Comparison of dinner with bedtime administration of insulin glargine in type 1 diabetic patients treated with basal-bolus regimen

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Abstract

Objective. – To establish the equivalence in efficacy (HbA1c) of insulin glargine injected at dinner versus bedtime in a large number of patients with type 1 diabetes using a fast-acting analogue (FAA) or regular human insulin (RHI) as prandial insulin in an insulin glargine-bolus regimen.

Research design and methods. – In a 26-week trial, 1178 patients with type 1 diabetes and treated with different basal-bolus regimens were randomized to receive insulin glargine once daily at dinner (n = 589) or at bedtime (n = 589) while continuing their previous prandial insulin (FAA: 75%; RHI: 25% of patients). The primary objective was to demonstrate equivalence in terms of HbA1c levels at endpoint.

Results. – Baseline characteristics were similar in the two groups. At endpoint, HbA1c (mean ± standard deviation [S.D.]) had decreased by 0.25 ± 0.66% to 7.77 ± 0.96% in the dinnertime group (P < 0.0001), and by 0.24 ± 0.76% to 7.83 ± 1.07% in the bedtime group (P < 0.0001). The HbA1c difference between dinner and bedtime was −0.022% (two-sided 90% confidence interval [CI] −0.09; 0.05), demonstrating statistical equivalence of HbA1c at endpoint between the two groups. Equivalence was also demonstrated within prandial groups: HbA1c difference between dinner and bedtime was −0.03% (two-sided 90% CI: −0.11; 0.06) for FAAs and −0.04% (two-sided 90% CI: −0.19; 0.11) for RHIs. The incidence of severe hypoglycaemia did not differ between the treatment groups.

Conclusion. – These data confirm that insulin glargine in combination with either FAA or RHI is equally effective and safe, whether it is administered at dinner or bedtime.

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The “basal-bolus” regimen is intended to provide effective control of diabetes by combining a basal insulin to control glucose production between meals and overnight, with a bolus insulin to limit hyperglycaemia after meals [1]. Traditional basal-bolus regimens manage daily basal insulin flow with an intermediate-acting insulin (such as NPH insulin once or twice daily) or a long-acting insulin (such as ultralente insulin), and achieve prandial regulation using a fast-acting insulin (such as regular human insulin [RHI]) or fast-acting analogues (FAA) titrated and injected at each meal. However, these traditional basal insulins are limited by their pharmacokinetic profiles: NPH insulin is associated with a peak of action 4–6 hours following administration [2,3], which can lead to unwanted hypoglycaemia, and ultralente insulin is associated with large day-to-day variability in absorption [4].

Insulin glargine (LANTUS®) is a long-acting basal insulin analogue with a 24-hour time–action profile [5,6]. This profile has the potential to provide greater flexibility in the management of type 1 diabetes by allowing the timing of the basal insulin injection to be tailored to the needs of the individual patient. Indeed, insulin glargine administered either before breakfast, before dinner or at bedtime has been shown to be safe and effective in combination with insulin lispro [7]. In addition, insulin glargine has been associated with equivalent or better glycaemic control versus NPH insulin, but with a lower risk of hypoglycaemia [8–10].

If these results can be substantiated in further studies and refined in combination with other bolus regimens, insulin glargine could provide patients with greater flexibility and with a decreased risk of hypoglycaemia in the management of type 1 diabetes. Therefore, we compared the efficacy and safety of insulin glargine when administered at dinner or at bedtime and in combination with FAAs or RHI.

2. Patients and methods

2.1. Patients

A total of 1178 male and female patients with type 1 diabetes and aged between 18 and 75 years were included and treated in the study; no limits were specified for baseline HbA1C. All patients had received insulin therapy for at least 1 year before study entry, and multiple daily injections (MDI) at least three-times daily, for at least 6 months. Previous insulin regimens were required to have included NPH insulin as basal insulin and FAAs or RHI as the bolus insulin. The bolus and basal insulins were injected separately or in premixed preparations.

Patients were excluded if they had a history of two or more severe hypoglycaemic episodes within 12 months before study entry, had active proliferative or pre-proliferative or unstable retinopathy, were likely to require treatment during the study period with anti-diabetic agents other than the study insulin preparations, were treated with oral corticosteroids, were known to abuse alcohol, had a major systemic disease or had impaired hepatic or renal function.

