Insulin Glulisine Provides Improved Glycemic Control in Patients With Type 2 Diabetes

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OBJECTIVE — Insulin glulisine is a novel analog of human insulin designed for use as a rapid-acting insulin. This study compared the safety and efficacy of glulisine with regular human insulin (RHI) in combination with NPH insulin.

RESEARCH DESIGN AND METHODS — In total, 876 relatively well-controlled patients with type 2 diabetes (mean HbA_{1c} 7.55%) were randomized and treated with glulisine/NPH ($n = 435$) or RHI/NPH ($n = 441$) for up to 26 weeks in this randomized, multicenter, multinational, open-label, parallel-group study. Subjects were allowed to continue the same dose of prestudy regimens of oral antidiabetic agent (OAD) therapy (unless hypoglycemia necessitated a dose change).

RESULTS — A slightly greater reduction from baseline to end point of HbA_{1c} was seen in the glulisine group versus RHI (−0.46 vs. −0.30% with RHI; $P = 0.0029$). Also, at end point, lower postbreakfast (156 vs. 162 mg/dl [8.66 vs. 9.02 mmol/l]; $P < 0.05$) and postdinner (154 vs. 163 mg/dl [8.54 vs. 9.05 mmol/l]; $P < 0.05$) blood glucose levels were noted. Symptomatic hypoglycemia (overall, nocturnal, and severe) and weight gain were comparable between the two treatment groups. There were no between-group differences in baseline–to–end point changes in insulin dose.

CONCLUSIONS — Twice-daily glulisine associated with NPH can provide small improvements in glycemic control compared with RHI in patients with type 2 diabetes who are already relatively well controlled on insulin alone or insulin plus OADs. The clinical relevance of such a difference remains to be established.

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Attaining and maintaining normoglycemic control are the treatment goals in type 2 diabetes in order to minimize long-term clinical risk (1). Although oral antidiabetic agents (OADs) may initially control hyperglycemia, most patients with type 2 diabetes will ultimately require insulin therapy, as β-cell function progressively declines (2,3). Ideally, glycemic control in insulin-treated patients should mimic physiologic insulin secretion, thereby maintaining levels as close to normoglycemia as possible at all times. Hence, there should be appropriate prandial replacement of the peaks in insulin activity to complement continuous 24-h basal insulin levels.

Regular human insulin (RHI) has been used as a mealtime therapy for many years. However, its onset of action is relatively slow and the action profile does not closely mimic physiologic mealtime insulin secretion, necessitating its recommended administration 30–45 min before meals (4). This requires meal planning that can be restrictive to patients' lifestyles; indeed, most patients administer RHI <30 min before mealtime (5). RHI is, therefore, unlikely to provide optimal glycemic control in most patients.

Glulisine is a novel rapid-acting insulin analog that differs from human insulin by the replacement of the amino acid asparagine with lysine at position 3 and lysine with glutamic acid at position 29 of the B-chain. Compared with RHI, glulisine has a more rapid onset of action and a shorter duration of action (6). The time-action profile of glulisine thus lends itself to greater treatment convenience compared with RHI, as its use requires less mealtime planning.

This study compared the effects of glulisine (Aventis Pharma) and RHI (Eli Lilly) on HbA_{1c}, self-monitored blood glucose profiles, hypoglycemia, and safety in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Subjects with established type 2 diabetes, aged ≥18 years, who had been on insulin therapy for ≥6 months before the study, with an HbA_{1c} level between 6.0 and 11.0%, were enrolled in the study.

This was a phase III, 1:1 randomized, multicenter, multinational, controlled, open-label, parallel-group study with a 1-week screening, 4-week run-in, and 26-week treatment phase. During run-in, all subjects received RHI and NPH insulin

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Abbreviations: ITT, intention to treat; OAD, oral antidiabetic agent; RHI, regular human insulin; TEAE, treatment-emergent adverse event.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

injections, both given twice daily. The study was conducted in accordance with Good Clinical Practice and conformed to the ethical principles of the Declaration of Helsinki. All study materials were reviewed and approved by an independent ethics committee or institutional review board.

