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ORIGINAL RESEARCH

Basal-Bolus Therapy with Insulin Detemir Using the 303 Algorithm in the US PREDICTIVE 303 Trial

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ABSTRACT

Introduction: The aim of this study was to compare a simplified patient-driven algorithm (303 Algorithm) to physician-driven adjustments in a subset of 193 patients with type 2 diabetes from the PREDICTIVE 303 study who were using basal-bolus insulin therapy. ***Methods:*** PREDICTIVE 303 was a 26-week, randomized, phase 4 study, in which subjects were either instructed to adjust their insulin detemir dose every 3 days by ±3 units if mean fasting plasma glucose (FPG) values were above 110 mg/dL or below 80 mg/dL (303 Algorithm), or had physicians adjust the insulin detemir dose according to usual practice (Standard-of-care). ***Results:*** Patients in both groups achieved similar reductions in glycated hemoglobin (–0.2% and –0.3% for 303 Algorithm and Standard-of care groups, respectively; between groups P=0.60). 303 Algorithm group patients achieved a greater reduction in FPG (–21.3 mg/dL vs. 0.2 mg/dL; between groups P=0.03). Both 303 Algorithm and Standard-of care groups experienced a similar rate of overall hypoglycemia, and similar weight reduction (–1.7 kg and –0.4 kg, respectively; between groups P=0.07). Over 82% of patients in both groups used insulin detemir once daily. ***Conclusions:*** Adjustments of a once-daily detemir dose by patients using the 303 Algorithm in a basal-bolus setting is equally effective in improving glycemic control in patients with type 2 diabetes compared with physician-directed basal dose adjustments.

Keywords: basal-bolus; insulin detemir; insulin titration; long-acting insulin analog; PREDICTIVE 303; type 2 diabetes

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INTRODUCTION

Insulin detemir is a long-acting basal insulin analog indicated for the treatment of patients with type 1 and type 2 diabetes.[1] When used as the long-acting basal component in basal-bolus insulin therapy,

insulin detemir has been shown to effect improvements in glycemic control with less hypoglycemia compared with neutral protamine hagedorn (NPH) insulin, and a weight-sparing effect compared with other basal insulin preparations.[2-6] Furthermore, insulin detemir's relatively flat time-action profile with a duration of action of ≤24 hours in patients with type 2 diabetes allows for once-daily dosing,[7] offering patients a simple and convenient therapy regimen. Compared with other basal insulin preparations, insulin detemir has also demonstrated less within-subject variability in its glucose-lowering effect, which is likely a result of its unique structure and mechanism of action, facilitated by its solubility in the subcutaneous tissue and albumin binding in the circulation.[7-9]

The Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation 303 (PREDICTIVE 303) study was a phase 4, randomized clinical trial in 5604 patients with type 2 diabetes from over 1000 mainly primary care practices in the United States, which completed in December 2006.[10] The aim of this study was to compare the efficacy and safety of insulin detemir in controlling glycemia in patients with type 2 diabetes using one of two dosing algorithms for insulin detemir titration: 1) patients were given a simple dosing algorithm to adjust their insulin detemir dose, the 303 Algorithm group; or 2) physicians applied their standard-of-care in adjusting their patient's insulin detemir dose, the Standard-of-care group. The analysis presented here shows data from the subgroup of patients from the PREDICTIVE 303 study who, prior to the study, were using basal-bolus insulin therapy.

MATERIALS AND METHODS

Patients with type 2 diabetes (age ≥18 years, glycated hemoglobin [HbA_{1c}] ≤12%, and body mass index ≤45 kg/m^2) were eligible for enrollment regardless of their antidiabetic regimens. Patients were excluded from the study if they anticipated a change in concomitant medication known to interfere with glucose metabolism (such as systemic steroids, nonselective beta-blockers, or monoamine oxidase inhibitors); were taking any glucose-lowering medication that was not approved in combination with insulin (such as glucagon-like peptide-1 analogs); had proliferative retinopathy or maculopathy; were known to have hypoglycemia unawareness (patients cannot recognize typical warning signs) or recurrent major hypoglycemia; were pregnant or breast feeding; or had other serious illness. Prior to trial initiation, the institutional review board reviewed and approved of the protocol, protocol amendment, consent form, and the subject information sheet. All patients enrolled in the study provided signed informed consent.

