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Efficacy and safety of insulin glulisine in Japanese patients with type 1 diabetes mellitus

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Aim: The rapid-acting insulin analogue insulin glulisine (glulisine) was compared with insulin lispro (lispro) for efficacy and safety in Japanese patients with type 1 diabetes mellitus (T1DM), using insulin glargine (glargine) as basal insulin.

Methods: This was an open, randomized, parallel-group, comparative non-inferiority study. The primary efficacy measure was change in adjusted mean haemoglobin A1c (HbA1c) from baseline to endpoint. Safety and treatment satisfaction using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) were also assessed. Patients were treated for 28 weeks with either glulisine or lispro administered 0–15 min before a meal. Doses were titrated to obtain 2-h postprandial plasma glucose (2h-PPG) of 7.11–9.55 mmol/l (128–172 mg/dl). All patients were concomitantly treated with glargine at bedtime, titrated to obtain a fasting (prebreakfast) plasma glucose level of 5.27–7.11 mmol/l (95–128 mg/dl).

Results: Baseline mean HbA1c values were similar for the glulisine (n = 132) and lispro (n = 135) groups (7.44 and 7.50% respectively). From baseline to endpoint, adjusted mean HbA1c increased by 0.10% in the glulisine group and by 0.04% in the lispro group. Non-inferiority of glulisine compared with lispro was shown. There were no significant differences between glulisine and lispro in adjusted mean 2h-PPG [glulisine, 9.06 mmol/l (163 mg/dl) vs. lispro, 8.13 mmol/l (146 mg/dl); p = 0.065] and change in adjusted mean daily rapid-acting insulin dose (glulisine, 0.26 U vs. lispro, 0.26 U; p = 0.994) at study endpoint. There was a significant difference for change in adjusted mean daily basal insulin dose from baseline to study endpoint (glulisine, −0.54 U vs. lispro, 0.26 U; p = 0.013). The most common serious adverse events were hypoglycaemia-related events (hypoglycaemia, hypoglycaemic seizure and hypoglycaemic coma) with no difference observed between the two groups [glulisine, 6.8% (9/132) vs. lispro, 4.4% (6/135); p = 0.437]. No noteworthy differences were observed for change in insulin antibodies from baseline to endpoint. Assessment of treatment satisfaction score and perceived frequency of hyperglycaemia and hypoglycaemia by DTSQ showed no changes from baseline in either group.

Conclusions: Glulisine was as effective as lispro with respect to change in HbA1c and was well tolerated when used in combination with glargine in Japanese patients with T1DM.

Keywords: HbA1c, insulin glulisine, type 1 diabetes mellitus
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Introduction

The Diabetes Control and Complications Trial demonstrated that intensified glycaemic control reduces the risk of the microvascular complications of type 1 diabetes mellitus (T1DM) [1–3]. The principal goal in the management of T1DM is to achieve normal blood glucose concentrations. Mimicking natural mealtime insulin profiles is a challenge in diabetes management with the goal of providing adequate control of blood glucose levels to avoid both postprandial hypo and hyperglycaemia.

Use of regular human insulin (RHI) has limitations in preventing postprandial hyperglycaemia, as its slow time to peak action requires administration 30–45 min before meals [4]. Rapid-acting insulin analogues were designed to overcome the limitations of RHI by providing a rapid onset of glucose-lowering activity and a shorter time to peak action, thus leading to tighter glycaemic control, particularly at mealtimes.

Insulin glulisine (glulisine) is a recombinant human insulin analogue in which asparagine at position B3 has been replaced by lysine, and lysine at position B29 has been replaced by glutamic acid. These amino acid replacements result in a more rapid onset and shorter duration of activity because of more rapid absorption after subcutaneous (SC) administration compared with RHI [5]. Glulisine shows both low self-association and stability in monomeric and dimeric forms in solution in the absence of zinc, thereby allowing it to be absorbed faster than RHI after SC injection. This confers a more rapid onset of action and adds to the flexibility of postprandial blood glucose control [6]. Consequently, glulisine can be administered within 15 min before or immediately after a meal, compared with 30 min before a meal for RHI [5,7]. Moreover, glulisine showed a faster onset of action than insulin lispro (lispro) in healthy volunteers across a wide range of body mass indices (BMIs) [8].