2.2. Study design

This multicenter, randomized (1:1), controlled, parallel group, open-label study was conducted from November 2001 to October 2003 at 276 investigational sites in France by 324 investigators who had selected 1–12 patients each. The study consisted of a 2-week screening period, followed by a 26-week treatment period. Patients were randomized to receive either insulin glargine at dinnertime (18:30–21:00 h) or bedtime (22:00–24:00 h) and continued administering their usual prandial insulin at mealtimes. This prandial insulin had to be the same preparation for each meal. At study end, an open, uncontrolled extension study was conducted for several months in patients continuing therapy.

Patients were familiarized with the use of home blood glucose (BG) monitors and were instructed in titrating the basal and prandial insulin preparations to meet the target BG values. Target BG levels were as follows: fasting pre-breakfast BG concentrations of 4.5–7.8 mmol/l, and 2-hour post-prandial (2 hours after the start of a meal) BG concentration of 6.7–8.9 mmol/l, without encountering hypoglycaemia. A titration algorithm for insulin glargine and prandial insulins was provided as a guideline for the investigators to allow for dose adjustment in order to enable patients to achieve target BG levels. Dosage adjustments were permitted during the whole of the treatment phase to achieve the pre-defined BG targets. The study was conducted in accordance with good clinical practice and conformed to the ethical principles of the Declaration of Helsinki. All patients gave written, informed consent before screening and entry into the study.

2.3. Objectives

The primary objective was to demonstrate equivalent efficacy of HbA1C at endpoint based on a per-protocol (PP) popu-
luation, with an intent-to-treat analysis performed as a secondary confirmation analysis. Additional comparisons were made between groups defined by the timing of insulin glargine administration (dinnertime or bedtime), and between groups defined by the timing of insulin glargine administration and the type of insulin used for boluses (RHI or FAA). At baseline and endpoint (26 ± 2 weeks), HbA1c was measured in a single central laboratory using high-performance liquid chromatography (normal range 4.0–6.0%; LCL, France).

Secondary objectives were to compare, at endpoint, the glycaemic profile and insulin dose, and the frequency of severe hypoglycaemic events. The latter were recorded in the patients’ diaries and categorized as follows: severe symptomatic hypoglycaemia, defined as the patient requiring the assistance of another person and either a BG concentration of < 2.0 mmol/l, or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration; nocturnal severe hypoglycaemia, defined as a severe hypoglycaemic event occurring while the patient was asleep, between bedtime and rising the next morning.

The elevation of pre-dinner BG levels despite good post-lunch BG levels in some patients has led to the hypothesis of an ‘afternoon phenomenon’ or ‘dusk phenomenon’. This phenomenon was assessed in a post-hoc analysis. The phenomenon was defined as patients who fulfilled all of the following criteria successively: HbA1c < 9% at Visits 6, fasting plasma glucose (FPG) < 7.8 mmol/l, pre-lunch BG < 7.2 mmol/l, post-lunch BG < 8.9 mmol/l and lastly pre-dinner >10 mmol/l.

Descriptive analyses were performed to examine the change from baseline to the end of the study in subgroups of patients who had been using different diabetes regimens at enrolment (premixed insulin versus basal-bolus). Adverse events were recorded by the investigator.

2.4. Statistical methods

The primary efficacy analysis investigated the mean HbA1c levels in the PP population, using the confidence interval (CI) approach to demonstrate equivalence between the dinnertime or bedtime groups, irrespective of the type of insulin used for the boluses. In addition, analyses were performed to demonstrate the equivalence between the two treatment groups, defined by the time of administration of insulin glargine and by the type of insulin used for the boluses. Two-sided 90% CIs were calculated for the adjusted mean difference of the primary comparison. The adjusted mean difference between treatment groups was estimated using analysis of covariance (ANCOVA), in which treatment effects were considered as fixed effect and the HbA1c baseline value as covariate. Equivalence was demonstrated if the two-sided 90% CI for the observed treatment difference lay entirely within the interval ± 0.3% HbA1c. If the primary goal was achieved, similar analyses were conducted to demonstrate that there were no differences in HbA1c between patients receiving insulin glargine before dinner or at bedtime within each of the prandial insulin groups (FAA or RHI). The sample size justification was based on a two-sided 90% CI approach with an equivalence margin of ± 0.3% HbA1c, a standard deviation (S.D.) equal to 1% HbA1c and a power close to 99.9% in order to have a global power for the second part of the main analysis close to 86%. The sample size was equal to 1200 patients randomly assigned to time insulin glargine groups (1060 patients for the PP analysis).