This post-hoc subanalysis of the PREDICTIVE 303 study focuses on patients with type 2 diabetes who were using basal-bolus insulin therapy prior to study enrollment (*n*=193).

Study Design and Treatment

Patients were encouraged to maintain contact with their physician throughout the study. Patients participated in a screening/baseline visit, and two additional visits at weeks 12 and 26; visits occurred at the study sites, which were predominantly primary care practices. Patients received a glucose meter (OneTouch® UltraSmart®; LifeScan,

CA, USA) and test strips, with appropriate instructions for use. All glucose measurements performed with capillary blood were automatically calibrated, or "adjusted," by the meter to plasma-equivalent glucose values. Insulin detemir (rDNA origin) (Levemir®; Novo Nordisk A/S, Bagsvaerd, Denmark) was supplied in the FlexPen® (3 mL, 100 U/mL).

Insulin detemir was to be used as the only basal insulin throughout the duration of the study. Patients were directed to use insulin detemir once daily in the evening at approximately the same time each day. For both the 303 Algorithm and Standard-of-care groups, the physician determined the initial dose of insulin detemir based on the package insert,[1] which recommended switching from a previous basal insulin to insulin detemir on a unit-to-unit basis. During the first 12 weeks, only the dose of the basal insulin was to be titrated. During the final 14 weeks, the investigator was encouraged to adjust any medication being taken to treat diabetes, including prandial insulin doses, in either of the treatment groups, if appropriate.

For logistical reasons, randomization was done by site. Study sites were randomized to either the 303 Algorithm group or the Standard-of-care group. Patients from the 303 Algorithm group sites were instructed to use a simple algorithm to adjust their insulin detemir dose every 3 days based on the average of three self-measured plasma-equivalent or adjusted fasting plasma glucose (aFPG) values:

- Mean aFPG <80 mg/dL (4.4 mmol/L): reduce dose by 3 units
- Mean aFPG between 80-110 mg/dL (4.4-6.1 mmol/L): no change in dose
- Mean aFPG >110 mg/dL (6.1 mmol/L): increase dose by 3 units.

Patients in the 303 Algorithm group were instructed to perform self-measured blood glucose (SMBG) testing before breakfast on a daily basis in order to self-titrate their insulin dose.

Physicians adjusted the insulin detemir dose for patients from the Standard-of-care group sites according to their usual practice. Throughout the study, patients in the Standard-of-care group were asked to perform SMBG before breakfast on the last 6 days before each scheduled visit.

Assessments

The safety analysis set included all patients who took at least one injection of insulin detemir post-baseline and had any report of safety information. The efficacy analysis set included all patients who were enrolled for at least 18 weeks and had at least one post-baseline visit at week 12 or week 26. Each patient in the efficacy analysis set was also to have one baseline measurement and one post-baseline measurement (week 12 or week 26) on at least one of the following parameters: fasting blood glucose (lab), HbA_{1c}, weight, or hypoglycemic events.

The main outcome variables for the efficacy evaluation were HbA_{1c} and the change in HbA_{1c} from baseline at the end of the 26-week treatment period. Change in HbA_{1c} was analyzed only in those patients who had HbA_{1c} values at baseline and at 26 weeks. A linear model with the treatment group as a fixed effect and baseline HbA_{1c} as a covariate was used to perform a treatment comparison between the 303 Algorithm group and Standard-of-care group, within the subgroup of patients. The goal of statistical testing was to demonstrate noninferiority of the 303 Algorithm

treatment method in comparison with the Standard-of-care treatment method. The noninferiority margin for HbA_{1c} was selected to be 0.4%, a margin consistently used and accepted in phase 3 trial programs.[11] For the overall PREDICTIVE 303 study, a sample size of 2000 patients per group was needed to detect with 85% power at a significance level of 0.025 (one-sided testing) a true difference of 0.25% in HbA_{1c} change from baseline between the two treatment groups (assuming an SD of 1.57% in each treatment group) and meet the noninferiority criteria. The 95% confidence intervals (CI) and the *P* value for the difference in the change in HbA_{1c} from baseline between the 303 Algorithm and Standard-of-care treatment groups were also assessed.

