Comparison of stepwise addition of prandial insulin to a basal-bolus regimen when basal insulin is insufficient for glycaemic control in type 2 diabetes: Results of the OSIRIS study

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Abstract

Aim. – The metabolic efficacy of adding prandial insulin in a stepwise manner to a straightforward basal-bolus regimen was compared in patients with type 2 diabetes mellitus (T2DM), suboptimally controlled by oral antidiabetic drugs (OADs) and once-daily basal insulin.

Methods. – In this international randomized, parallel-group, non-inferiority study, 811 patients with poorly controlled type 2 diabetes using basal insulin were switched to insulin glargine (GLAR) for 6 months while continuing OADs. Patients with HbA1c > 7% and FPG < 120 mg/dL (n = 476) were then randomized to either group 1, GLAR + metformin (MET) + 3 × insulin glulisine (GLU), group 2, GLAR + MET + 1–3 × GLU, or group 3, GLAR + MET + insulin secretagogue (IS) + 1–3 × GLU, for 12 months. Objectives were to show the non-inferiority of efficacy of group 2 vs group 1 and vs group 3. Non-inferiority of group 2 vs group 1 was concluded if the upper limit of the 95% confidence interval (CI) for the HbA1c difference was ≤ 0.4%.

Results. – The adjusted HbA1c difference of group 2 vs 1 for the per-protocol population crossed the non-inferiority margin (0.228, 95% CI: −0.018–0.473). There was significantly less weight gain in group 2 compared with group 1, but adverse events were otherwise similar between the two groups. In patients with HbA1c < 8% at baseline, non-inferiority was achieved in group 2 vs group 1.

Conclusion. – Although non-inferiority was not achieved, stepwise intensification of GLU added to GLAR showed efficacy close to that of the basal-bolus approach and with significantly less weight gain.

Keywords: Type 2 diabetes; Basal-bolus; Prandial insulin; Insulin glargine; Insulin glulisine; Randomised trial

Résumé

Compareraient de l’administration par paliers d’insuline prandiale avec un schéma basal-bolus chez des patients de type 2 non équilibrés par insulinothérapie basale : résultats de l’étude OSIRIS.

Contexte. – Nous avons comparé l’efficacité métabolique de l’administration par paliers d’insuline prandiale avec un schéma basal-bolus d’emblée chez des diabétiques de type 2 (DT2) non équilibrés par antidiabétiques oraux (ADO) et insulinothérapie basale une fois pour jour.

Méthodes. – Dans cette étude de non-inferiorité, internationale, randomisée, en groupes parallèles, 811 patients atteints de DT2 mal équilibré par insuline basale ont été mis sous insuline glargine (GLAR) pendant six mois tout en poursuivant la prise d’ADO. Les patients présentant un HbA1c supérieur à 7 % et une glycémie à jeun inférieure à 120 mg/dL (n = 476) ont été assignés de façon aléatoire au groupe 1 : GLAR + méformine (MET) + 3 × insulin glulisine (GLU) ; au groupe 2 : GLAR + MET + 1–3 × GLU ; ou au groupe 3 : GLAR + MET + insulino-sécrétagogue (IS) + 1–3 × GLU, pour 12 mois. Les objectifs étaient de montrer l’infériorité de l’efficacité de groupe 2 par rapport à groupe 1 et groupe 3. L’infériorité de groupe 2 par rapport à groupe 1 était conclue si le haut de la limite de l’intervalle de confiance à 95 % (CI) pour la différence d’HbA1c était ≤ 0,4%.

Résultats. – La différence ajustée d’HbA1c de groupe 2 par rapport à 1 pour la population protocole a dépassé le seuil d’infériorité (0,228, 95% CI: −0,018–0,473). Il y avait significativement moins de gain de poids dans le groupe 2 par rapport au groupe 1, mais les événements indésirables étaient de manière autrement similaire entre les deux groupes. Dans les patients avec HbA1c < 8 % à l’baseline, l’infériorité non-inferieure a été réalisée dans le groupe 2 par rapport au groupe 1.

