Randomized Comparison of Pramlintide or Mealtime Insulin Added to Basal Insulin Treatment for Patients With Type 2 Diabetes

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OBJECTIVE — To compare the efficacy and safety of adding mealtime pramlintide or rapid-acting insulin analogs (RAIAs) to basal insulin for patients with inadequately controlled type 2 diabetes.

RESEARCH DESIGN AND METHODS — In a 24-week open-label, multicenter study, 113 patients were randomly assigned 1:1 to addition of mealtime pramlintide (120 μg) or a titrated RAI to basal insulin and prior oral antihyperglycemic drugs (OADs). At screening, patients were insulin naive or had been receiving <50 units/day basal insulin for ≤6 months. The basal insulin dosage was titrated from day 1, seeking fasting plasma glucose (FPG) ≥70–<100 mg/dl. Pramlintide and an RAI were initiated on day 1 and week 4, respectively. The proportion of patients achieving A1C ≤7.0% without weight gain or severe hypoglycemia at week 24 was the primary end point.

RESULTS — More pramlintide- than RAI-treated patients achieved the primary end point (30 vs. 11%, P = 0.018) with a similar dose of basal insulin. Pramlintide and an RAI yielded similar mean ± SEM values for FPG and A1C at 24 weeks (122 ± 7 vs. 123 ± 5 mg/dl and 7.2 ± 0.2 vs. 7.0 ± 0.1%, respectively) and similar least squares mean reductions from baseline to end point (−31 ± 6 vs. −34 ± 6 mg/dl and −1.1 ± 0.2 vs. −1.3 ± 0.2%, respectively). Both RAIAs but not pramlintide caused weight gain (+4.7 ± 0.7 vs. +0.0 ± 0.7 kg, P < 0.0001). Fewer patients reported mild to moderate hypoglycemia with pramlintide than with the RAI (53 vs. 82%), but more patients reported nausea (21 vs. 0%). No severe hypoglycemia occurred in either group.

CONCLUSIONS — In patients taking basal insulin and OADs, premeal fixed-dose pramlintide improved glycemic control as effectively as titrated RAIAs. The pramlintide regimen sometimes caused nausea but no weight gain and less hypoglycemia.

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ment severe hypoglycemia within the last 6 months, or had a history of hypoglycemia unawareness. Patients with gastroparesis or those who required medications to alter gastric motility were excluded, as were patients using exenatide or sitagliptin, any antiobesity agents, systemic glucocorticoid agents, or investigational medications. Patients with eating disorders, a history of bariatric surgery, or plans to lose weight were excluded, as were patients with any significant medical conditions or advanced diabetes complications.

Ethical considerations

The study protocol was approved by applicable institutional review boards and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study initiation.

Study design and interventions

This was a randomized, open-label, parallel-group, multicenter 24-week study conducted at 29 centers throughout the U.S. between April 2007 and May 2008 (a complete list of the participating investigators can be found in the Appendix). After the screening visit, eligible patients visited the study center on day 1 (baseline) and at weeks 4, 8, 12, 18, and 24. Scheduled telephone visits to review self-monitored glucose measurements and direct insulin adjustment occurred between visits. Random assignment 1:1 to pramlintide (Amylin Pharmaceuticals, San Diego, CA) or to an RAIA (insulin lispro, insulin aspart, or insulin glulisine) occurred at baseline and an RAIA at each subsequent visit or (for the dinnertime dose) at bedtime. Patients self-monitored blood glucose daily according to individualized advice from site investigators. A seven-point glucose profile consisting of measurements taken 15 min before and 1.5–2 h after the start of each of the three meals and at bedtime was completed during the week before each visit. At each visit, weight, body circumference, and vital signs were measured and blood glucose values were reviewed. Participants were counseled on adjustment of basal and mealtime insulin dosage (RAIA group) at each visit. A1C was measured at all study visits, and FPG was measured at screening, baseline, and weeks 4, 12, and 24. No specific lifestyle modification was advised; patients were asked to maintain usual diet and exercise patterns.