Additional outcome variables for the efficacy evaluation included baseline FPG, change in FPG from baseline and variability in FPG, proportion of subjects achieving HbA_{1c} <7.0%, HbA_{1c} values and the change in HbA_{1c} from baseline for patients with baseline HbA_{1c} <9.0% and ≥9.0%, dose of insulin detemir, and changes in body weight. Variability in FPG was measured by the coefficient of variation (CV) of self-monitored fasting blood glucose values of each visit for each patient and was calculated as 100 times the ratio of the sample SD to the sample mean. The CV was based on up to six measurements of before-breakfast SMBG testing; if a patient had less than two SMBG measurements at a visit, the CV for that visit was not calculated. Blood samples were drawn at all study site visits for analysis of HbA_{1c} and FPG by a central laboratory (Quest Diagnostics, Lyndhurst, NJ, USA). Body weight was also measured at all visits.

The proportion of patients reaching targeted HbA_{1c} values (<7%) with or without hypoglycemia at weeks 12 and 26 was compared between treatments using a Chi-squared test. A *t* test was used to obtain *P* values for the change in data from day 1 within treatment groups. For comparison of data between treatment groups, the change in parameters from day 1 was analyzed in an analysis of covariance (ANCOVA) model with treatment as fixed effect and baseline value as covariate. Statistical analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC, USA).

The safety data collected included adverse events and hypoglycemic events. Incidence of hypoglycemic events (daytime, nocturnal, and major) was included in the safety evaluation. Rates from the two treatment groups were compared by a two-sided 95% CI for the rate ratio; the two rates were considered different if one was not contained in the CI. Hypoglycemic events were generally defined as: 1) symptoms of hypoglycemia that resolve with oral carbohydrate intake, glucagon, or intravenous glucose; 2) any symptomatic or asymptomatic blood glucose of <56 mg/dL (3.1 mmol/L). A nocturnal hypoglycemic event was defined as an episode consistent with hypoglycemia that occurred between 11 PM and 6 AM. Major hypoglycemic events were defined as events with severe central nervous system symptoms consistent with hypoglycemia in which the patient was unable to treat himself/herself and had blood glucose of <56 mg/dL (3.1 mmol/L), or reversal of symptoms after food intake, glucagon, or intravenous glucose. Hypoglycemic events were measured by number of events per patient, per year.

RESULTS

Demographics and Baseline Characteristics of Patients Using Basal-Bolus Insulin Therapy Prior to the Study

This subgroup analysis of the PREDICTIVE 303 study included 193 patients (3% of patients in the entire study) who were using basal-bolus insulin therapy prior to study enrollment. The safety population was comprised of 193 patients, while the efficacy population included 192 patients. One patient was excluded from the efficacy population for having a follow-up time greater than 36 weeks. Among this basal-bolus subgroup of 193 patients, 191 patients completed the study; data were missing for one patient and one lost contact. Patients in the 303 Algorithm and Standard-of-care groups within this subgroup exhibited similar baseline characteristics (Table 1). Mean HbA_{1c} among all patients was 8.2% and mean FPG was 163 mg/dL (9.1 mmol/L). Overall, 16% of patients had an HbA_{1c} of <7%, while 24% of patients had an HbA_{1c} that exceeded 9%.

Approximately 88% of patients were using insulin glargine as their basal insulin; the remainder were using NPH insulin. On day 1 of the study, 174 patients (90.2%) transitioned to basal-bolus insulin therapy with insulin detemir as the basal insulin; two of

Table 1. Patient demographics and baseline characteristics*.

	303 Algorithm	Standard-of-care	Total
n	101	92	193
Age, years	57.1±13.1	62.4±11.9	59.6±12.8
Gender, female/male, *n* (%)	45 (45)/56 (55)	46 (50)/45 (49)	91 (47)/101 (52)
Weight, kg	89.4±20.3	91.9±18.8	90.6±19.6
BMI, kg/m^2	31.2±6.5	32.6±5.9	31.8±6.2
Duration of type 2 diabetes, years	15.3±10.2	16.1±10.6	15.7±10.3
HbA_{1c}, %	8.3±1.4	8.2±1.3	8.2±1.4
HbA_{1c} categories, *n* (%)			
<7%	16 (15.8)	15 (16.3)	31 (16.1)
7%-7.5%	13 (12.9)	13 (14.1)	26 (13.5)
7.6%-8.0%	21 (20.8)	20 (21.7)	41 (21.2)
8.1%-8.5%	8 (7.9)	14 (15.2)	22 (11.4)
8.6%-9.0%	16 (15.8)	10 (10.9)	26 (13.5)
>9%	27 (26.7)	20 (21.7)	47 (24.4)
FPG, mg/dL	165.5±79.7	159.1±66.8	162.5±73.8