Rapid-acting insulin analogues are well suited as bolus insulin when used with basal insulins, such as glargine, for the treatment of patients with T1DM [9]. Good glycaemic control has been shown in patients with T1DM, where glulisine given in combination with glargine was non-inferior to lispro and RHI in terms of haemoglobin A1c (HbA1c) [10,11]. Glulisine was well tolerated, without notable or consistent differences from lispro or RHI in the incidence or type of adverse events [10–12].

Improvements to overall treatment effectiveness can have a positive impact on patients' satisfaction with treatment, which can be assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [13,14]. Rapid-acting insulin analogues, glargine monotherapy and their combination have been shown to improve treatment satisfaction when compared with older treatment regimens [15–19]. Treatment satisfaction was included as a secondary endpoint in the current study.

Current treatment practice in Japan is to start insulin treatment once T1DM is diagnosed, which is followed by a continuous insulin regimen tailored to the patient's requirements such as a regimen of rapid-acting (bolus) insulin in combination with long-acting (basal) insulin, to achieve and maintain good glycaemic control [20]. Interestingly, insulin analogues (including glulisine) appear to have slightly faster absorption, higher exposure and corresponding action–time characteristics in a Japanese population compared with a Caucasian population [6]. Considering these differences, basal–bolus therapy might be affected; therefore, it was considered important to conduct a study in a Japanese diabetic population to confirm the safety and efficacy of such a regimen following confirmation in a more racially diverse population [10].

The primary objective of this study was to demonstrate non-inferiority of glulisine in glycaemic control compared with lispro on a basal–bolus insulin regimen using glargine in Japanese patients with T1DM.

Methods

This was a randomized, open-label, parallel-group, multicentre, comparative, non-inferiority clinical study conducted among Japanese patients with T1DM at 24 sites in Japan from 2004 to 2006. The study was approved by the appropriate Institutional Review Boards and was performed in full compliance with good clinical practice and the principles of the Declaration of Helsinki, including amendments. Written informed consent was obtained from each participating patient before the study.

Eligible patients were Japanese outpatients aged $\geq$18 and $\leq$75 years with T1DM, who had at least 1 year of continuous insulin treatment who were treated with bolus insulin before every meal and a basal insulin once or twice daily for at least 12 weeks before informed consent. They could not be receiving treatments or have diseases considered to interfere with the conduct of the study. All patients were to have a BMI $<$35 kg/m^2, HbA1c $\geq$6.0%–11.0% and 2-h postprandial serum C-peptide concentrations $<$0.333 nmol/l (1.0 ng/ml).

Diet Therapy and Exercise Therapy

Investigators checked whether a patient's diet and exercise were adequate during the screening phase. If inadequate, the patient was provided with instructions for intensive diet and exercise therapies until the start of the run-in phase. The diet and exercise therapies were to be continued without change during the run-in and treatment phases.

Treatment Regimens

The study consisted of a 4-week screening phase, a 4-week lispro and glargine run-in phase, and a 28-week treatment phase (figure 1). Eligible patients were randomly assigned (minimization method) to either glulisine or lispro treatment in a 1:1 ratio. All doses were adjusted throughout the study by self-monitoring of blood glucose (SMBG) values, symptoms and laboratory findings, with attention given to any events of hypoglycaemia. All SMBG values were measured using a plasma-referenced blood glucose meter.