Conclusion. – Bien qu’l’infériorité non-inferieure ne soit pas réalisée, l’intensification progressive de GLU ajouté à GLAR a montré une efficacité proche de celle de l’approche basal-bolus avec significativement moins de gain de poids.

Keywords: Type 2 diabetes; Basal-bolus; Prandial insulin; Insulin glargine; Insulin glulisine; Randomised trial

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3 × GLU pendant 12 mois. L’objectif était de démontrer la non-inferiorité de l’efficacité du groupe 2 par rapport au groupe 1 et du groupe 2 par rapport au groupe 3. La non-inferiorité du groupe 2 par rapport au groupe 1 était établie lorsque la limite supérieure de l’intervalle de confiance à 95 % (IC) de la différence d’HbA1c était inférieur ou égale à 0,4 %.

Résultats. – La différence d’HbA1c corrigée du groupe 2 versus 1 pour la population per protocole a franchi la marge de non-inferiorité (0,228 [IC à 95 % = 0,188–0,473]). Le gain de poids dans le groupe 2 était significativement inférieur à celui du groupe 1. Les événements indésirables étaient semblables entre les groupes. Chez les patients présentant une HbA1c inférieure à 8 % à la randomisation, la non-inferiorité était obtenue dans le groupe 2 versus groupe 1.

Conclusions. – Bien que la non-inferiorité n’ait pas été obtenue, l’intensification par paliers de GLU combinée à GLAR a montré une efficacité proche du schéma basal-bolus, avec un gain de poids significativement inférieur.

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Mots clés : Diabète de type 2 ; Schéma basal-bolus ; Insuline prandiale ; Insuline glargine ; Insuline glulisine ; Essai randomisé

1. Introduction

Successful glycaemic control in patients with type 2 diabetes mellitus (T2DM) requires the effective use of hypoglycaemic drugs over time. While lifestyle interventions and oral antidiabetic drugs (OADs) are effective in the early stages of T2DM [1], given the progressive nature of the disease, the majority of patients will eventually require an insulin-based combination therapy [2–4]. The current consensus on how to initiate insulin in these patients is to use a long-acting insulin analogue to supplement basal insulin to normalize fasting blood glucose [1].

However, when basal insulin (in combination with OADs) is no longer providing sufficient glycaemic control, many clinicians become uncertain as to the optimal treatment approach, and especially concerning how to use rapid-acting insulin analogues to supplement prandial insulin [5]. As reported in the new American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guidelines, a number of intensification treatment options are available [3,6], and one of the most effective is to add rapid-acting insulin to basal insulin. While overall hyperglycaemia reflects contributions from both basal and post-prandial hyperglycaemia [7], basal or fasting blood glucose appears to contribute more to higher HbA1c levels. In comparison, the current evidence suggests that, following basal insulin treatment, postprandial glucose makes up a relatively greater contribution to overall hyperglycaemia. As such, the addition of rapid-acting insulin to target postprandial glucose excursions following basal insulin therapy appears to be a sensible approach to the management of patients with T2DM [5].

Although the current evidence suggests that a basal-bolus regimen including the addition of a premeal rapid-acting insulin analogue to ongoing basal insulin provides the most physiological and flexible prandial coverage [3], it is not practical for all patients. Moreover, both patients and healthcare professionals have psychological barriers against initiating and intensifying insulin therapy, as well as concerns about the risk of hyperglycaemia, weight gain and disease progression [8]. A lack of medication intensification due to ‘clinical inertia’ (defined as the inefficient implementation of healthcare due to poor patient adherence to medical recommendations and/or poor healthcare-provider adherence to current guidelines) has also recently been identified as a critical barrier to achieving glycaemic goals [9,10].