Data reported as mean±SD unless otherwise stated.
*Data from safety population.
BMI=body mass index; FPG=fasting plasma glucose; HbA_{1c}=glycated hemoglobin.

these patients were also using oral antidiabetic drugs (OADs). Nineteen patients (9.8%) transitioned to basal-only therapy with insulin detemir ± OADs. Ninety-five percent of patients started insulin detemir once daily.

Glycemic Control

The data reported in Table 2 is from the efficacy analysis set; patients were excluded from the efficacy analysis set if they had no efficacy measurements for at least one of the parameters at two visits and were not enrolled for at least 18 weeks.

HbA_{1c}

Patients in the 303 Algorithm and Standard-of-care groups achieved similar reductions in HbA_{1c} after 12 weeks (–0.2% and –0.2%, respectively; between-group difference 0.0%, *P*=0.95) and after 26 weeks (–0.2% and –0.3%, respectively; between-group difference 0.1%, *P*=0.60) (Table 2). Therefore, self-titration of insulin detemir dosing using the 303 Algorithm was observed to be noninferior to physician titration in patients using basal-bolus therapy after 26 weeks. Compared to baseline (see Table 1), a greater percentage of patients in both the 303 Algorithm and Standard-of-care groups was able to achieve an HbA_{1c} of <7% after 26 weeks (28% and 20%, respectively; between groups *P*=0.20), and the majority of these patients did so without experiencing any hypoglycemia during the 4 weeks prior to the week 26 visit (19% and 14%, respectively; between groups *P*=0.40).

FPG

Similar reductions in FPG were achieved by patients in the 303 Algorithm and Standard-of-care groups after 12 weeks (–20.8 mg/dL [1.2 mmol/L] and –10.3 mg/dL [0.6 mmol/L], respectively; between-group difference –10.5 mg/dL [0.6 mmol/L], *P*=0.25). However, after 26 weeks, patients in the 303 Algorithm group achieved a greater reduction in FPG than those patients in the Standard-of-care group, who experienced no change in FPG (–21.3 mg/dL [1.2 mmol/L] and 0.2 mg/dL [0.01 mmol/L], respectively; between-group difference –21.4 mg/dL [1.2 mmol/L], *P*=0.03) (Table 2).

At the end of the study, a greater reduction in within-subject variability of self-measured FPG was observed in patients in the Standard-of-care group compared with the 303 Algorithm group (–5.8 and –1.1, respectively; between-group difference 4.7, P=0.03). The Standard-of-care group experienced a significant reduction in variability from baseline (Table 2).

Safety

Hypoglycemia

At baseline, the rates (events per patient per year) of overall, daytime, and nocturnal hypoglycemic events were similar among patients in the 303 Algorithm and Standard-of-care groups. While at 26 weeks patients in both groups experienced similar rates of overall hypoglycemia, the Standard-of-care group experienced a lower rate of daytime hypoglycemic events (8.5 vs. 12.0, between groups *P*=0.01), but a greater rate of nocturnal hypoglycemia (10.1 vs. 5.4, between groups *P*=0.01) (Figure 1) compared with the 303 Algorithm group.

Patients in the 303 Algorithm group experienced a significant reduction from baseline in the rate of all hypoglycemic events after

Table 2. Glycemic control and body weight at end of study (from efficacy analysis set*).