In the run-in phase, lispro and glargine doses were initially determined by reference to the doses of insulin in the patient's prior treatment regimen. The titration goal for lispro was a 2-h postprandial plasma glucose (2h-PPG) value (by SMBG) of 7.11–9.55 mmol/l (128–172 mg/dl) and for glargine, a fasting (pre-breakfast) plasma glucose (FPG) value (by SMBG) of 5.27–7.11 mmol/l (95–128 mg/dl). During the treatment phase, the starting dose for glulisine was determined after review of the patient's clinical data at the last visit in the run-in phase, with appropriate adjustment to meet the titration goals. For patients randomized to glulisine, the dose was to be the same as that in the lispro run-in phase. The titration goal for glulisine was a 2h-PPG value (by SMBG) of 7.11–9.55 mmol/l (128–172 mg/dl); the glargine and lispro titration goals remained unchanged during the run-in and treatment phases.

Glulisine and lispro were self-injected via the SC route 0–15 min before each meal via the OptiPen® Pro1 and HumaPen® Ergo devices respectively. Glargine was self-injected SC once daily at bedtime via the OptiPen® Pro1 device for both treatment groups. Glulisine and lispro could be injected into the abdomen, thigh or upper arm, although patients were strongly encouraged to use the abdominal area as the preferred injection site.

Assessments and Outcome Definitions

The primary efficacy variable was the mean change in HbA1c from baseline to endpoint. The endpoint for each patient was defined as the last available HbA1c value measured during the treatment phase.

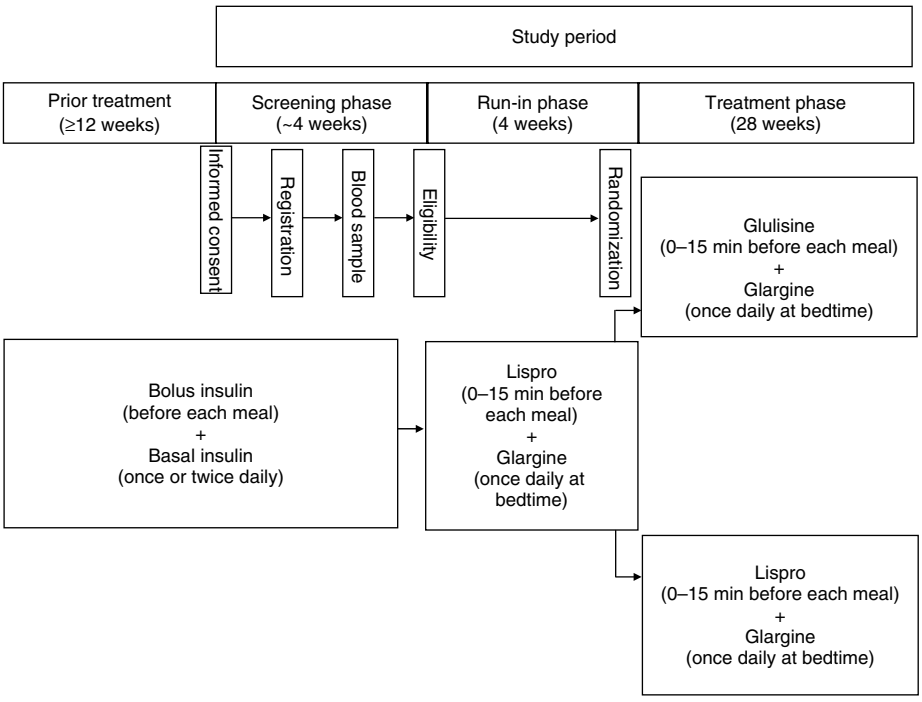

Fig. 1 Study timeline portraying scheduled interventions.

Secondary efficacy variables included the following: changes in HbA1c from baseline to weeks 4, 8, 12, 16, 20, 24 and 28; consecutive changes from baseline in HbA1c assessed every 4 weeks to week 28; changes in 2h-PPG from baseline to week 12, week 28 and endpoint; consecutive changes in the 7-point blood glucose profile (preprandial and 2-h postprandial measurements for breakfast, lunch and evening meal and a bedtime measurement, by SMBG from baseline to week 12, week 28 and endpoint); blood glucose excursions, calculated as the difference between the preprandial blood glucose value and the corresponding 2h-PPG value (by SMBG) at baseline, week 12, week 28 and endpoint; changes in insulin doses from baseline to weeks 4, 8, 12, 28 and endpoint; and the incidence of symptomatic hypoglycaemia, which was defined as an event with clinical symptoms that were considered by the patient to be due to hypoglycaemia.