The OPAL (Orals Plus Apidra® and Lantus®) and ELEONOR studies investigated whether a less-intensive approach with a single injection of prandial insulin (basal-plus strategy) would be more convenient and reduce both postprandial glucose excursions as well as HbA1c levels [11,12]. The OPAL study provided evidence that a single bolus of glulisine added to glargine and OADs significantly reduced HbA1c when administered either at breakfast or with the main meal of the day [12]. The ELEONOR study also demonstrated that adding one dose of glulisine prior to the meal with the highest postprandial glucose excursion to optimize basal glargine facilitated glycaemic control regardless of the use of traditional or telecare blood glucose monitoring [11]. Furthermore, the ELEONOR study showed that a basal-plus strategy that substantially improves metabolic control while minimizing the risk of hypoglycaemia had a positive effect on physical and psychological well-being and treatment satisfaction [13]. Similarly, the STEPwise study demonstrated the efficacy of the stepwise addition of insulin aspart to once-daily insulin detemir based on either perceived meal size or postprandial glucose increments [14].

The Opposing Step-by-Step Insulin Reinforcement to Intensified Strategy (OSIRIS) study was an 18-month trial that investigated three strategies for the stepwise addition of prandial glulisine to a basal regimen of glargine and metformin, with patients continuing their previous OADs. In this study, the specific hypothesis tested was whether the stepwise regimen would yield equivalent glycaemic control, but with fewer unwanted effects, compared with a multiple daily injection (MDI) insulin regimen, while the specific question to answer was whether continuation of an insulin secretagogue (IS) would enhance the stepwise regimen.

2. Methods

2.1. Patients

The primary eligibility criteria included male and female patients with a diagnosis of T2DM, aged 18 to 75 years, with BMI scores ≤ 40 kg/m² and HbA1c > 7%. Patients had to be receiving treatment with basal neutral protamine Hagedorn (NPH) insulin, insulin zinc, insulin glargine or insulin detemir, and at least two OADs, including an IS at any dosage and
metformin (at the maximum tolerated dosage) for more than 6 months; they also had to give their informed written consent to participate. Patients were excluded from the study if they had been treated with thiazolidinediones or insulins other than basal insulin, or if they had proliferative retinopathy, other clinically relevant major diseases, or hepatic or renal dysfunction.

2.1.1. Study design

The OSIRIS trial was a multinational, multicentre, comparative, open-label, randomized, parallel-group study involving 103 centres in 18 countries across Asia, Europe and Mexico. Following patient selection (visit 1), the study comprised a 6-month initial period (visits 2–6) followed by a 12-month randomized treatment period (visits 7–12; Fig. S1; see supplementary material associated with this article online). During the initial 6-month period, all patients received glargine as a single daily injection in the evening, plus their previous OAD treatment, to titrate the insulin dose to achieve fasting blood glucose (FBG) levels ≤ to 120 mg/dL (≤ 6.7 mmol/L). Patients, who were still poorly controlled with basal insulin therapy plus OADs despite having achieved the FBG goal, but with HbA1c > 7%, were randomized to one of three therapeutic approaches for the next 12 months. The first approach was to combine glargine and three bolus injections of glulisine in a standard basal-bolus regimen while maintaining metformin (group 1), but stopping IS use. The two other approaches consisted of more progressive increases in glulisine boluses. In addition to glargine with metformin only (group 2) or metformin with an IS (sulphonylurea or glinide; group 3), patients initially received only a single bolus of glulisine prior to their most hyperglycaemic meal. If after 4 months HbA1c was > 7%, FBG ≤ to 110 mg/dL (≤ 6.1 mmol/L) and postprandial blood glucose (PPBG) ≤ to 160 mg/dL (≤ 8.9 mmol/L), then a second or third bolus was given whereas, if PPBG was > 160 mg/L, the glulisine titration was reinforced. The initial glulisine dose was one-half the meal PPBG (in mmol/L) and titrated according to an algorithm based on PPBG. Blood glucose (BG) was measured as a six-point profile (before and 2 hours after each meal) at the time of inclusion (visit 2), during randomization at visits 8, 10 and 12, and at the study endpoint.