Randomization was stratified according to whether subjects were treated with OADs at randomization. Subjects were randomized to subcutaneous injections of glulisine or RHI 0–15 and 30–45 min, respectively, before breakfast and dinner. If required, based on the clinical judgment of the investigator, more than two injections of glulisine or RHI were permitted. Both treatment groups received twice-daily injections of NPH insulin as basal therapy. The number of meal time insulin injections and the timing of NPH insulin administration were established during run-in and maintained during the treatment phase. Mixing of glulisine or RHI with NPH insulin just before injection was allowed. No formal insulin dose algorithms were given. Adjustment of glulisine and RHI doses was at the investigator's discretion if necessary to achieve 2-h postprandial blood glucose 120–160 mg/dl (6.7–8.9 mmol/l), while avoiding hypoglycemia. NPH insulin doses were adjusted according to a predefined insulin titration regimen to achieve preprandial blood glucose 90–120 mg/dl (5.0–6.7 mmol/l), while avoiding hypoglycemia. Continuation of prestudy OAD dose and regimen was permitted, unless hypoglycemia necessitated a dose reduction for safety reasons.

Glycemic control parameters

HbA_{1c} levels. Glycated hemoglobin in whole blood was analyzed by a single central laboratory (Diabetes Diagnostic Laboratory, Columbia, MS), which was certified by the U.S. National Glycohemoglobin Standardization Program. GHb results were reported as "HbA_{1c} equivalents" and are directly traceable to the Diabetes Control and Complications Trial reference. Measurements were taken at baseline and weeks 12 and 26.

Self-monitored blood glucose profiles. Using self-monitoring devices (plasma-referenced [North America] and whole-blood–referenced [Australia] meters were provided by the study sponsor), seven-point blood glucose profiles (morning fasting [prebreakfast], before lunch and dinner, after all three meals, and at bedtime) were measured on 3 different days in the weeks preceding clinic visits at baseline and weeks 12 and 26. All blood glucose values were converted to whole-blood–referenced blood glucose for consistency in data reporting.

Hypoglycemia

Overall, nocturnal and severe symptomatic hypoglycemia were monitored. Symptomatic hypoglycemia was defined as an event with clinical symptoms considered to result from hypoglycemia. Nocturnal symptomatic hypoglycemia was defined as symptomatic hypoglycemia occurring while the patient was asleep (between bedtime and rising in the morning). Severe symptomatic hypoglycemia was defined as symptomatic hypoglycemia requiring assistance from another person and confirmed by blood glucose <36 mg/dl (<2.0 mmol/l) or associated with prompt recovery following oral carbohydrate, intravenous glucose, or glucagon administration.

Insulin dose

Bolus and basal daily insulin doses and total daily number of injections were recorded.

Safety

Local and systemic treatment-emergent adverse events (TEAEs) were investigator and patient reported. Severe symptomatic hypoglycemia was systematically reported as a possibly related serious TEAE. Lipid levels, *Escherichia coli* antibody levels, hematologic parameters, and clinical chemistry were analyzed. Changes from baseline in insulin antibody levels (cross-reactive, glulisine specific, and human insulin specific) were evaluated as percentage bound radiolabeled insulin of total radiolabeled insulin (% B/T).

Statistical methods

Based on 1:1 randomization and assuming a nonevaluable rate of 20%, 846 subjects (423 per treatment group) needed to be randomized to demonstrate noninferiority of glulisine versus RHI (upper confidence limit of the two-sided 95% CI for the between-treatment adjusted mean difference ≤0.4% HbA_{1c}) with at least 90% power. The primary analysis was comparison of baseline to end point–adjusted change in HbA_{1c} using one-sided ANCOVA at a significance level of $\alpha = 2.5\%$; all other statistical tests were two sided, at a significance level of $\alpha = 5\%$. To assess noninferiority, the upper bound of the CI for the between-treatment difference in the adjusted mean baseline to end point change in HbA_{1c} was compared with the predefined noninferiority margin of 0.4% HbA_{1c}. Noninferiority was demonstrated if the upper bound of CI was <0.4%. If noninferiority was demonstrated, a corresponding check of statistical superiority (upper bound of CI <0.0%) was performed without an α penalty because this is a closed procedure. Changes in HbA_{1c} from baseline to weeks 12 and 26, self-monitored blood glucose, and insulin dose were evaluated by ANCOVA. Baseline between-treatment comparisons for continuous variables were analyzed by ANOVA. Comparisons of hypoglycemia incidence were conducted using the Cochran-Mantel-Haenszel test. Mean values were adjusted for center, stratum, baseline, and OAD use at randomization. The intention-to-treat (ITT) population (all randomized subjects who received study medication) was evaluated for all efficacy and safety variables.