Safety was assessed by recording adverse events (including severe symptomatic hypoglycaemia), routine laboratory values (haematology and biochemistry), antibody (insulin and *Escherichia coli* protein) levels, body weight, sedentary blood pressure, standard 12-lead electrocardiogram and funduscopic examination.

Treatment satisfaction was a secondary outcome and was assessed using the DTSQ [14,21,22] during the screening phase, at baseline and at week 28 (or withdrawal). The overall treatment satisfaction score was calculated as the sum of DTSQ item 1, Satisfaction; item 4, Convenience; item 5, Flexibility; item 6, Understanding; item 7, Recommend to others; and item 8, Wish to continue. Item 2, Perceived hyperglycaemia frequency, and item 3, Perceived hypoglycaemia frequency were treated as separate variables. The quality of life instrument was not designed to measure treatment satisfaction related to the device.

Statistical Analyses

Efficacy and safety variables were analysed using the intention-to-treat (ITT) population. The ITT population was defined as all patients randomized and treated with at least one dose of the study medication during the treatment phase. For some continuous variables, only those with both a baseline value and at least one value during the treatment phase were included in the analysis.

The primary efficacy analysis of change in HbA1c from baseline to endpoint was conducted using an analysis of covariance (ANCOVA) model, with treatment as fixed effect and baseline HbA1c as covariate. A two-sided 95% confidence interval (CI) was calculated for the adjusted mean difference between treatment groups from the ANCOVA model. Non-inferiority of glulisine in comparison with lispro was shown if the upper boundary of the two-sided 95% CI was below the predefined non-inferiority margin of 0.45%.

The rationale for using this non-inferiority margin is as follows. According to the report of the HbA1c standardization committee of the Japan Diabetes Society [23,24], a difference of 5.7–5.8% in observed values is considered a clinically significant change in blood glucose control. The inclusion criterion for HbA1c in this study was HbA1c $\geq$6.0 and $\leq$11.0%. Assuming that the mean HbA1c of the enrolled subjects is 8.0%, a change in HbA1c exceeding 0.456% (8.0% $\times$ 0.057) may be considered of clinical significance; therefore, a change in HbA1c exceeding 0.45% would be clinically important. In addition, in the two Japanese phase III clinical studies investigating glargine [25,26], the non-inferiority margin of 0.45% was used.

An ANCOVA model was also used for secondary efficacy variables. Analyses of hypoglycaemia, treatment satisfaction and antibody variables used a ranked ANCOVA model with treatment as fixed effect and corresponding ranked baseline values as covariates. Changes from baseline to each visit and endpoint in insulin antibody variables were analyzed within treatment group using a Wilcoxon signed rank sum test. Fisher's exact test was used for treatment-emergent adverse-event (TEAE) evaluation.

In addition, descriptive statistics and frequency tables were also provided for continuous variables and categorical variables respectively. All statistical tests were two-sided and p values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS® version 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Disposition and Analysis Populations

Patient flow through the study is summarized in figure 2. The ITT population comprised 267 patients, all of whom were treated as randomized.

Baseline demographics and clinical characteristics were similar in both groups (table 1); however, there were non-significant differences in gender proportions (37.9% of patients in the glulisine group were male vs. 46.7% of patients in the lispro group), and the duration of diabetes and duration of previous insulin treatment were slightly longer in the glulisine than the lispro group. Adherence to treatment throughout was similar in both groups (data not shown).