2.2. Insulin titration

The initial dose of insulin glulisine was calculated as the PPBG (in mmol/L) divided by two. Glulisine was then titrated every 3 to 4 days to obtain a PPBG of 110 to 160 mg/dL (6.1–8.9 mmol/L). Group 1 received three daily bolus injections (one injection immediately before each meal). Groups 2 and 3 initially received one daily bolus injection immediately before the meal with the highest PPBG, which then could be adjusted to two daily bolus injections before the two meals with the highest PPBG after 4 months and to three daily bolus injections after 8 months.

The initial dose of glargine was calculated as the dose of previous basal insulin in cases of one daily injection, or the total dose of previous insulin – 20% in cases of more than one daily injection. Glargine was thereafter titrated every 3 to 4 days to achieve FBG levels of 80 to 110 mg/dL (4.4–6.1 mmol/L). During the initial 6-month study period, patients received a single daily injection in the evening at dinnertime or at bedtime (based on patient and/or investigator preferences and according to the study protocol). A switch in the timing of the daily injection (dinnertime or bedtime) was not permitted once the choice had been made. Initial OAD treatment was maintained (at least metformin + IS). During the 12-month randomized treatment period, the patients in group 1 received the same dosage of insulin glargine + three daily boluses of glulisine + metformin (IS use was stopped), group 2 patients received insulin glargine + one to three daily boluses of glulisine + metformin (IS use was stopped) and group 3 patients received insulin glargine + one to three daily boluses of glulisine + metformin + IS (unchanged dosage).

2.3. Study objectives

The overall aim of the OSIRIS study was to establish an optimal treatment for the management of patients with T2DM who require intensification of basal insulin therapy. The primary objective of the study was to show non-inferiority in terms of efficacy (HbA1c) of glargine plus metformin combined with one to three bolus injections of glulisine introduced progressively (group 2) compared with the standard basal-bolus regimen plus metformin (group 1). In addition and only if non-inferiority was achieved, a further analysis was conducted to show non-inferiority in terms of HbA1c of group 2 compared with glargine plus metformin and IS combined, with one to three bolus injections of glulisine introduced progressively (group 3). Secondary objectives were to compare the six-point BG profiles (measured before and 2 hours after each meal), percentages of subjects with HbA1c ≤ 7% at study end, insulin dosages, incidence of hypoglycaemia, changes in body weight over time and treatment satisfaction among the three-treatment groups. Symptomatic hypoglycaemia was defined as an event with clinical symptoms that were considered to result from hypoglycaemia and was associated with prompt recovery after oral carbohydrate administration. Severe hypoglycaemia was defined as an event with clinical symptoms considered to have resulted from hypoglycaemia where the subject required the assistance of another person and had BG levels < 36 mg/dL (< 1.99 mmol/L), or was associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

2.4. Statistical analysis

The primary analysis of efficacy, the change in HbA1c from randomization to endpoint, was carried out in the per-protocol (PP) population (randomized and treated subjects with both baseline and endpoint HbA1c values, and no major protocol violations). Changes in HbA1c from randomization to endpoint were calculated with two-sided 95% CIs from the differences in adjusted means (group 2 – group 1 and group 2 – group 3) obtained by analysis of covariance (ANCOVA), where the change in HbA1c was the dependent variable, the treatment (three levels) was the fixed effect and the value of HbA1c before randomization was the covariate. The non-inferiority of group 2

vs group 1 was concluded if the upper limit of the CI of the difference (group 2 – group 1) was ≤ to 0.4% (statistical tests were performed at the 2.5% one-sided level). If the non-inferiority of group 2 compared with group 1 was confirmed, the same test would then be performed to establish the non-inferiority of group 2 vs group 3.