	303 Algorithm	Standard-of-care	Total
HbA_{1c}, %			
n	101	91	192
Day 1	8.3±1.4	8.1±1.3	8.2±1.4
n	99	86	185
12 weeks	8.1±1.6	8.0±1.2	8.1±1.4
Change from day 1 (12 weeks)	−0.2±0.1	−0.2±0.1	−0.2±1.0
P value, vs. day 1 (12 weeks)	0.0284	0.0799	0.0049
Difference (303 Algorithm – Standard-of-care) (95% CI)	0.0 (−0.3 to 0.3)		
P value, between groups (12 weeks)	0.9460		
n	99	89	188
26 weeks	8.1±1.6	7.9±1.3	8.0±1.5
Change from day 1 (26 weeks)	−0.2±0.1	−0.3±0.1	−0.3±1.2
P value, vs. day 1 (26 weeks)	0.0667	0.0249	0.0043
Difference (303 Algorithm – Standard-of-care) (95% CI)	0.1 (−0.2 to 0.4)		
P value, between groups (26 weeks)	0.5967		
FPG, mg/dL			
n	100	88	188
Day 1	165.5±79.7	158.5±67.0	162.2±73.9
n	97	84	181
12 weeks	140.9±63.2	149.5±58.3	144.9±61.0
Change from day 1 (12 weeks)	−20.8±6.2	−10.3±6.7	−15.5±85.3
P value, vs. day 1 (12 weeks)	0.0144	0.4406	0.0169
Difference (303 Algorithm – Standard-of-care) (95% CI)	−10.5 (−28.2 to 7.3)		
P value, between groups (12 weeks)	0.2489		
n	98	88	186
26 weeks	142.2±66.4	160.4±75.0	150.8±71.0
Change from day 1 (26 weeks)	−21.3±6.8	0.2±7.3	−10.7±86.1
P value, vs. day 1 (26 weeks)	0.0075	0.7202	0.0970
Difference (303 Algorithm – Standard-of-care) (95% CI)	−21.4 (−41.0 to −1.9)		
P value, between groups (26 weeks)	0.0326		

(Continued)

26 weeks (31.6 vs. 17.6, $P<0.05$), and non-significant reductions in the rates of daytime and nocturnal hypoglycemia. Patients in the Standard-of-care group experienced a significant reduction in daytime hypoglycemic events (29.8 vs. 8.6, $P<0.0001$), a sig-

Table 2. *(Continued)*.

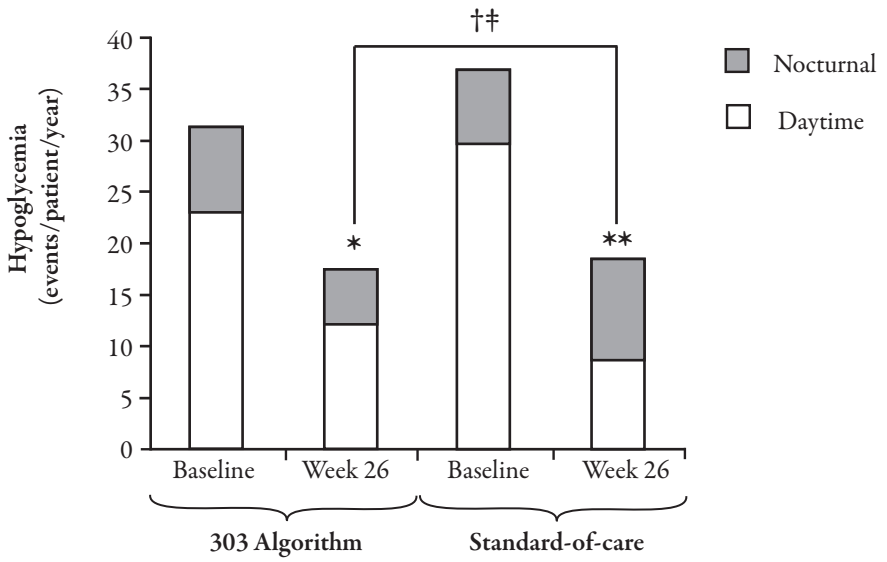
	303 Algorithm	Standard-of-care	Total
Within-subject variability (CV)			
n	70	72	142
Day 1	29.1±20.3	25.4±14.9	27.2±17.8
n	95	81	176
26 weeks	25.4±14.3	22.4±13.1	24.0±13.8
Change from day 1 (26 weeks)	−1.1±1.5	−5.8±1.5	−3.4±17.4
P value, vs. day 1 (26 weeks)	0.3886	0.0075	0.0270
Difference (303 Algorithm – Standard-of-care) (95% CI)	4.7 (0.6 to 8.9)		
P value, between groups (26 weeks)	0.0277		
Weight, kg			
n	101	91	192
Day 1	89.4±20.3	92.0±18.8	90.6±19.6
n	99	89	188
26 weeks	88.0±20.5	91.5±18.7	89.7±19.7
Change from day 1 (26 weeks)	−1.7±0.50	−0.4±0.52	−1.1±5.0
P value, vs. day 1 (26 weeks)	0.0058	0.2749	0.0034
Difference (303 Algorithm – Standard-of-care) (95% CI)	−1.3 (−2.7 to 0.1)		
P value, between groups (26 weeks)	0.0725		