The analyses for all secondary variables were exploratory analysis of variance (ANOVA) or ANCOVA if the assumptions of normality were met. For categorical variables, Pearson’s Chi-square or Fisher’s exact tests were used to compare treatment group proportions.

3. Results

3.1. Patients

A total of 1178 patients were randomized to insulin glargine at dinnertime (n = 589) or bedtime (n = 589). These patients were included in the safety population as they had received at least one dose of study medication. In total, 47 patients (4%) discontinued the treatment before Visit 6 and 79 patients were excluded from the full analysis time-set (FAS) population (mostly owing to missing HbA1c values at baseline); the time-analysis population thus included 1099 randomized and treated patients. The PP population included 900 patients (dinnertime: n = 446; bedtime: n = 454) after exclusion of 199 patients due to violations of inclusion or exclusion criteria (n = 18), cessation of treatment for more than 15 days (n = 1), receipt of other types of insulin (n = 5) and measurement of the final HbA1c before 24 weeks or after 30 weeks in patients treated for at least 24 weeks (n = 175). Within the FAA group, 331 and 338 patients were taking glargine at dinnertime and bedtime, respectively (PP population). In the RHI group, 115 and 116 patients were taking glargine at dinnertime and bedtime, respectively. The median duration of treatment during the treatment phase was equal to 26 weeks in the safety population. The duration of exposure was similar in the groups of patients given insulin glargine at bedtime or dinnertime.

3.1.1. Patient characteristics

Baseline characteristics for all patients in the safety population are presented in Table 1 and were similar to the characteristics of the other analysis populations. Overall, the PP population had a mean (± S.D.) age of 40.5 (12.7) years and a mean duration of diabetes of 16.1 (10.2) years.

Patients included in this large cohort had used a wide variety of insulin regimens before enrollment: 633 patients (70%) had been using a basal-bolus regimen (with a FAA as prandial insulin [69%] and NPH as basal insulin [64%]) and 267 patients (30%) had been using a regimen with at least one premixed insulin, particularly a mixture containing a FAA. Following randomization, where the prandial insulin was kept identical to the previous regimen, the most frequent regimen for prandial boluses was FAA three-times daily (74.3% of
patients). There was no difference between the PP and FAS population.

3.2. Glycaemic control

3.2.1. HbA1c

The mean change in HbA1c from baseline (Visit 2) to the end of the study was statistically significant within each treatment group in the time-analysis population. Patients given insulin glargine at dinnertime had a mean ± S.D. decrease in HbA1c levels of 0.25 ± 0.66% from baseline to 7.77 ± 0.96% at the end of the study, compared with a decrease of 0.24 ± 0.76% to 7.83 ± 1.07% in patients treated at bedtime. The results in the two study groups were equivalent, as shown by a two-sided 90% CI for the adjusted mean difference of the primary comparison, which did not exceed ± 0.3% HbA1c (Fig. 1). The adjusted mean difference for the final HbA1c value between dinnertime and bedtime administration of insulin glargine was $-0.022$ [90% CI $-0.09; 0.05$].

The proportion of patients achieving an HbA1c < 7% at the end of the study was also similar in each group: 20.2% in the dinnertime group and 19.4% in those treated at bedtime. Regarding the use of different diabetes regimens at enrolment, patients who had previously used premixed insulin ($n = 267$) had mean baseline HbA1c of 8.28 ± 1.13% and a mean final value of 7.92 ± 1.03%; in comparison, those who had received basal-bolus therapy ($n = 633$) had a value of 7.95 ± 1.01% at baseline and a final value of 7.75 ± 1.01%.