Sample size was determined on the basis of the following assumptions: a standard deviation (SD) of HbA1c change of 1.1%; a non-inferiority margin of 0.4% for HbA1c; a statistical power of 80% for showing the non-inferiority of group 2 to group 1; and a conditional power of 80% for showing the non-inferiority of group 2 to group 3 (if the non-inferiority of group 2 to group 1 was established). Using the fact that the two tests were clearly correlated (data from group 2 were involved in both tests), 106 evaluable subjects in group 1, 137 in group 2 and 86 in group 3 were required, making a total of 329 evaluable patients. Assuming an expected rate of 15% for non-evaluable patients, a total number of 388 patients had to be randomized. It was also estimated that only 50% of the patients included in the study would fulfill the criteria for randomization, which meant that 776 patients had to be included in the study.

The evolution of HbA1c, BG profiles, body weight and dosages of glulisine were analyzed descriptively in the intention-to-treat (ITT) population (all randomized and treated subjects for whom analysis variables were available).

The safety population comprised all randomized subjects who received at least one dose of glulisine after randomization. The safety analysis included the number and percentage of subjects with at least one symptomatic hypoglycaemia event, and rates of symptomatic hypoglycaemias per subject-year were calculated for each group. Severe hypoglycaemia was considered a serious adverse event (SAE).

3. Results

3.1. Patient status

A total of 811 patients with T2DM poorly controlled with basal insulin [mean ± SD HbA1c, 9.1 ± 1.4% and self-monitored FBG 147 ± 43 mg/dL (8.2 ± 2.4 mmol/L)] were switched to glargine for 6 months while continuing oral therapy. Of these 811 included in the initial period, 476 were randomized (Fig. 1) and 63 prematurely withdrew during the initial period, while 272 patients were not randomized at the end of this period (mainly because of mean FBG > 120 mg/dL). Of the patients who were randomized, 12 were not treated (the most common reason was that the subject did not wish to continue with the study). The PP randomized, the adjusted HbA1c difference in group 2 – group 1 was concluded if the upper limit of the CI of the difference (group 2 – group 1) was ≤ to 0.4% (statistical tests were performed at the 2.5% one-sided level). If the non-inferiority of group 2 compared with group 1 was confirmed, the same test would then be performed to establish the non-inferiority of group 2 vs group 3.

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3.2. Primary objectives

Overall, glycaemic control was poor at randomization with a mean (SD) HbA1c of 8.4% (1.1) and FBG of 104.6 mg/dL (10.5) [5.8 (0.6) mmol/L] (Table 1). The mean percentage change in HbA1c from randomization to endpoint in the PP population was greatest in group 1 [−0.69% (0.09); Table S1; see supplementary material associated with this article online]. Stepwise intensification of glulisine added to glargine (group 2) showed a reduction in HbA1c close to that with basal-bolus treatment (Fig. 2). However, the adjusted difference in group 2 vs group 1 for the PP population (primary analysis) failed to show non-inferiority (0.228, 95% CI: −0.018–0.473), as the upper limit of the 95% CI of the group 2 – group 1 mean-adjusted difference from randomization in HbA1c was ≥ 0.4%. On the other hand, in a subgroup analysis of patients with HbA1c ≤ 8% at randomization, the adjusted HbA1c difference in group 2 (n = 81) vs group 1 (n = 55) did show non-inferiority (0.087, 95% CI: −0.175–0.349) as the upper limit of the 95% CI was < 0.4%. Nevertheless, as non-inferiority was not achieved for the primary analysis (group 2 vs group 1), no non-inferiority test was done to evaluate the group 2 – group 3 differences.