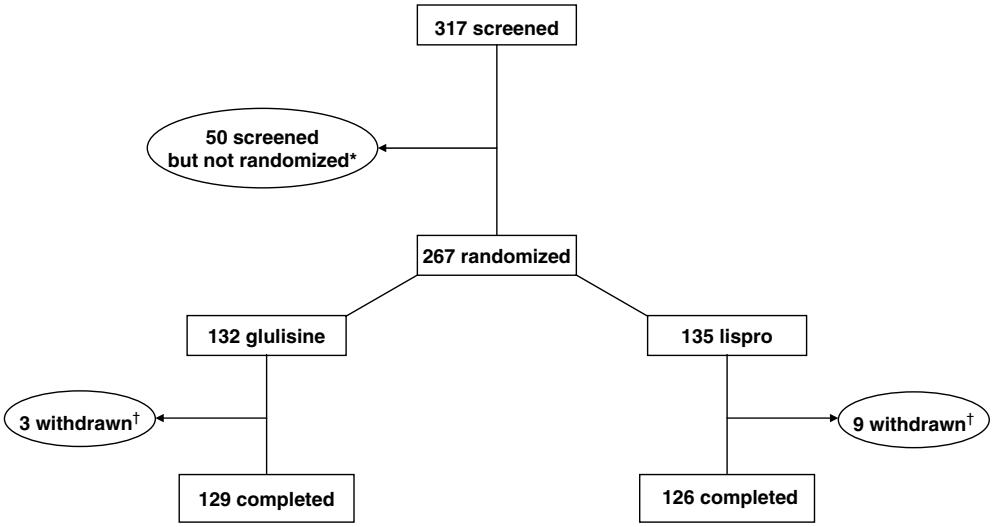

Fig. 2 Patient disposition. All randomized patients were treated. *The most common reasons for screening failure were that serum C-peptide was ≥0.333 ngolli (1.0 ng/ml) at the screening visit (27 patients) or HbA1c level was not within the specified range for inclusion (eight patients). †The most common reasons for withdrawal were 'subject did not wish to continue' and 'other', each of which affected five patients.

Table 1 Demographics and clinical characteristics at baseline (intention-to-treat population)

	Treatment		
Characteristic	Glulisine (n = 132)	Lispro (n = 135)	Total (n = 267)
Male, n (%)	50 (37.9)	63 (46.7)	113 (42.3)
Age (years)	38.9 ± 14.3	38.8 ± 12.9	38.9 ± 13.6
Aged ≥ 65 years, n (%)	8 (6.1)	4 (3.0)	12 (4.5)
BMI (kg/m^2)	23.11 ± 2.91	22.81 ± 2.70	22.96 ± 2.81
HbA1c (%)	7.44 ± 0.93	7.50 ± 0.96	7.47 ± 0.94
Age at diabetes diagnosis (years)	26.8 ± 17.3	28.4 ± 15.7	27.7 ± 16.5
Duration of diabetes (years)	12.8 ± 9.5	11.1 ± 7.1	11.9 ± 8.4
Duration of previous insulin treatment (years)	12.8 ± 9.1	11.5 ± 7.0	12.1 ± 8.1

Data are arithmetic means ± s.d. unless otherwise noted. BMI, body mass index; HbA1c, haemoglobin A1c.

At study entry, the most common bolus insulin in both treatment groups was rapid-acting insulin (87.1 and 88.1% of glulisine- and lispro-treatment patients respectively) with the remaining patients receiving RHI. The most common basal insulin in both treatment groups was glargine (78.8 and 77.0% in the glulisine and lispro groups respectively) with the remaining patients receiving NPH insulin. Patients were treated with lispro and glargine in a 4-week run-in phase to stabilize glucose levels following any changes in insulin treatment.

Clinical Outcomes

Haemoglobin A1c

Based on the predefined non-inferiority margin of 0.45%, glulisine was non-inferior to lispro, as the upper boundary of the two-sided 95% CI (−0.09 to 0.21%) was below 0.45%. Glycaemic control (change in HbA1c from baseline to endpoint) was similar for both groups, with an adjusted mean increase of 0.10% in the glulisine group and 0.04% in the lispro group (table 2).