Data reported as mean±SD unless otherwise stated.
Change from day 1 data for 303 Algorithm and Standard-of-care groups is reported as mean±SE.
P value vs. day 1 is based on *t* test on change from day 1.
Change from day 1 data for 303 Algorithm and Standard-of-care groups and *P* value, between groups is from analysis of covariance (ANCOVA) model with treatment as fixed effect and baseline value as covariate; for within-subject variability data, baseline dose is the covariate.
CV=100×SD/mean.
*Patients were excluded from the efficacy analysis set if they had no efficacy measurements for at least one of the parameters at two visits and were not enrolled for at least 18 weeks.
CI=confidence interval; CV=coefficient of variation; FPG=fasting plasma glucose; HbA_{1c}=glycated hemoglobin.

nificant reduction in overall events, and a small nonsignificant increase in nocturnal events (Figure 1).

No significant differences were observed in the rate of all major hypoglycemic events between the 303 Algorithm and Standard-of-care groups at 26 weeks (0.25 and 0.42, respectively; between groups *P*=0.66). Patients in both the 303 Algorithm and Standard-of-care groups experienced a reduction in the rate of all major hypoglycemic events compared to baseline (baseline vs. 26 weeks: 2.29 vs. 0.25 and 2.97 vs. 0.42, respectively). Both groups combined experienced significant reductions in the rates of overall, daytime, and nocturnal major hypoglycemic events at week 26.

Figure 1. Rate of hypoglycemic events (daytime and nocturnal) at baseline and week 26 for the 303 Algorithm and Standard-of-care groups of patients. Change from baseline: *P=0.0453 for change from baseline in all (daytime + nocturnal) hypoglycemic events; **P<0.0001 for change from baseline in daytime hypoglycemic events. Between groups: †P=0.0059 for nocturnal hypoglycemic events at 26 weeks; ‡P=0.0069 for daytime hypoglycemic events at 26 weeks.



Adverse Events

Among the 101 patients treated with insulin detemir in the 303 Algorithm group, eight patients (7.9% of patients) reported a total of 10 serious adverse events (SAEs); three of these SAEs were reported as related to insulin detemir and were categorized as diabetic ketoacidosis (one event) and hypoglycemia (two events). Twenty-six patients in this group reported a total of 52 adverse events (AEs). The most common AEs were categorized as metabolism and nutrition disorders (eight events) and nervous system disorders (11 events). Eleven of the AEs were reported as related to insulin detemir.

Among the 92 patients in the Standard-of-care group, ten (10.9%) reported a total of 11 SAEs; two of these SAEs were reported as related to insulin detemir and were categorized as unstable angina (one event) and hypoglycemia (one event). Twenty patients in this group reported a total of 36 AEs; the most common AEs were categorized as infections and infestations (10 events), gastrointestinal disorders (four events), and musculoskeletal and connective tissue disorders (four events). Three of the AEs were reported as related to insulin detemir.

Body Weight

A similar weight reduction was experienced by patients in the 303 Algorithm and Standard-of-care groups after 26 weeks (–1.7 kg and –0.4 kg, respectively, for change from baseline; between-group difference –1.3 kg; P=0.07) (Table 2). Over 65% and 53% of patients in the 303 Algorithm and Standard-of-care groups, respectively, reported weight loss or no weight gain.

Insulin Dose

Basal Insulin Regimen and Dose

At baseline, 81% of patients used their basal insulin in a once-daily regimen at an average dose of 0.5 units/kg; 19% of patients used their basal insulin in a twice-daily regimen at an average dose of 0.6 units/kg. All patients previously using NPH insulin were transitioned to a once-daily regimen of insulin detemir (~0.4 units/kg); for those patients using NPH twice daily prior to the study there was approximately a 20% reduction in basal insulin dose. In general, patients were transitioned from insulin glargine (~0.5 units/kg) to insulin detemir (~0.5 units/kg) on a unit-to-unit basis; 94% of patients using insulin glargine prestudy were transitioned to a once-daily regimen with insulin detemir; the remaining 6% of patients were transitioned to a twice-daily or more regimen.