3.3. Secondary objectives

In the ITT population, mean BG profile values decreased in all three groups (Fig. S2; see supplementary material associated with this article online), although the decreases were significantly greater in group 1 than in groups 2 and 3 for post-breakfast (P = 0.033) and post-dinner (P = 0.019) values. Target HbA1c values ≤ 7% were achieved by 27.1% of the patients in group 1, 18.4% in group 2 and 22.4% in group 3. However, the difference between groups 1 and 2 was not significant (−8.72%, 95% CI: −17.92–0.48). The mean daily dose of glargine increased steadily from visit 2 to randomization and then leveled off in all groups, indicating effective titration of basal insulin at randomization. Mean daily doses of glulisine increased steadily from randomization to endpoint in all three groups (Table S1; see supplementary material associated with this article online). Also, the percentage of patients using less than three bolus injections of glulisine with HbA1c ≤ 7% at endpoint was greater in group 3 (19.0%) than in group 2 (12.3%), although the difference was not significant (−6.76%; 95% CI: −15.68–2.16). The mean total daily dose of insulin (glargine and glulisine) was highest in group 1 throughout the treatment period. Overall, the number of bolus injections taken by patients in groups 2 and 3 were considerably lower than those in group 1 by the study end (94% of patients received three bolus injections in group 1 vs 22.8% in group 2 and 19.5% in group 3).

There was no statistically significant difference between treatment arms in the rate (events per patient–year) of overall symptomatic hypoglycaemia as confirmed by BG levels less or equal to 3.9 mmol/L. However, the rate of nocturnal symptomatic hypoglycaemia (BG ≤ 3.9 mmol/L) was significantly lower in group 2 [0.66% (2.37)] than in group 3 [0.92% (2.37); P = 0.0460]. No other statistically significant differences
between treatment groups were found in rates of other types of hypoglycaemia. Among patients in the safety population who achieved the target HbA1c of $\leq 7\%$, symptomatic hypoglycaemia was lowest in group 2. All hypoglycaemia results are shown in Table S2 (see supplementary material associated with this article online). Moderate weight gain was seen in all three groups, but was significantly less in group 2 than group 1 ($P=0.040$; Table S1 and Fig. S3; see supplementary material associated with this article online). Also, in terms of overall treatment satisfaction, Diabetes Treatment Satisfaction Questionnaire Status change (DTSQc) global scores (scale 0–48) were similar across all three-treatment groups, with mean (SD) scores of 11.5 (7.3) in group 1, 12.5 (6.5) in group 2 and 12.6 (5.1) in group 3.

3.4. Safety and tolerability

No adverse events occurred at rates $>5\%$ in any of the treatment groups, and the main adverse events were hypertension (group 1, 2.8%; group 2, 3.6%; group 3, 4.9%), nasopharyngitis (group 1, 2.1%; group 2, 2.5%; group 3, 4.9%), influenza (group 1, 4.2%; group 2, 1.5%; group 3, 1.6%) and bronchitis (group 1, 2.8%; group 2, 3.0%; group 3, 0.8%). A total of 42 patients (9.1%) experienced at least one SAE, but only four were considered treatment-related: one case of hypoglycaemia in group 2; one case of hypoglycaemic seizure in group 1; and two cases of wrong drug administration in group 2. One death each was seen in group 2 (pancreatic carcinoma) and in group 3 (sepsis).
Table 1
Patient demographics in the per-protocol population at randomization.