Study end points

The primary end point was the proportion of patients achieving the following prespecified criteria at week 24: 1) A1C ≤7.0%, 2) no weight gain from baseline, and 3) no severe hypoglycemia. Severe hypoglycemia was defined as an event requiring assistance of another individual and/or administration of glucagon injection or intravenous glucose. Secondary end points included the individual components of the composite end point, insulin dose, A1C, change in A1C, proportion of patients reaching A1C ≤6.5%, FPG, postprandial glucose increments, changes in weight, changes in waist circumference, and adverse events including the incidence, severity, and time courses of hypoglycemia and nausea.

Statistical analyses

A sample size of 45 patients per group was predicted to provide 90% power to detect a 27% difference in the proportion of patients achieving the primary end point (α = 0.05). Analyses were performed on patients within the intent-to-treat (ITT) population including all randomly assigned patients receiving at least one dose of study medication. Missing individual data were imputed from the last scheduled visit (last observation carried forward). Insulin dose was analyzed in the ITT observed population. Measured values for insulin dose, A1C, FPG, and glucose increments are presented as arithmetic mean ± SEM.

Fisher’s exact test was used to compare the proportion of patients achieving the primary end point. The Cochran-Mantel-Haenszel test that controlled for A1C at screening was used as a confirmatory test. Intergroup comparisons of continuous changes from baseline were assessed with ANOVA models including treatment group, A1C at screening (≤9.0% or >9.0%), insulin treatment before screening, and baseline value (for parameters other than A1C). Data were reported as least squares mean change ± SEM.

RESULTS

Patient disposition, baseline demographics, and therapies

Of 113 patients randomly assigned, 48 (84%) pramlintide-treated and 50 (89%) RAIA-treated patients completed the study (Table 1). One patient in the pramlintide group withdrew consent before ingesting study medication, resulting in an ITT population of 56 patients per treatment group. Baseline characteristics were well matched between groups (Table 1). Before the study, 46% of patients used insulin and 91% of patients used at least one OAD.

Basal insulin dosage increased steadily throughout the study, resulting in similar mean doses at week 24: 52 ± 4 units/day (0.48 ± 0.04 unit·kg⁻¹·day⁻¹) for pramlintide-treated patients and 57 ± 4 units/day (0.52 ± 0.04 units·kg⁻¹·day⁻¹) for RAIA-treated patients and 57 ± 4 units/day (0.52 ± 0.04 units·kg⁻¹·day⁻¹) for patients in the RAIA arm (Fig. 1A). After 24 weeks, RAIA-treated patients administered a mean daily dose of 37 ± 3 units (0.34 ± 0.03 unit·kg⁻¹·day⁻¹) of insulin lispro, aspart, or glulisine. Numbers of patients initiating therapy with insulin lispro, aspart, or glulisine were 16 (29%), 31 (55%), and 9 (16%), respectively. To achieve glycemic results similar to those of the pramlintide group, patients in the RAIA group used an average of 80% more insulin (basal + rapid-acting) at week 24 (94 vs. 52 units, respectively).

Forty-six participants (82%) continued to take 120 µg pramlintide before the treatment period.
Daily basal insulin dose at baseline (units/day) 20

Baseline demographics

| ITT population | 56 | 56 |
|----------------|----|----|
| Sex (male/female) | 34/22 | 37/19 |
| Race (Caucasian/other) | 48/8 | 43/13 |
| Age (years) | 55 ± 11 | 54 ± 10 |
| Weight (kg) | 108 ± 22 | 103 ± 18 |
| BMI (kg/m²) | 36 ± 6 | 36 ± 6 |
| Diabetes duration (years) | 10 ± 7 | 9 ± 6 |
| HbA1C (%) | 8.2 ± 0.8 | 8.3 ± 0.8 |
| FPG (mg/dl) | 155 ± 40 | 164 ± 50 |
| OAD use at randomization | 50 | 52 |
| Average number of oral medications per patient | 1.9 | 1.7 |
| Sulfonylurea | 34 | 29 |
| Metformin | 36 | 38 |
| Thiazolidinediones | 16 | 15 |
| Combined drug formulations | 5 | 2 |
| Insulin use before randomization | 27 | 24 |
| Daily basal insulin dose at baseline (units/day) | 20 ± 10 | 24 ± 12 |
| Type of basal insulin initiated after randomization | | |
| Insulin glargine q.d. | 37 | 45 |
| Insulin glargine b.i.d. | 1 | 0 |
| Insulin detemir q.d. | 18 | 11 |
| Insulin detemir b.i.d. | 0 | 0 |

Data are n or means ± SD.

meals throughout the study. Two participants reduced the dosage to 60 μg because of nausea.