3.2.2. Glycaemic profile

The self-monitored eight-point BG variables between the treatment groups paired with the prandial insulin groups showed superimposable profiles for all measurements throughout the study (Fig. 2).

Table 1

Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dinnertime Population safety ($n = 589$)</th>
<th>Dinnertime Population PP ($n = 446$)</th>
<th>Bedtime Population safety ($n = 589$)</th>
<th>Bedtime Population PP ($n = 454$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (n [%])</td>
<td>Male 299 (50.8)</td>
<td>224 (50)</td>
<td>302 (51.3)</td>
<td>234 (52)</td>
</tr>
<tr>
<td></td>
<td>Female 290 (49.2)</td>
<td>222 (50)</td>
<td>287 (48.7)</td>
<td>220 (49)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.9 ± 12.1</td>
<td>40.3 ± 12.5</td>
<td>40.5 ± 13.1</td>
<td>40.8 ± 12.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5 ± 3.6</td>
<td>24.2 ± 3.6</td>
<td>24.4 ± 3.3</td>
<td>24.8 ± 3.4</td>
</tr>
<tr>
<td>BMI male</td>
<td>24.7 ± 3.0</td>
<td>24.9 ± 3.1</td>
<td>23.8 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>BMI female</td>
<td>24.2 ± 4.1</td>
<td>23.8 ± 3.4</td>
<td>24.8 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis of diabetes (n [%])</td>
<td>&lt; 20 years old 244 (41.4)</td>
<td>170 (39.4)</td>
<td>249 (42.3)</td>
<td>189 (42.8)</td>
</tr>
<tr>
<td></td>
<td>≥ 20 years old 345 (58.6)</td>
<td>261 (60.5)</td>
<td>340 (57.7)</td>
<td>254 (57.5)</td>
</tr>
<tr>
<td>Duration of previous insulin treatment (years)</td>
<td>15.2 ± 10.1</td>
<td>15.6 ± 9.8</td>
<td>15.1 ± 10.4</td>
<td>16.4 ± 10.1</td>
</tr>
<tr>
<td>Patients with diabetic complications (n [%])</td>
<td>Retinopathy 185 (31.4)</td>
<td>122 (28.3)</td>
<td>199 (33.8)</td>
<td>152 (34.3)</td>
</tr>
<tr>
<td></td>
<td>Microalbuminuria ≥ 30 mg/day 51 (8.7)</td>
<td>42 (9.7)</td>
<td>49 (8.3)</td>
<td>40 (9.9)</td>
</tr>
<tr>
<td></td>
<td>Macroalbuminuria ≥ 300 mg/day 10 (1.7)</td>
<td>7 (1.6)</td>
<td>6 (1.0)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td></td>
<td>Painful neuropathy 22 (3.7)</td>
<td>17 (3.9)</td>
<td>17 (2.9)</td>
<td>15 (3.4)</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease 14 (2.4)</td>
<td>12 (2.7)</td>
<td>23 (3.4)</td>
<td>19 (4.3)</td>
</tr>
<tr>
<td>HbA1c levels at baseline [%]</td>
<td>8.01 ± 1.10</td>
<td>8.02 ± 1.08</td>
<td>8.08 ± 1.10</td>
<td>8.07 ± 1.11</td>
</tr>
</tbody>
</table>

Data presented as mean ± S.D., unless otherwise indicated; BMI=body mass index.

* a full analysis set.
3.2.3. Fasting BG

The decrease in mean self-monitored fasting blood glucose (FBG) was similar in the two treatment groups from baseline to endpoint. Furthermore, FBG was not influenced by the type of prandial insulin used (Fig. 3).

3.2.4. FBG targets and HbA1c

The levels of HbA1c were linked with FBG levels in both the dinnertime and bedtime glargine groups, suggesting that targeting FBG with insulin glargine could markedly improve HbA1c (Table 2).

