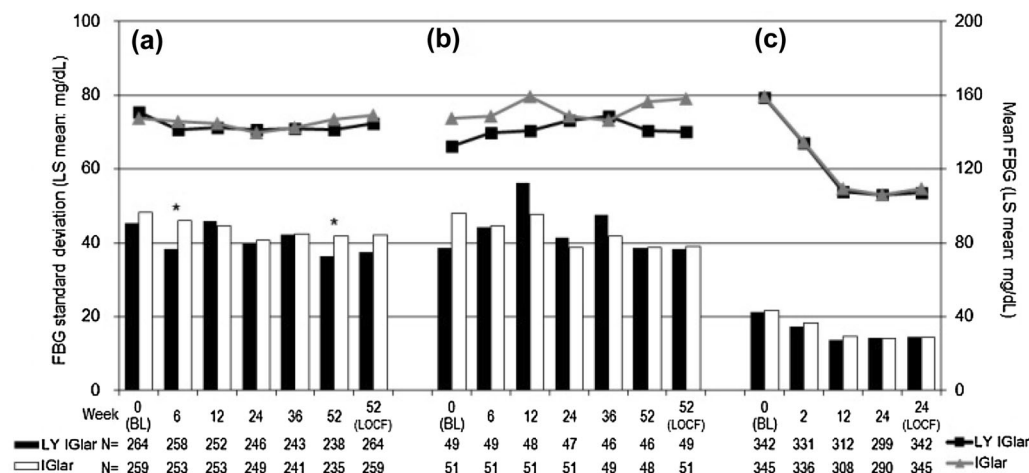
Fig. 1 Intrapatient between-day FBG variability. **a** All patients with T1D. **b** Japanese patients with T1D. **c** Patients with T2D. Intrapatient between-day FBG variability calculated using standard deviation of FBG from SMBG (standard deviation of 3 values per visit) (bar graph; left axis). To display dispersion, mean FBG is also shown (line graph; right axis). Treatment comparisons at each visit were analyzed using ANCOVA: *$p < 0.05$ LY IGlar vs IGlar. For **a** and **b**, data from weeks 2, 18, 30, 44, and week 24 (LOCF) are not shown. No statistical significance was observed at these visits or endpoints. ANCOVA analysis of covariance, BL baseline, FBG fasting blood glucose, IGlar Lantus insulin glargine, LOCF last observation carried forward, LS least-squares, LY IGlar LY2963016 insulin glargine, N number of patients with data, SMBG self-monitored blood glucose, T1D type 1 diabetes, T2D type 2 diabetes

dL in the subgroup of Japanese patients. There were no statistically significant differences between treatment groups at any visit or at endpoint (LOCF) in patients with T1D (Fig. 3a, b). In the population with T2D, LS means of intrapatient within-day blood glucose variability in both treatment groups ranged from 32.1 to 40.0 mg/dL, and no statistically significant differences were observed at any visit or at endpoint (LOCF) (Fig. 3c).

DISCUSSION

This is the first report of comparisons of intrapatient blood glucose variability between LY IGlar and IGlar using data from the ELEMENT-1 and ELEMENT-2 studies. In this analysis, intrapatient blood glucose variability was assessed and compared using three measures: intrapatient between-day FBG variability, intrapatient between-day daily mean blood glucose variability, and intrapatient within-day blood glucose variability.

Intrapatient between-day FBG variability showed day-to-day variability of FBG, which was used as part of dose adjustment algorithms in both ELEMENT-1 and ELEMENT-2, as it is used in actual clinical settings. Intrapatient between-day daily mean blood glucose variability and intrapatient within-day blood glucose variability were calculated using all measurements from 7-point SMBG profiles to show day-to-day and within-day variability in blood glucose, respectively. All three measures of intrapatient blood glucose variability after treatment with LY IGlar were similar to those with IGlar in the overall populations of patients with T1D and T2D and in the subgroup of Japanese patients with T1D.

In the LY IGlar development program, phase 1 studies with healthy volunteers showed similarities of both inter- and intrasubject PK and PD between LY IGlar and IGlar in an experimental setting using euglycemic clamps [6]. Similarity of average interpatient glycemic control (i.e., HbA1c) with LY IGlar and IGlar has also been reported in ELEMENT-1 and
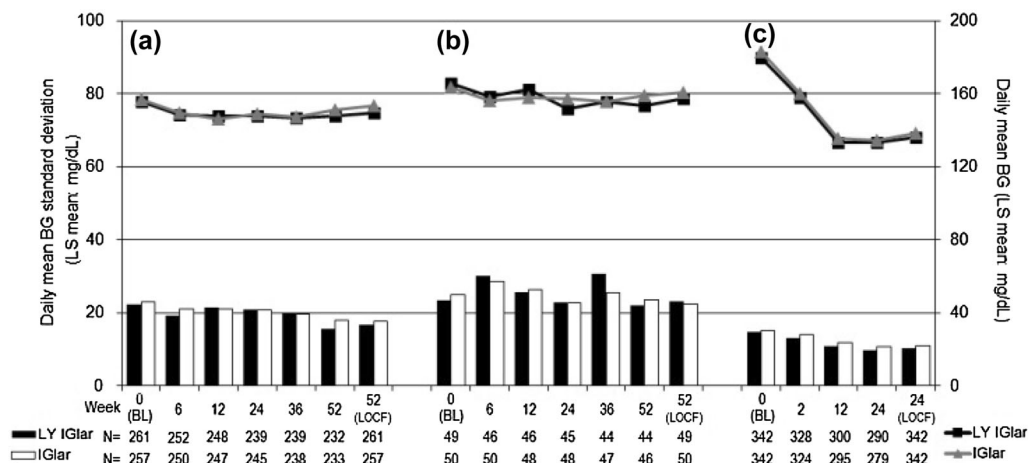
Fig. 2 Intrapatient between-day daily mean BG variability. **a** All patients with T1D. **b** Japanese patients with T1D. **c** Patients with T2D. Intrapatient between-day daily mean BG variability calculated using standard deviation of daily mean BG from 7-point SMBG profiles (standard deviation of 3 values per visit) (bar graph; left axis). To display dispersion, daily mean BG is also shown (line graph; right axis). Treatment comparisons at each visit were analyzed using ANCOVA; not significant at all visits. For **a** and **b**, data from weeks 2, 18, 30, 44, and week 24 (LOCF) are