Over time, mean HbA1c values compared with baseline were similar in the glulisine and lispro treatment groups, with values decreasing in both groups until week 4 (glulisine, −0.18% vs. lispro, −0.12%) and then increasing slightly from week 12 (glulisine, −0.15% vs. lispro, −0.17%) until week 28 (glulisine, 0.10% vs. lispro, 0.08%).

Blood Glucose Profiles

The 2h-PPG values at baseline were 7.73 mmol/l (139.22 mg/dl) and 8.17 mmol/l (147.24 mg/dl) for glulisine- and lispro-treated patients respectively. There were no noteworthy differences between glulisine and lispro for adjusted mean 2h-PPG [glulisine, 9.06 mmol/l (163.26 mg/dl) vs. lispro, 8.13 mmol/l (146.39 mg/dl);

Table 2 Change in HbA1c (%) from baseline to endpoint (intention-to-treat population)

	HbA1c (%)		
Time point	**Glulisine (n = 132)**	**Lispro (n = 135)**	**Glulisine vs. lispro difference (95% CI)***
Baseline			
Mean ± s.d.	7.44 ± 0.93	7.50 ± 0.96	—
Endpoint			
Mean ± s.d.	7.54 ± 0.97	7.54 ± 0.98	—
Change from baseline at endpoint			
Mean ± s.d.	0.10 ± 0.71	0.03 ± 0.58	—
Adjusted mean ± s.e.†	0.10 ± 0.05	0.04 ± 0.05	0.06 ± 0.076 (−0.09 to 0.21)

CI, confidence interval; HbA1c, haemoglobin A1c; s.e., standard error.
*95% CIs were compared with the non-inferiority margin of 0.45%.
†Change from baseline was analysed using an analysis of covariance with treatment and the corresponding baseline value as factors.

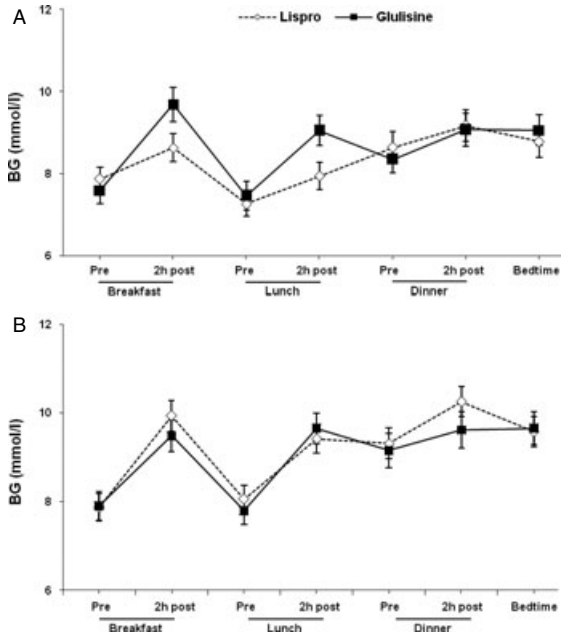

Fig. 3 Mean blood glucose (BG) profile over of the duration of a day (intention-to-treat population). A, at baseline; B, at endpoint. Error bars indicate standard error. All BG values were measured using plasma-referenced blood glucose meter.

p = 0.0647] at endpoint. The daily blood glucose profiles over the duration of a day at baseline and at endpoint are shown in figure 3. Blood glucose excursions were measured at breakfast, lunch and dinner, all of which showed no significant differences between groups. Similarly, there was no statistically significant difference between groups for adjusted mean daily blood glucose excursions [glulisine, 1.15 mmol/l (20.78 mg/dl) vs. lispro, 1.57 mmol/l (28.22 mg/dl); p = 0.2290] at endpoint.