3.2.5. Two-hour post-prandial BG

Although the type of prandial insulin used did not affect HbA1c levels, the glycaemic profile was flatter with FAAs compared with RHI, particularly for the control of 2-hour post-prandial BG. Furthermore, subjects with HbA1c < 7.5% had better control of all pre- and post-prandial glucose levels

Table 2

<table>
<thead>
<tr>
<th>FBG</th>
<th>≤5.5 mmol/l</th>
<th>5.5–6.7 mmol/l</th>
<th>6.7–7.8 mmol/l</th>
<th>&gt;7.8 mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.19 (n = 72)</td>
<td>7.48 (n = 75)</td>
<td>7.90 (n = 78)</td>
<td>8.05 (n = 194)</td>
</tr>
<tr>
<td>Insulin glargine at dinnertime HbA1c (%)</td>
<td>7.4 (n = 82)</td>
<td>7.62 (n = 65)</td>
<td>7.78 (n = 79)</td>
<td>8.11 (n = 196)</td>
</tr>
</tbody>
</table>

Fig. 2. BG profiles (mean of last three visits) in patients with type 1 diabetes receiving insulin glargine at dinnertime or bedtime with FAAs (A) or RHI (B) at mealtimes.

Fig. 3. Baseline and endpoint self-monitored FBG values in patients given insulin glargine at dinnertime or at bedtime with FAA or RHI at mealtimes.
compared with other subjects indicating that, in addition to the choice of prandial insulin and target FBG, titration to target post-prandial glucose level is important for good glycaemic control (Fig. 4).

### 3.2.6. The pre-dinner glycaemic level

The pre-dinner BG level was lower in subjects receiving prandial RHI versus FAA, regardless of the time of insulin glargine administration: 8.2 ± 2.5 versus 9.2 ± 3.3 mmol/l (insulin glargine dinner group) and 8.2 ± 3.0 versus 9.1 ± 3.2 mmol/l (insulin glargine bedtime group). The elevation of pre-dinner BG levels despite good post-lunch BG levels in some patients has led to the hypothesis of an ‘afternoon phenomenon’ or ‘dusk phenomenon’. All the patients who, during the treatment period, had registered three complete eight-point profiles at Visit 4 (Week 8), Visit 5 (Week 17 ± 1) and Visit 6 (Week 26 ± 2) were considered (n = 669) and for each one the mean of the three values at each point was calculated. From 669 subjects, 174 subjects fulfilled the first four criteria (HbA\(_{1c}\) < 9% at Visit 6, FPG < 7.8 mmol/l, pre-lunch BG < 7.2 mmol/l, post-lunch BG < 8.9 mmol/l). Of these patients, 24 (13.8%) had a high pre-dinner BG level > 10 mmol/l: in the FAA patients, 12 out of 66 in the insulin glargine dinnertime group and seven out of 69 in the insulin glargine bedtime group; in the RHI patients, three out of 18 in the insulin glargine dinnertime group and two out of 21 in the insulin glargine bedtime group.

### 3.3. Insulin dose

The mean daily insulin glargine dose at the end of the study was similar for both treatment groups (22.2 ± 9.8 IU in the dinnertime group and 22.0 ± 9.9 IU in the bedtime group). This corresponded to a mean dose of 0.31 ± 0.12 IU/kg per day. However, the mean daily doses of insulin glargine used by patients receiving FAA and RHI were 22.7 ± 10.1 and 20.4 ± 8.8 IU, respectively. The mean daily doses of bolus insulin were 30.8 IU for RHI and 25.6 IU for FAA. The insulin glargine/total insulin ratio was 47% in patients receiving FAA and 40% in patients receiving RHI.

### 3.4. Body weight

At baseline, mean body weight was 70.5 kg (female: 64.1 kg; male: 76.7 kg) in patients receiving insulin glargine at dinnertime and 70.0 kg (female: 63.2 kg; male: 76.5 kg) in those treated at bedtime, and did not change over the study period (mean change 0.14 ± 2.46 kg).