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 385)</th>
<th>Group 1a (n = 120)</th>
<th>Group 2b (n = 165)</th>
<th>Group 3c (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>58.5 (8.7)</td>
<td>120 (59.1)</td>
<td>58.6 (8.6)</td>
<td>57.7 (9.4)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>158 (41.0)</td>
<td>46 (38.3)</td>
<td>66 (40.0)</td>
<td>46 (46.0)</td>
</tr>
<tr>
<td>Body mass index, n</td>
<td>382</td>
<td>119</td>
<td>163</td>
<td>100</td>
</tr>
<tr>
<td>Mean (SD), kg/m²</td>
<td>30.1 (4.9)</td>
<td>30.3 (4.8)</td>
<td>29.8 (4.9)</td>
<td>30.5 (4.8)</td>
</tr>
<tr>
<td>Mean duration of illness, years (SD)</td>
<td>12.5 (6.7)</td>
<td>13.0 (7.1)</td>
<td>12.6 (6.5)</td>
<td>11.9 (6.5)</td>
</tr>
<tr>
<td>Mean duration of OAD, Treatment, years (SD)</td>
<td>384</td>
<td>120</td>
<td>164</td>
<td>100</td>
</tr>
<tr>
<td>Mean duration of insulin, Treatment, years (SD)</td>
<td>384</td>
<td>120</td>
<td>164</td>
<td>100</td>
</tr>
<tr>
<td>HbA1c, n</td>
<td>385</td>
<td>120</td>
<td>165</td>
<td>100</td>
</tr>
<tr>
<td>Mean, % (SD)</td>
<td>8.4 (1.1)</td>
<td>8.5 (1.1)</td>
<td>8.4 (1.1)</td>
<td>8.3 (1.1)</td>
</tr>
<tr>
<td>Fasting blood glucose, n</td>
<td>385</td>
<td>120</td>
<td>165</td>
<td>100</td>
</tr>
<tr>
<td>Mean, mg/dL (SD)</td>
<td>104.6 (10.5)</td>
<td>104.2 (10.3)</td>
<td>103.9 (11.3)</td>
<td>106.1 (9.3)</td>
</tr>
<tr>
<td>Mean, mmol/L (SD)</td>
<td>5.8 (0.6)</td>
<td>5.8 (0.6)</td>
<td>5.8 (0.6)</td>
<td>5.9 (0.5)</td>
</tr>
</tbody>
</table>

a Glargine + three bolus injections of glulisine.
b Glargine + one bolus injection of glulisine, with two further doses at months 4 and 8 if HbA1c greater than 7% [target postprandial blood glucose (PPBG) 110–160 mg/dL (6.1–8.9 mmol/L)].
c Glargine + insulin secretagogue and one bolus injection of glulisine, with two further doses at months 4 and 8 if HbA1c greater than 7% [target PPBG 110–160 mg/dL (6.1–8.9 mmol/L)].

4. Discussion

In the present study, none of the treatment groups achieved optimal glycaemic control. However, with all three insulin-intensification regimens, patients did show improvement from randomization to study endpoint in overall glycaemic control, including decreases in both HbA1c and mean BG profiles. Patients with long-term T2DM constitute a difficult-to-treat population characterized by suboptimal adherence to treatment, as well as medical and psychosocial problems [15]. Our findings reflect the challenging nature of attaining good glycaemic control in such patients.

Our primary study objective, which was to demonstrate non-inferiority in controlling HbA1c with glargine plus one to three bolus injections of glulisine introduced progressively (group 2) compared with glargine plus three bolus injections of glulisine (group 1), was not achieved. As previously mentioned, the lack of non-inferiority demonstrated in our study may be due in part to the inefficient implementation of healthcare due to poor patient adherence and/or investigator adherence to the study protocol. However, the primary objective was achieved in a subgroup of patients whose HbA1c was ≤ 8% at randomization.

Although non-inferiority was not demonstrated, stepwise intensification of glulisine added to glargine showed efficacy that was similar to that of the basal-bolus approach, but with significantly less weight gain. This safety pattern is important particularly for patients with long-standing T2DM who frequently have co-morbidities and cardiovascular risk factors and/or a history of cardiovascular disease. Continuing insulin secretagogues did not improve patient outcomes in terms of HbA1c, hypoglycaemia or insulin dosage, probably because these patients had limited β-cell function. The patients in groups 2 and 3 did not use as many bolus injections as those in group 1 by the study endpoint (partly as a function of the protocol, whereby the insulin dose was correlated to the glulisine dose), which may be regarded as an advantage in some patients. However, glycaemic control was short of excellent in both those groups, implying that there may be a behavioral difficulty in this population contributing to an inadequate bolus injection regimen. In

any case, the potential clinical impact of inadequate intensification using a stepwise regimen must be recognized when aiming for good glycaemic control.