The average daily dose of insulin detemir at week 26 was 0.7 units/kg and 0.6 units/ kg for patients in the 303 Algorithm and Standard-of-care groups, respectively. Patients in the 303 Algorithm group increased their dose of insulin detemir to a greater extent over 26 weeks than patients in the Standard-of-care group (between-group difference for increase in insulin detemir dose over 26 weeks, 0.1 units/kg [303 Algorithm – Standard-of-care]; between groups P=0.02). Possibly reflecting protocol guidelines, within the 303 Algorithm and Standard-of-care groups, the majority of the insulin detemir dose titration occurred within the first 12 weeks (+0.2 units/kg for both groups; P<0.05 for change from day 1 to week 12). From weeks 12 to 26, only a small increase in dose was observed in the 303 Algorithm group, while a small decrease in insulin detemir dose was observed in the Standard-of-care group. At 26 weeks, 90% and 82% of patients in the 303 Algorithm and Standard-of-care groups, respectively, were using insulin detemir once daily.

Bolus Insulin Dose

The average daily bolus dose was apparently not titrated and was not statistically different at study end among patients in the 303 Algorithm group (bolus dose at week 26, 0.4 units/kg; week 26 - day 1, –0.1 units/kg; P=0.54). In contrast, patients in the Standard-of-care group had a non-significant increase in their bolus insulin dose by study end (bolus dose at week 26, 0.6 units/kg; week 26 - day 1, +0.2 units/kg; P=0.27); however, this increase in bolus insulin dose was primarily implemented by only 19% of patients in this group (bolus dose at week 26, 1.4 units/kg; week 26 - day 1, 0.8 units/kg).

At the end of the study, all patients reported using only insulin, ie, no OADs, in a basal-bolus regimen.

DISCUSSION

Basal-bolus insulin therapy using a combination of rapid- and long-acting insulin analogs offers a physiological approach to managing type 2 diabetes. This subgroup analysis of the PREDICTIVE 303 study focuses specifically on patients who were using basal-bolus insulin therapy prior to the study and replaced the basal component of their therapy with insulin detemir. The results reported from this subgroup analysis agree with the overall findings reported in the PREDICTIVE 303 study, ie, adjustments of

basal insulin dose by patients using the 303 Algorithm are equally effective in improving glycemic control as physician-directed dose adjustments.[10]

Basal-bolus insulin therapy in patients with type 2 diabetes represents a considerable challenge, especially when performed in the primary care setting where resources, including patient education support, may be limited. An approach that increases patient involvement in self-management may be more effective in improving glycemic control.[12,13] Such approaches empower patients to set goals and make daily decisions, as well as assume responsibility for their daily diabetes care.[14] More specifically, educating and empowering the patient to participate in insulin dose adjustments in collaboration with the healthcare provider can have considerable beneficial effects on diabetes management and patient self-efficacy.[15] While patient-driven basal insulin dose adjustments have shown both comparable safety and efficacy compared to physician-led insulin dose changes in subjects with type 2 diabetes on basal insulin replacement ± OADs,[10,16] this is the first published study in which patient-driven basal dose adjustments are performed in the setting of basal-bolus insulin replacement in this patient population.

Comparison of Patient-Driven Versus Physician-Directed Titration of Insulin Detemir in Basal-Bolus Therapy

Comparable reductions in HbA_{1c} were observed between patients in the 303 Algorithm and Standard-of-care groups. However, patients self-titrating insulin detemir achieved greater reductions in FPG from baseline, likely a result of greater titration of insulin detemir dose over the course of the study. Despite improvements in glycemic control in both groups, glycemic levels were not optimized at the end of the study. The fact that this study was not an enforced treat-to-target study, meaning that investigators were not closely monitored and supervised regarding implementation of algorithm-driven insulin dose adjustments, such as was the case in other studies,[17,18] could partly explain these results. In addition, this subgroup of patients likely represented a challenging study population, as they entered the study under relatively poor glycemic control despite using basal-bolus insulin therapy and, other than some simple instructions for basal insulin dose adjustments, were provided with little additional diabetes management education.