not shown. No statistical significance was observed at these visits or endpoints. ANCOVA analysis of covariance, BG blood glucose, BL baseline, IGlar Lantus insulin glargine, LOCF last observation carried forward, LS least-squares, LY IGlar LY2963016 insulin glargine, N number of patients with data, SMBG self-monitored blood glucose, T1D type 1 diabetes, T2D type 2 diabetes
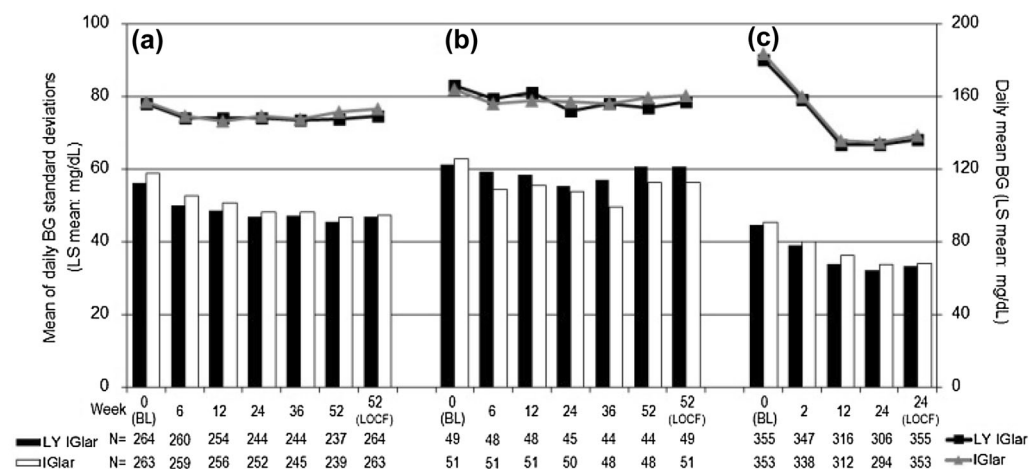

Fig. 3 Intrapatient within-day BG variability. **a** All patients with T1D. **b** Japanese patients with T1D. **c** Patients with T2D. Intrapatient within-day daily mean BG variability calculated using mean of daily BG standard deviations from 7-point SMBG profiles (mean of 3 values per visit) (bar graph; left axis). To display dispersion, daily mean BG is also shown (line graph; right axis). Treatment comparisons at each visit were analyzed using ANCOVA; not significant at all visits. For **a** and **b**, data from weeks 2,

18, 30, 44, and week 24 (LOCF) are not shown. No statistical significance was observed at these visits or endpoints. ANCOVA analysis of covariance, BG blood glucose, BL baseline, LOCF last observation carried forward, LS least-squares, N number of patients with data, SMBG self-monitored blood glucose, T1D type 1 diabetes, T2D type 2 diabetes

ELEMENT-2 [7, 8]; however, average interpatient HbA1c values cannot be used to appropriately estimate intrapatient glycemic control [11–13]. Assessment of intrapatient blood glucose variability of LY IGlar and IGlar using data from ELEMENT-1 and ELEMENT-2 (conducted in settings more similar to that of regular clinical practice than the biopharmaceutical studies mentioned above) indicated that intrapatient glycemic control was also similar between LY IGlar and IGlar. In combination with the similarity in interpatient average glycemic control reported previously, comprehensive similarity in glycemic control has been demonstrated for LY IGlar and IGlar in patients with T1D or T2D.

Since blood glucose variability captures fluctuations in daily glucose profiles, it is also considered a predictor of hypoglycemia [19]. Even though HbA1c has been used as the primary measure of glycemic control, it only reflects long-term (over 1–2 months) average blood glucose levels. HbA1c cannot capture shorter-term fluctuations and is only weakly associated with the risk of severe hypoglycemia [20]. The results from this analysis further support the similarity of glycemic control achieved with LY IGlar and IGlar in both the short (as measured by blood glucose variability) and the long term (as measured by HbA1c).

One limitation of this analysis is that the blood glucose variability measures were derived from 7-point SMBG profiles, which only provide snapshots of glucose concentrations, unlike continuous glucose monitoring, which captures blood glucose levels over time [21]. Even though the studies were designed to collect data at the times when maximum and minimum blood glucose were likely to be observed, actual maximum and minimum values may not have been captured.

CONCLUSIONS

Intrapatient blood glucose variability was similar between LY IGlar and IGlar in patients with T1D or T2D. In addition, the intrapatient blood glucose variability measures were also similar between LY IGlar and IGlar in a subgroup of Japanese patients with T1D. This analysis of intrapatient blood glucose variability provides additional support for the similarity of LY IGlar and IGlar.

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Data Availability. The data sets analyzed during the current study are not publicly available. Lilly provides access to the individual patient data from studies on approved medicines and indications as defined by the sponsor-specific information on http://clinicalstudydatarequest.com. Researchers need to have an approved research proposal submitted through http://clinicalstudydatarequest.com. Access to the data will be provided in a secure data sharing environment after signing a data sharing agreement.

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