RESULTS — A total of 1,186 patients entered screening; 878 were randomized and 876 received study medication (glulisine: $n = 435$; RHI: $n = 441$). This comprised the ITT population. Of the 876 treated patients, 64 withdrew (glulisine: $n = 28$; RHI: $n = 36$) after treatment start. Main reasons for withdrawal included did not wish to continue (glulisine: $n = 12$; RHI: $n = 13$), lost to follow-up (glulisine: $n = 5$; RHI: $n = 6$), and TEAEs (glulisine: $n = 5$; RHI: $n = 6$).

Baseline characteristics (Table 1) were similar between the two treatment groups, except for age and duration of diabetes. Patients randomized to glulisine were older (mean age 58.9 ± 10.20 years vs. 57.7 ± 9.90 with RHI; $P = 0.04$) and had a significantly longer mean duration of diabetes versus the RHI group (14.7 ± 8.12 vs. 13.4 ± 7.55 years; $P = 0.02$). The majority of subjects in the glulisine and RHI treatment groups used NPH insulin before entry into the study (388 [89.2%] and 386 [87.5%] subjects, respectively). Before the study, premixed insulin was being used by 169 (38.9%) patients in the glulisine group and 169 (38.3%) subjects in the RHI group.

Table 1—*Demographics and baseline characteristics of patients with type 2 diabetes receiving glulisine and RHI (ITT population)*

Variable	Glulisine	RHI	*P*
n	435	441	—
Sex			
Male	244 (56.1)	219 (49.7)	0.07
Female	191 (43.9)	222 (50.3)	—
Age (years)	58.9 ± 10.20	57.7 ± 9.90	0.04
BMI (kg/m^2)	34.60 ± 6.88	34.51 ± 7.02	0.79
Duration of diabetes (years)	14.7 ± 8.12	13.4 ± 7.55	0.02
Age at diagnosis of diabetes (years)	44.8 ± 10.30	44.8 ± 9.68	0.86
HbA_{1c} (%)	7.58 ± 0.937	7.52 ± 0.959	0.51
Mean daily insulin dose (units)			
Basal	59.6 ± 34.70	57.1 ± 31.18	0.40
Short acting	32.5 ± 25.36	31.3 ± 23.57	0.46
OAD use at randomization	245 (56.3)	263 (59.6)	0.32
Race			
White	372 (85.5)	376 (85.3)	—
Black	48 (11.0)	51 (11.6)	—
Asian	8 (1.8)	9 (2.0)	—
Multiracial	7 (1.6)	5 (1.1)	—
Hispanic origin	34 (7.8)	26 (5.9)	—

Data are means ± SD or *n* (%), unless otherwise indicated.

Glycemic control

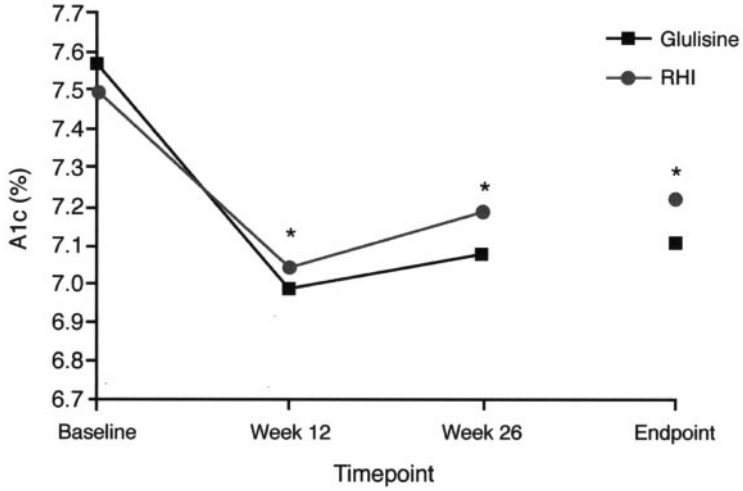
Baseline to end point change in HbA_{1c}. Baseline HbA_{1c} was comparable between the treatment groups (Table 1), and both groups showed significant baseline to end point reductions in mean HbA_{1c} levels (−0.46 and −0.30%, for glulisine and RHI, respectively). Noninferiority of glulisine compared with RHI was demonstrated by virtue of the fact that the upper bound of the 95% CI was <0.4% (baseline-adjusted mean difference −0.16, 95% CI −0.26 to −0.05). The upper limit of the 95% CI was <0.0%, which established statistical superiority for glulisine ($P = 0.0029$). In both groups, just over one-half of the patients reached $HbA_{1c} \leq 7\%$ (53.5 and 50.6% of patients on glulisine and RHI, respectively).