### 3.5. Severe hypoglycaemia

Owing to the size of the trial, only the incidence of severe hypoglycaemia was determined in the safety population. By Month 6, 76 patients (6.50%) had reported 116 events of severe hypoglycaemia, with no differences in the number of incidences between each injection time group. The percentages of incidences for each treatment group were as follows: patients receiving FAA: 6.85% in the insulin glargine at dinnertime group, 5.69% in the insulin glargine at bedtime group; patients receiving RHI: 7.95% in the insulin glargine at dinnertime group, 6.00% in the insulin glargine at bedtime group. From 116 events, 68 events occurred during the day and 48 were nocturnal. The incidence was 12 events/100 patient-years for diurnal severe hypoglycaemia and eight events/100 patient-years for nocturnal severe hypoglycaemia, without statistical difference between groups.
3.6. Follow-up

At the end of the randomized trial, 1077 patients were entered into an extension trial and treated with insulin glargine, ensuring that the usual medical care conditions were met. After 1 year, 397 patients had centralized HbA1c measurements available. For these patients, HbA1c levels remained unchanged between Visit 6 (26 weeks) and Visit 7 (52 weeks): 7.81 ± 1.00% and 7.85 ± 0.99%, respectively. The decrease in HbA1c of 0.27% from baseline to endpoint was maintained after the 6-month study period for up to 12 months of treatment. During the extension trial, 28 patients (2.6%) experienced severe hypoglycaemia (three diurnal events/100 patient-years and one nocturnal event/100 patient-years).

4. Discussion

The principal purpose of this study was to confirm that two different injection times of the long-acting insulin analogue insulin glargine, combined with prandial insulin (RHI or FAA), were equivalent with regard to efficacy and safety. The study was specifically designed to reflect the characteristics of a large population of patients with type 1 diabetes who were previously treated with multiple injection regimens, and who had various clinical care backgrounds. The data evaluated in this study show that insulin glargine was equally effective at reducing HbA1c levels at the end of the study, regardless of whether injections were given at dinnertime or bedtime. This equivalence was also apparent within the groups of patients receiving bolus treatment with RHI or a FAA. These results are substantiated by the fact that the glycaemic profiles of the dinnertime and bedtime injection groups are superimposable and by the fact that the FPG values are similar. Furthermore, these findings are supported by the equivalence of the treatment groups in terms of insulin dose and the frequency of severe hypoglycaemia.

Our results confirm the results of previous studies that demonstrate the flexibility of insulin glargine [7] in a larger population, with FBG levels identical to those in the Hamann study (dinnertime: 7.9 ± 0.2 versus 7.9 ± 3.6 mmol/l; bedtime: 8.0 ± 0.2 versus 8.0 ± 3.6 mmol/l) and superimposable final glycaemic profiles. In a recent 16-week trial [11] using insulin aspart as prandial insulin and insulin detemir administered twice daily (before breakfast and either at dinnertime or at bedtime) as basal insulin, the administration of insulin detemir at dinnertime or bedtime showed HbA1c levels at endpoint of 7.8 ± 0.1% for both groups. However, in contrast to our findings, the FPG levels differed between the dinner and bedtime groups (9.8 ± 0.4 and 8.9 ± 0.4 mmol/l, respectively), and the glycaemic profiles were not superimposable [11].

Glycaemic control improved significantly when patients switched to insulin glargine plus bolus insulin, as shown by a mean reduction in HbA1c of 0.25%. Furthermore, as demonstrated in the open, uncontrolled extension study, this reduction in glycaemic control was maintained over 12 months of treatment, along with a reduction in the occurrence of severe hypoglycaemia. These positive benefits of switching to insulin glargine were not dependent on either the timing of the injections or the choice of bolus regimen, which allowed for greater flexibility in the treatment regimen.

During the study, the tight glycaemic objectives defined in this protocol were demanding and only the upper limits of the targets were achieved, as shown by the glycaemic control at endpoint (only 20% of patients achieved HbA1c targets of < 7%). In a previous trial with insulin glargine in combination with lispro [7], this HbA1c target was achieved by 29.8% of patients receiving treatment at dinner and by 25.8% of those receiving treatment at bedtime. However, it should be noted that there were differences in patient characteristics between the Hamann study and our own. In particular, in our study, patients had higher HbA1c levels at baseline versus the Hamann study (dinnertime: 8.02 ± 1.08% versus 7.6 ± 0.8%; bedtime: 8.07 ± 1.11% versus 7.6 ± 0.8%), which likely contributed to the better glycaemic control achieved in the Hamann study. The experience of a real basal-bolus regimen as opposed to the MDI regimen could assist in the attainment of better glycaemic control. An earlier, smaller, single-center study in 51 patients with type 1 diabetes previously treated with NPH insulin four-times daily as the basal insulin plus mealtime lispro insulin, showed greater decreases in HbA1c levels after 3 months’ therapy, in patients receiving once-daily insulin glargine plus mealtime lispro insulin (from 6.9% to 6.5%; 0.4%) compared with patients who continued the NPH insulin/lispro insulin regimen (6.9–7.0%; +0.1%) [12].