**Primary end point**
The primary composite end point comprised several highly desirable goals assessed after 24 weeks of treatment: A1C ≤7.0%, no weight gain from baseline, and no severe hypoglycemia (Table 2). Significantly more pramlintide-treated than RAIA-treated patients achieved this end point (30 vs. 11%, P = 0.018). Among the components of the composite, only the percentage of patients without weight gain at week 24 differed significantly between pramlintide- and RAIA-treated patients (59% vs. 16%, P < 0.0001). No significant differences in the frequency of achieving A1C ≤7.0% or in the incidence of severe hypoglycemia were observed between groups.

**Secondary end points**

**A1C.** Mean A1C at 24 weeks was 7.2 ± 0.2% with addition of pramlintide and 7.0 ± 0.1% with addition of an RAIA (Fig. 1B). The least squares mean reduction of A1C from baseline was −1.1 ± 0.2 for pramlintide and −1.3 ± 0.2 for RAIA (P = 0.46 between groups). A1C ≤6.5% at 24 weeks was achieved by 16 of 56 (29%) of patients treated with pramlintide and by 19 of 56 (34%) of patients treated with an RAIA (P = 0.68 between groups). A1C values were stable after week 12 (Fig. 1B).

**Weight and waist circumference.** A significant between-group difference in weight was observed throughout the study (Fig. 1C). At week 24, mean weights were 106 ± 3 kg (pramlintide) versus 109 ± 3 kg (RAIA). Least squares mean changes in weight from baseline were +0.0 ± 0.7 kg (pramlintide) versus +4.7 ± 0.7 kg (RAIA) (P < 0.0001).

Differences in waist measurements were consistent with weight differences. Waist circumferences at week 24 were 115 ± 2 and 120 ± 2 cm for the pramlintide and RAIA groups, respectively. Least squares mean changes in waist circumference from baseline were −0.6 ± 0.9 and +2.2 ± 0.9 cm, respectively (P = 0.016).

**FPG.** Similar basal insulin titration in both treatment arms resulted in similar mean FPG concentrations at week 24: 122 ± 7 mg/dl (pramlintide) and 123 ± 5 mg/day (RAIA) (Fig. 1D). The least squares mean change of FPG from baseline was −31 ± 6 mg/dl (pramlintide) and −34 ± 6 mg/dl (RAIA) (P = 0.65). An FPG concentration <100 mg/dl was achieved at week 24 by 17 of 56 (30%) of pramlintide-treated and 15 of 56 (27%) of RAIA-treated patients (P = 0.83).

**Postprandial glucose increments.** Postprandial glucose increments were similar between treatment groups at week 24 (Fig. 2A). No significant difference in the least squares mean change in postprandial increment from baseline to week 24 was found between treatment groups (−17 ± 5 mg/dl [pramlintide] vs. −27 ± 5 mg/dl [RAIA], P = 0.17).

**Adverse events.** The most common adverse events were hypoglycemia and nausea (Fig. 2B). Although no episodes of severe hypoglycemia were observed, mild or moderate hypoglycemia occurred more frequently than nausea in both treatment groups and was observed in more patients treated with RAIAAs (82%) than with pramlintide (55%). Hypoglycemic events occurred more frequently in the pramlintide treatment group in the first 4 weeks but were more common in the RAIA treatment group from 18 to 24 weeks (Fig. 2C). Nausea was reported only in the pramlintide group (12 of 56 [21%]), most often early in treatment (10 of 56 patients in the first 4 weeks), and declined over time (Fig. 2D). Two patients (4%) withdrew from pramlintide therapy and the study because of nausea.