Change in HbA_{1c} over the course of the study. There was a significant reduction from baseline in HbA_{1c} in both groups over the course of the study (Fig. 1), with statistically significantly greater reductions from baseline observed with glulisine versus RHI from 12 weeks onwards ($P < 0.05$ for all time points measured) (Fig. 1).

Self-monitored blood glucose profile. At baseline, self-monitored seven-point blood glucose profiles were comparable in the two groups. However, blood glucose values were lower with glulisine versus RHI at all on-treatment points, with statistical significance reached at 2 h postbreakfast and 2 h postdinner ($P < 0.05$) (Fig. 2).

Symptomatic hypoglycemia

There were no statistically significant between-treatment differences in the incidences or monthly rates of overall, nocturnal, or severe symptomatic hypoglycemia from month 4 to treatment end, a time at which patients were fully acclimated to the study. In both the glulisine and RHI groups, a similar proportion of patients experienced at least one episode



	Baseline	Week 12	Week 26	Endpoint
Glulisine	7.57	6.99	7.08	7.11
RHI	7.50	7.04	7.19	7.22
P value	0.4701	0.0165	0.0341	0.0029

Figure 1—*Mean HbA_{1c} over time. *Between-treatment difference: P < 0.05. HbA_{1c} is measured as HbA_{1c} equivalents.*

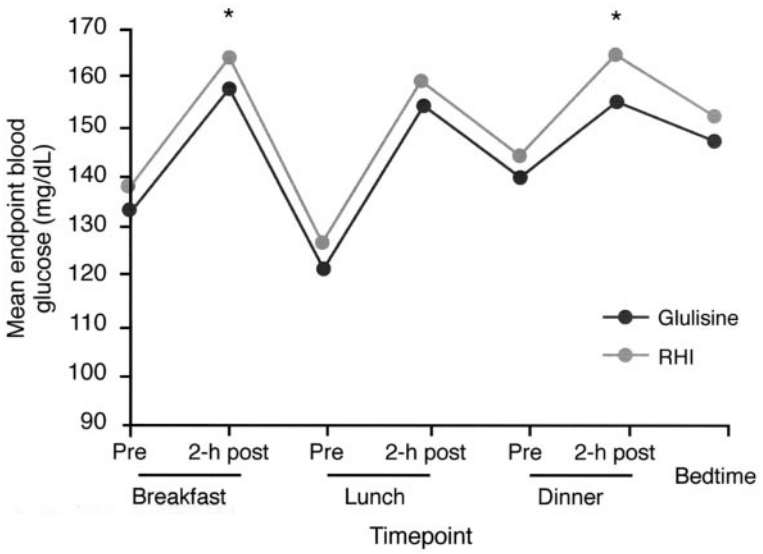


Figure 2—*Mean daily blood glucose profiles at study end point. *Between-treatment difference:* $P < 0.05$.

of symptomatic (51.7 vs. 53.6%, respectively; $P = 0.600$), nocturnal (21.4 vs. 24.5%, respectively; $P = 0.303$), or severe hypoglycemia (1.4 vs. 1.2%, respectively; $P = 0.645$). Symptomatic hypoglycemia rates were similar in the insulin glulisine and RHI groups (0.95 vs. 1.04 events/patient-month, respectively; $P = 0.186$), as were nocturnal hypoglycemia rates (0.14 vs. 0.21 events/patient-month, respectively; $P = 0.109$). Severe hypoglycemia rates were low at 0.0041 events/patient-month for glulisine and 0.0037 events/patient-month for RHI, and similar between treatment groups (between-treatment $P = 0.353$). This between-treatment similarity was consistent over the entire treatment period (data not shown).