In addition to improvements in efficacy and safety endpoints, and consistent with the findings reported by Nicolucci et al. [13], our present findings also suggest that a basal-plus approach may have a positive effect on overall treatment satisfaction and quality-of-life. As reported in the new ADA/EASD guidelines [3], a number of intensification treatment options may be considered in patients with T2DM not adequately controlled by OADs and basal insulin. One approach is to administer a premixed, fixed combination of an intermediate insulin with regular insulin or a rapid-acting insulin analogue twice daily prior to the morning and evening meals [16]. While premixed insulins are a valuable addition to the treatment armamentarium, they may not provide adequate glycaemic control in all patients and offer less flexibility than other approaches [17]. The combination of basal insulin with a glucagon-like peptide−1 (GLP−1) mimetic has resulted in improvements in HbA1c and PPBG, with concomitant weight loss and no marked increase in the risk of hypoglycaemia [18]. An alternative approach to the premixed insulins and GLP−1 mimetic is the use of a basal-bolus approach with insulin-intensification. By administering short-acting analogues before each meal, patients are able to more closely mimic the normal physiological pattern of insulin secretion and so reduce glucose excursions [19–21]. This approach is often considered the most physiological and flexible of the available treatment options; however, some patients with T2DM may find this regimen too complex to apply. Another approach that is commonly used in clinical practice is the basal-plus stepwise treatment regimen. The basal-plus approach involves a single injection of prandial insulin prior to the meal that induces the largest PPBG excursion. While less well studied than either the basal-bolus or premixed regimens, our present findings along with those of the OPAL [12], ELEONOR [11,13] and STEPwise [14] studies suggest that intensification of insulin using a basal-plus regimen can effectively control hyperglycaemia and improve quality-of-life outcomes in patients with T2DM, with less weight gain and fewer bolus injections per day. Furthermore, the present study also provides evidence that prandial insulin injections can be introduced as and when the need to achieve or maintain good glycaemic control arises.

5. Conclusion

Thus, although the basal-plus stepwise regimen failed to achieve non-inferiority to the basal-bolus regimen, the improvement in HbA1c was close to that of the basal-bolus regimen, with significantly less weight gain and fewer bolus injections needed per day. In addition, in patients with HbA1c ≤ 8%, non-inferiority was achieved with the basal-plus regimen. The latter may therefore be a practical method of insulin-intensification because of its greater simplicity and safety, and its efficacy is not enhanced by continuation of an insulin secretagogue.

Disclosure of interest

Denis Raccah has received honoraria from Sanofi for his participation in the steering committee of this study, and has also received compensation for board membership from Merck, Bristol-Myers Squibb, Novartis, MSD, Novo Nordisk, Eli Lilly and Sanofi. Pascale Labard is an employee of Sanofi. Alfred Penfornis has received honoraria from Sanofi for his participation in the steering committee of this study, and has also received compensation for board membership from AstraZeneca, Bristol-Myers Squibb, Novartis, Novo Nordisk and Sanofi, and consulting fees from Novo Nordisk, Merck-Serono and Pierre Fabre. Louis Monnier received compensation fees for participation in the steering committee. Douglas Robertson has received honoraria from Sanofi for his participation in the steering committee of this study, and has also received compensation for board membership from Novartis, Novo Nordisk, Roche and Sanofi. Thomas Haak has received honoraria for board membership of Sanofi, MSD, Roche, BMS and Colgate Palmolive. Juan Soler has received honoraria from Sanofi for participation in the steering committee of this study. Dominique Huet has nothing to disclose.

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Appendix A. Supplementary data

Supplementary material (Tables S1–2 and Figs. S1–3) associated with this article can be found at http://www.sciencedirect.com, at http://dx.doi.org/10.1016/j.diabete.2012.08.010.

References