Insulin Doses

Adjusted mean within-treatment changes in daily rapid-acting insulin doses were similar for both groups from baseline to endpoint (0.26 U both groups; p = 0.9935), but daily basal insulin doses were significantly reduced with glulisine compared with lispro (−0.54 U vs. 0.26 U respectively; p = 0.0132; table 3). Adjusted mean change from baseline to endpoint for total daily insulin dose was reduced by 0.25 U in the glulisine group, but increased by 0.50 U in the lispro group; however, the difference was not significant (p = 0.2819).

Hypoglycaemia

The mean monthly rate (events per patient-month) of all symptomatic hypoglycaemia (glulisine, 3.93 vs. lispro, 3.86; p = 0.1642), severe symptomatic hypoglycaemia (glulisine, 0.02 vs. lispro, 0.02; p = 0.6583) and severe nocturnal symptomatic hypoglycaemia (glulisine, 0.00 vs. lispro, 0.01; p = 0.6637) events were similar for both groups throughout the entire treatment phase.

Safety

The incidence of TEAEs was similar in the two treatment groups, although overall slightly fewer patients in the glulisine group [75.0% (99/132)] had TEAEs than in the lispro group [80.0% (108/135)]. Slightly fewer patients in the lispro group experienced TEAEs possibly related to the study treatment [6.7% (9/135)] or serious TEAEs [5.9% (8/135)] than did patients in the glulisine group [9.1% (12/132) and 7.6% (10/132) respectively]. The most common serious TEAEs were those related to hypoglycaemia [glulisine, 6.8% (9/132) vs. lispro, 4.4% (6/135); p = 0.4370]. There were no TEAEs that led

Table 3 Change in insulin dose from baseline to endpoint (intention-to-treat population)

Time point; insulin dose type	Mean dose ± s.e.		Difference (95% CI) (glulisine−lispro)	p value
	Glulisine (n = 131)	Lispro (n = 135)		
Baseline*				
Total daily	45.28 ± 1.579	47.96 ± 1.556	−2.68 ± 2.217 (−7.05 to 1.68)	0.2276
Daily rapid-acting	29.59 ± 1.161	31.70 ± 1.144	−2.11 ± 1.630 (5.32 to 1.10)	0.1970
Daily basal	15.69 ± 0.634	16.26 ± 0.625	−0.57 ± 0.890 (−2.33 to 1.18)	0.5210
Change from baseline to endpoint†				
Total daily	−0.25 ± 0.495	0.50 ± 0.488	−0.75 ± 0.696 (−2.12 to 0.62)	0.2819
Daily rapid-acting	0.26 ± 0.400	0.26 ± 0.394	0.00 ± 0.562 (−1.10 to 1.11)	0.9935
Daily basal	−0.54 ± 0.226	0.26 ± 0.223	−0.79 ± 0.318 (−1.42 to −0.17)	0.0132

CI, confidence interval; s.e., standard error.

*Baseline was compared between treatments using an analysis of variance with treatment as a factor.

†Change from baseline was analysed using an analysis of covariance with treatment and the corresponding baseline value as factors.

to death in this study. No patients receiving glulisine were withdrawn because of TEAEs. Two patients in the lispro group withdrew from the study because of severe cellulitis (n = 1) and intervertebral disc protrusion of moderate intensity (n = 1).

Antibodies

At endpoint, median cross-reactive and human insulin-specific antibody levels had decreased relative to baseline in the glulisine group. The percentage of patients with increases in cross-reactive antibodies exceeding the 95% quantile was similar for the two treatment groups: 5.4% (7/130) in the glulisine group vs. 4.5% (6/134) in the lispro group. A slight increase from baseline to endpoint in glulisine-specific antibody formation was noted in the glulisine group (+0.010% of bound antibodies in relation to the total). No patients in either treatment group showed abnormal changes in *E. coli* protein antibody from baseline to week 28 or from baseline to endpoint (data not shown).

Body Weight

No significant changes in body weight from baseline to any of the evaluable time points were observed for either treatment group (data not shown).