In both groups, most of the increase in insulin detemir dose (~0.2 units/kg) occurred in the first 12 weeks of the study, with only minimal basal insulin dose adjustments thereafter. While no significant adjustments in bolus insulin dose were implemented in the 303 Algorithm group, approximately 19% of patients within the Standard-of-care group had increases in their bolus insulin dose during the last 14 weeks of the study (~0.8 units/kg), concomitant with a reduction in the insulin detemir dose during the same period.

The rate of total hypoglycemic events was similar between the two groups at the end of the study. Interestingly, patients in the 303 Algorithm group experienced a relatively lower rate of nocturnal hypoglycemia even while achieving lower FPG, while those in the Standard-of-care group experienced a lower rate of daytime hypoglycemia.

The observation that patient-driven titration of insulin detemir was as effective

and safe as physician-directed titration is a significant result for patients and physicians in their management of type 2 diabetes. Patients within this subgroup using basal-bolus insulin therapy prior to the study might have been more experienced insulin users. While patients were not likely apprehensive about using insulin, concerns regarding hypoglycemia and learning a new titration regimen might have been expected. The findings of no increase in either hypoglycemic events or body weight in patients adjusting basal insulin detemir in a basal-bolus setting might encourage adherence to therapy and self-titration of insulin doses, as well as increase the confidence of the patient to more actively pursue glycemic targets.[19] Further, these findings may also alleviate physicians' concerns related to the complexity of titrating basal insulin therapy and the ability of patients to actively participate in insulin self-adjustments.

Summary of Data in Patients Using Basal-Bolus Insulin Therapy with Insulin Detemir

The outcomes in this trial were similar to other studies using basal-bolus insulin therapy in subjects with type 2 diabetes, in which the use of insulin detemir in combination with insulin aspart or regular insulin resulted in slightly less weight gain and glycemic variability, and a lower risk of nocturnal hypoglycemia compared with the use of NPH as basal insulin replacement.[3,5,20,21]

After switching to insulin detemir, patients in the Standard-of-care group experienced somewhat less within-subject variability in FPG levels compared to baseline, possibly contributing to a lower risk of hypoglycemia and improved patient adherence.[22] Accordingly, patients within this PREDICTIVE 303 study subgroup generally experienced a reduction in the rate of hypoglycemic events, including major hypoglycemia, by study end. This observation is consistent with numerous clinical studies that have demonstrated a reduced risk of hypoglycemia when comparing insulin detemir to NPH insulin, while obtaining similar improvements in glycemic control.[5,17,23]

At study end the majority of patients in both treatment groups experienced a small weight loss, or no change in weight, despite increases in their total insulin dose and improved glycemic control, a finding consistent with other trials where the use of insulin detemir was compared to other basal insulin preparations.[20,23,24] A recent pooled analysis of two clinical studies in which insulin detemir or NPH insulin was used as the basal component of basal-bolus therapy also revealed less weight gain with insulin detemir compared with NPH insulin at comparable levels of glycemic control.[25] Patients treated with insulin detemir had minimal weight gain, while patients with the largest body mass index (>35 kg/m^2), on average, actually lost weight.

Limitations of the Study

The 303 Algorithm should be used to adjust basal insulin doses under "usual" circumstances, as a means to optimize basal insulin replacement and glycemia. While the adjustments made using this algorithm can address slowly changing insulin sensitivity, eg, due to weight change, increased physical activity over time, etc, the algorithm is not meant to be used for emergency or high stress situations, eg, emerging infections or intense exercise, in which rapid shifts in insulin sensitivity can occur. Rapid shifts in insulin sensitivity require adjustments in rapid-acting

insulin dosing via corrective insulin doses and meal time coverage with insulin and should be based on actual glycemia and predicted resistance due to the stress encountered.

CONCLUSION

In summary, patients with type 2 diabetes self-titrating their insulin detemir dose as the basal component of basal-bolus insulin therapy with the 303 Algorithm achieved similar improvements in glycemic control compared to physician-directed insulin dose adjustments; however, patients following the 303 Algorithm more aggressively titrated their dose of insulin detemir. The modest improvements in glycemic control in both groups were accompanied by reductions in both the rate of hypoglycemia and body weight, as well as less within-patient variability in blood glucose levels. The simple 303 Algorithm for the titration of a once-daily dose of insulin detemir offers patients and physicians a practical strategy to optimize diabetes management with insulin detemir in basal-bolus insulin therapy, and in effect complements physician-directed management of more complex diabetes cases.

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