Insulin dose

No between-treatment differences in insulin doses were detected throughout the study. Total daily insulin dose was similar with glulisine versus RHI at baseline (91.6 vs. 88.6 units; $P = 0.3770$). The same was true of daily basal (59.1 vs. 57.3 units; $P = 0.4025$) and short-acting insulin (32.5 vs. 31.3 units; $P = 0.4644$) doses at baseline. At end point, total daily insulin dose increased similarly with glulisine versus RHI (9.3 vs. 11.1 units; $P = 0.2427$), as did the daily basal insulin dose (5.7 vs. 6.0 units; $P = 0.7741$) and the daily short-acting insulin dose (3.7 vs. 5.0 units; $P = 0.1756$). The number of short-acting injections per day was also similar in both groups at end point (2.27 with glulisine vs. 2.24 with RHI).

A total of 78.7% of patients reported mixing the short-acting insulin with NPH insulin (glulisine: 74.1%; RHI: 83.1%) before injection by syringe; 25.7% mixed their insulins once daily and 53.0% mixed twice daily. The proportion of patients mixing the insulins in a syringe once and twice daily was similar in the two treatment groups.

OAD use

Subjects were allowed to continue taking OADs during the treatment period, and randomization was stratified according to whether the subjects were already being treated with OADs before the study. At randomization, OADs were being used by 508 (58%) subjects (245 in the glulisine group and 263 in the RHI group). Of these, 133 (26.2%) were taking a sulfonylurea (61 [14%] patients in the glulisine group and 72 [16.3%] patients in the RHI group), and the treatments were balanced for sulfonylurea use at baseline. At end point, 512 (58.4%) patients were taking OADs (4 patients began OAD therapy and 4 stopped their OAD therapy during the course of the study). Consistent with the overall results, a subgroup comparison of patients using OADs at baseline versus those who did not showed a larger decrease in HbA_{1c} in the glulisine group versus RHI.

Safety

Adverse events. A total of 358 glulisine-treated patients (82.3%) and 351 RHI-treated patients (79.6%) experienced TEAEs during the treatment phase. Fifty-five (12.6%) patients in the glulisine group and 51 (11.6%) patients in the RHI group experienced serious TEAEs. Serious nonhypoglycemia TEAEs were reported in 80 (9.1%) of the 876 patients during the study (glulisine: $n = 40$ [9.2%]; RHI: $n = 40$ [9.1%]); none of these were considered possibly related to study medication. There were three deaths (glulisine: $n = 1$ [0.2%]; RHI: $n = 2$ [0.5%]), none of which were deemed to be treatment related or associated with a severe hypoglycemic event. The incidences of potential systemic hypersensitivity (6.9% with glulisine vs. 5.2% with RHI) and injection site reactions (3.2% with glulisine vs. 2.3% with RHI) were similar in both treatment groups.

Laboratory and other safety data. The two groups were similar in terms of hematology, clinical chemistry, and lipids in the change from baseline, predefined abnormal values, and clinically noteworthy values. A rise in *E. coli* antibody levels from negative or borderline to positive was similarly infrequent in both treatment groups and not associated with the reporting of potential systemic hypersensitivity TEAEs. The adjusted mean change in body weight at end point was similar in both treatment groups (glulisine: 1.8 kg; RHI: 2.0 kg; $P = 0.369$).

Insulin antibodies

At baseline, median cross-reactive insulin antibody levels were comparable in the glulisine (0.13% B/T) and RHI (0.20% B/T) groups. Baseline to end point changes in cross-reactive insulin antibody levels were not statistically significant in either group. Mean change from baseline in the glulisine group was 0.298 ± 2.01% B/T, with a median value of 0.01% B/T and 5, 10, and 95% quartiles of −1.12, −0.59, and 3.22, respectively. Mean change from baseline in the RHI group was 0.093 ± 1.5321% B/T, with a median value of 0.02% B/T and 5, 10, and 95% quantiles of −1.37, −0.57, and 1.30, respectively.