Treatment Satisfaction

Median (range) DTSQ scores at baseline were 25.0 (6 to 36) and 24.0 (9 to 36) for glulisine- and lispro-treatment patients respectively, and mean (range) change from baseline to endpoint was 0.0 (−15 to 13) and 0.0 (−16 to 11) respectively. There were no statistically significant differences between the two treatment groups for change in treatment satisfaction score (the sum of items 1, 4, 5, 6, 7 and 8; p = 0.3127) or for changes in the perceived frequency of hyperglycaemia (item 2; p = 0.5448) or hypoglycaemia (item 3; p = 0.2077) at endpoint.

Discussion

This randomized, open-label study is the first to demonstrate non-inferiority for glulisine compared with lispro in achieving glycaemic control in Japanese patients with T1DM, using glargine in a basal-bolus regimen. Glulisine was proved to be non-inferior to lispro with respect to reduction in HbA1c values from baseline to endpoint. Glulisine and lispro showed very similar results in terms of other measures of efficacy including mean 2h-PPG over time, mean daily blood glucose at endpoint, blood glucose excursions and change in mean daily bolus insulin dose over time. Both regimens were equally well tolerated, as indicated by the absence of notable differences in the TEAEs reported for the two regimens.

These data support the results of a similar previous study with participants from different racial groups, in which non-inferiority and similar efficacy and tolerability were shown for the two insulin analogues [10]. The efficacy and safety results for glulisine treatments in subjects with T1DM are shown to be similar for Japanese patients (the current study) and a more racially diverse population [10]. In addition, results from a recent exploratory study in healthy, lean-to-obese subjects show that the early insulin exposure and action of glulisine were slightly, but consistently, greater than with lispro [8]. The improved pharmacokinetic/pharmacodynamic properties of glulisine, as shown by phase I data, may be related to the differences in formulation between glulisine and lispro [6,8,27].

Specifically, glulisine is formulated without zinc, which facilitates its absorption on SC injection and allows for a more rapid onset of action than zinc-formulated insulin analogues. The glulisine regimen also attenuates basal insulin requirements [10]. At endpoint in the current Japanese study, lower doses of basal insulin were needed for patients on the glulisine regimen compared with those on the lispro regimen. However, the differences in daily basal insulin doses were small, and the clinical relevance of this finding needs to be further investigated.

Tight glycaemic control is a very important outcome in T1DM management, as poor control may increase the risk of microvascular complications such as neuropathy, retinopathy and nephropathy [28–31]. Basal-bolus regimens using glargine as basal insulin help maintain good glycaemic control [9]. A glargine-glulisine regimen offers tight glycaemic control with the potential for reduced basal insulin dose; however, both rapid-acting insulin analogues used in this study offer flexibility and convenience, as both can be injected either before or immediately after meals [11,32]. The characteristics of these basal–bolus regimens should appeal to patients and physicians alike.

Quality of life aspects for patients with diabetes regimens may sometimes be overlooked, with some physicians placing greater emphasis on gaining and maintaining good glycaemic control [33]. As outlined above, tight glycaemic control may lead to reduced diabetic complications. However, improvement in quality of life is also an important treatment goal, especially from the patient's perspective, and is another way in which more flexible treatments can impact on patient's lifestyle [34]. In the current study, assessment of treatment satisfaction score and perceived frequency of hyperglycaemia and hypoglycaemia by the DTSQ showed no changes from baseline in either treatment group. A limitation of the assessment of treatment satisfaction in this study is that most patients were using a glargine-rapid-acting insulin regimen before the study; consequently, they would have already had a reasonable degree of treatment satisfaction. Therefore, it would have been more difficult to register any improvements in the DTSQ score from baseline to endpoint in the current study.

In conclusion, glulisine proved to be non-inferior to lispro with respect to reduction in HbA1c from baseline to endpoint in Japanese patients with T1DM, using insulin glargine as basal insulin. No specific safety concerns were raised during the study. Consequently, glulisine may offer the advantage of similar glycaemic control and tolerability as lispro but with a lower basal insulin dose requirement.

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