Eight serious adverse events were reported in six patients during the study: one patient in the pramlintide group (coronary artery disease) and five patients in the RAIA group (coronary artery disease, congestive heart failure, ischemic cerebral infarction, syncope, noncardiac chest pain, cellulitis, and biliary dyskinesia).
CONCLUSIONS—This head-to-head comparison demonstrated that pre-meal pramlintide and RAIA have similar glycemic effects when either agent is added to titrated basal insulin with or without an OAD. On average, pramlintide reduced A1C from 8.2 to 7.2%, and an RAIA reduced A1C from 8.3 to 7.0% after 24 weeks of treatment. Reductions in A1C, FPG, and postmeal glycemic increments were not statistically different between treatment groups. However, changes in body weight accompanying improved glycemic control differed between treatments. By the most conservative assessment (the between-treatment difference of change from baseline in all patients receiving study medication, last observation carried forward), RAIA treatment contributed to a 4.7 kg (10.3 lb) gain compared with pramlintide treatment over 24 weeks. With similar glycemic effects and no severe hypoglycemic events with either treatment, the composite primary end point favored pramlintide over an RAIA because of the difference in weight gain.

Other clinical differences between these therapies are related to unwanted effects. The incidence of hypoglycemia was greater with an RAIA plus basal insulin than with pramlintide plus basal insulin (82 vs. 55%). Nausea occurred more frequently with pramlintide, and two patients (4%) withdrew from the study. However, as in other clinical studies, reports of nausea associated with pramlintide declined steadily during continued treatment.

This study builds on findings of a 16-week study that compared administration of pramlintide versus placebo during titration of basal insulin with continuation of an OAD, in which glycemic control improved more with pramlintide than with placebo and no severe hypoglycemia was reported (15). Weight declined a mean of 1.6 kg with pramlintide but increased 0.7 kg with placebo. The larger absolute body weight difference between groups in this study is probably due to RAIA-associated weight gain.

The potential clinical importance of weight gain associated with treatment for hyperglycemia has been studied for many years and remains controversial. An unfavorable relationship between adiposity and a variety of medical outcomes, including cardiovascular disease, is well established (17,18). Recently, an obser-
A observational study of ~4,900 patients with type 2 diabetes showed a 13% increase in risk for fatal or nonfatal coronary heart disease with each 1-unit increase of BMI over ~6 years (19). Furthermore, evidence suggests that intended weight reduction reduces cardiovascular risk factors (20) and mortality (21). However, direct evidence that weight gain associated with insulin treatment is harmful is lacking. Notably, at the end of 10 years of randomized treatment, the U.K. Prospective Diabetes Study (UKPDS) showed a marginally significant reduction of myocardial infarction (16%, P = 0.052) with insulin or sulfonylurea treatment compared with dietary treatment, despite greater weight gain. Follow-up after cessation of randomized treatment showed persistence of the difference over time, and the advantage of insulin or sulfonylurea became statistically significant with more events (15% lower A1C in this group (25)). Potential underlying mechanisms include the doubled occurrence of weight gain >10 kg with intensive treatment, the threefold increase of severe hypoglycemia, or both.

This study had several limitations. It was a small study, powered to address the composite primary outcome but not separate clinical outcomes, and the open-label design allows the possibility of unintended bias. The 4-week delay in initiating an RAIA to avoid insulin-induced hypoglycemia from simultaneous initiation of basal and rapid-acting insulin was also a limitation. Because of the difference in the timing of RAIA initiation, the potential for weight gain in the RAIA group may be underestimated at week 24, but glycemic outcomes at week 24 did not seem to be affected, as insulin doses, A1C, and FPG in both treatment groups stabilized after 12 weeks, well before the study’s end. The incidence of nausea accompanying initiation of pramlintide (~20%) was confirmed as a leading drawback of starting treatment at 120 mg. Both nausea associated with pramlintide and hypoglycemia/weight gain associated with an RAIA might have been mitigated by more gradual titration. The small imbalance in use of detemir as the basal insulin (18 with pramlintide and 11 with an RAIA) is of uncertain significance. Differences in overall costs between the pramlintide and RAIA regimens might exist but are not addressed in this study of efficacy and safety.

Overall, these findings support the role of mealtime pramlintide as a potential alternative to RAIA for patients using basal insulin treatment with or without OADs who are not achieving glycemic goals. Longer-term studies to evaluate cardiovascular and microvascular outcomes of controlling after-meal hyper-
Pramlintide versus mealtime insulin

glycemia without weight gain and hypoglycemia would be helpful to inform clinical treatment decisions for patients with type 2 diabetes.

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APPENDIX

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