The insulin glargine regimen introduced a new method for insulin adjustment with a basal insulin titration strictly independent of each prandial insulin bolus titration. Therefore, it is possible that a greater decrease in HbA1c could be attained in patients more experienced in the management of this regimen, if more intensive coaching was provided or if there was greater homogeneity in the titration of insulin doses. Being more confident with the lower risk of nocturnal hypoglycaemia compared with previous basal insulin such as NPH insulin [8, 9], we suggest a lower threshold for fasting glucose (< 6.7 mmol/l).

The glycaemic profiles observed in this study reflect the lifestyle and eating habits of the French study participants who typically eat a high fat and caloric lunch followed by a long interprandial period before dinner. Taking into consideration these particular eating behaviors, and as both prandial insulins, RHI and FAA, may play a role in the adaptation to the meal composition and distribution, physicians could modulate the insulin regimen to obtain a smoother profile in their patients. Moreover, the post-prandial and bedtime glucose targets may be lowered even further.

The ‘afternoon phenomenon’ has appeared to be less important in our study than in another publication [13] but the criteria of analysis were different. Our post-hoc analysis showed a subgroup of patients well controlled with insulin glargine plus prandial insulin during nocturnal and diurnal periods, except at the end of the afternoon. This raises the issue that in some patients the duration of action of insulin glargine may be slightly less than 24 hours and, when injected in the evening, results in an increase in BG levels in the late afternoon of the
following day. Additional studies and common definition are needed to validate the ‘afternoon phenomenon’.

Although the Diabetes Control and Complications Trial (DCCT) results established the benefit of good glycemic control (mean HbA1c level: 7.2%), they were associated with a high level of severe hypoglycemia (62 events/100 patient-years) [14]. Thus, the aim of insulin therapy thereafter was to decrease both HbA1c levels and the incidence of severe hypoglycemia. The Epidemiology of Diabetes Interventions and Complications Study further demonstrated that a mean HbA1c level of 8.2% in patients previously included in the DCCT from intensive or conventional arms was associated with a rate of severe hypoglycemia of 25.4 events/100 patient-years [15]. In addition, a significant decrease of 0.25 ± 0.20% to 8.15% in the HbA1c level occurred after the introduction of insulin lispro in a MDI regimen, with no increase in the number of severe hypoglycaemic episodes (40 events/100 patient-years) [16]. In 2003, our trial with 1178 insulin glargine-treated patients showed that not only did the HbA1c level decrease by 0.25 to 7.80% with this therapy but, in addition, the incidence of severe hypoglycemia (< 2 mmol/l or prompt recovery with sugar) was low and comparable with the conventional arm of the DCCT, which demonstrated a mean HbA1c level of 9.1%. The incidence of events continued to decrease over time to 10 events/100 patient-years over a 65-week period, which included the 26-week controlled, randomized trial and the extension trial, with less visits and monitored reporting. In a previous trial, which demonstrated the flexibility of insulin glargine and an overall HbA1c level of 7.6% at endpoint [7], the percentage of patients reporting severe hypoglycemia (confirmed by BG levels < 2 mmol/l) was 4.7% in those receiving dinner-time insulin glargine and 3.9% in those receiving bedtime insulin glargine. As such, the results from our study indicate that, 10 years after the DCCT findings, glycemic control in patients with type 1 diabetes could be improved by the introduction of insulin glargine to treatment regimens.

In conclusion, this large study demonstrated that once-daily insulin glargine in a basal-bolus regimen is equally effective and well tolerated whether it is injected before dinner or at bedtime in patients with type 1 diabetes receiving prandial FFA or RHI. Insulin glargine has the advantage of allowing flexibility in the selection of administration times and in the choice of bolus regimen and may, therefore, enhance patients’ compliance with insulin therapy, thereby providing improved glycemic control with a low risk of severe hypoglycaemia.

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