CONCLUSIONS — This is the largest study described to date that compares a rapid-acting insulin analog with RHI in patients with type 2 diabetes. There is a

growing trend in the diabetes community toward reaching ever more normoglycemic control (7,8). Consequently, the inadequate glycemic control achieved historically by patients with type 2 diabetes is becoming increasingly unacceptable. There is no doubt that the addition of basal insulin to ongoing OAD therapy, particularly in treat-to-target insulin titration regimens, significantly improves glycemic control in most patients; however, some patients may remain suboptimally controlled (9). It is through the control of postprandial hyperglycemia using short-acting insulin at mealtimes that the best levels of glycemic control will be achieved in patients with type 2 diabetes.

In addition to the benefits of controlling postprandial excursions, it is becoming increasingly apparent that postprandial hyperglycemia may be an important predictor of cardiovascular mortality from an epidemiologic standpoint (10). In addition, recent evidence demonstrates that in patients with type 2 diabetes on oral agents and on no insulin treatment, the relative contribution of postprandial glucose is more relevant in the lowest quintiles of HbA_{1c} (11). In light of this evidence, it is important to maximize postprandial glycemic control and evaluate any new short-acting insulin designed to do this in patients with type 2 diabetes.

The purpose of this study was to compare the efficacy and safety of glulisine with RHI in patients with type 2 diabetes. The study was designed to reflect real-world clinical practice as much as possible by allowing patients to continue with prestudy OAD regimens. The study included ~900 patients. There were no between-treatment differences in any category of symptomatic hypoglycemia with glulisine versus RHI, despite the statistically significant improvement in glycemic control with glulisine relative to RHI. Weight gain was also comparable between treatment groups.

The greater baseline to end point reduction in HbA_{1c} observed with glulisine versus RHI in this study was small and statistically significant, although the clinical relevance of such a difference remains to be established. Such a difference has not been observed previously in type 2 diabetic patients in studies with other rapid-acting insulin analogs (although significant reductions in the incidence of hypoglycemia versus RHI have been observed with other short-acting insulin analogs) (12). Certain aspects of the study design may have contributed to the observed between-treatment difference in baseline to end point change in HbA_{1c}. The open-label design could have introduced bias in favor of the newer study treatment; however, this type of open-label design has been, and remains, a necessity with any study comparing a rapid-acting insulin analog with RHI because of the considerable differences in the timing of the administration of these two types of insulin. In this study, attempts were made to reduce treatment bias through measurement of HbA_{1c} at a central laboratory and blinding investigators to these centrally measured HbA_{1c} levels until databases were locked after the study end. The large sample size of the study may also account, in part, for a determination of statistical significance for a difference that is of unclear clinical relevance at this time.

Any between-treatment differences in glycemic control were not a result of increased short-acting, basal, or total insulin doses; OAD usage; or the number of insulin injections per day. Published studies (13,14) with other rapid-acting insulin analogs in combination with NPH insulin in type 1 diabetes suggest that these analogs may require greater basal insulin supplementation compared with RHI even to maintain equivalent levels of glycemic control.

It is noteworthy that the patients included in this study were considerably overweight; the mean BMI was >34 kg/m^2 in both groups. Most published studies of the pharmacokinetics and pharmacodynamics of rapid-acting insulin analogs have been in lean healthy subjects or patients with type 1 diabetes. Thus, there are little published data on the pharmacokinetics and pharmacodynamics of these agents in type 2 diabetic patients, the vast majority of whom are overweight. Studies are currently underway to evaluate the activity of glulisine in obese individuals.

In conclusion, this is the largest study to date evaluating the use of a rapid-acting insulin analog in patients with type 2 diabetes in a multiple insulin injection regimen. The results demonstrate that glulisine, which offers greater treatment convenience due to its time-action profile, provides small and statistically significant improvements in glycemic control (which remain to be proven clinically relevant) compared with RHI. Glulisine, therefore, may prove a valuable addition to the armamentarium of therapeutic tools for the management of diabetes.

APPENDIX

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