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Addition of biphasic insulin aspart 30 to optimized metformin and pioglitazone treatment of type 2 diabetes mellitus: The ACTION Study (Achieving Control Through Insulin plus Oral ageNts)

P. Raskin,[1] G. Matfin,[2] S. L. Schwartz,[3] L. Chaykin,[4] P.-L. Chu,[2] R. Braceras[2] and A. Wynne[5]

[1]Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA
[2]Clinical Development, Medical and Regulatory Affairs, Novo Nordisk Inc., Princeton, NJ, USA
[3]Diabetes & Glandular Disease Clinic Center, San Antonio, TX, USA
[4]Department of Endocrinology, Aventura Hospital & Medical Center, Aventura, FL, USA
[5]Diabetes & Endocrinology Center, Topeka, KS, USA

Aim: Efficacy and safety of biphasic insulin aspart (BIAsp 30, 30% short-acting and 70% intermediate-acting insulin aspart) added to an optimized treatment of metformin and pioglitazone (met/pio) were compared with treatment with optimized met/pio in type 2 diabetes patients.

Methods: This randomized, 34-week, parallel-group study enrolled insulin-naive, type 2 diabetes patients (HbA_{1c} 7.5–12.0%) previously using two oral antidiabetic (OAD) agents. During an 8-week run-in period, treatment was changed to met/pio and doses were adjusted up to 2500 mg/day and 30 or 45 mg/day respectively. Subjects either continued met/pio alone or added BIAsp 30 initiated at 6 units twice daily and titrated to target plasma glucose (PG) (4.4–6.1 mmol/l).

Results: At end-of-study, subjects treated with BIAsp 30+met/pio ($n = 93$) had a mean ($\pm$s.d.) HbA_{1c} reduction significantly greater than treatment with met/pio ($n = 88$) ($1.5\% \pm 1.1$ vs. $0.2\% \pm 0.9$, $p < 0.0001$ between groups). Subjects treated with BIAsp 30+met/pio were more likely to reach The American Association of Clinical Endocrinologists and European Association for the Study of Diabetes/American Diabetes Association HbA_{1c} targets of ≤ 6.5 and $<7.0\%$, respectively, than with met/pio only ($HbA_{1c} \leq 6.5\%$: 59 vs. 12%; $HbA_{1c} < 7.0\%$: 76 vs. 24%). At end-of-study, self-monitored glucose profile values at all eight daily time points were significantly less for the BIAsp 30+met/pio group compared with the met/pio group, and minor hypoglycaemia (defined as $PG < 3.1$ mmol/l) was more frequent (8.3 vs. 0.1 events/year, $p < 0.001$). Both groups gained weight during treatment (BIAsp 30+met/pio, 4.6 ± 4.3 kg; met/pio, 0.8 ± 3.2 kg; $p < 0.001$).

Conclusion: Addition of insulin in type 2 patients treated with met/pio is an effective way to achieve glycaemic targets. Treatment with BIAsp 30+met/pio achieved significantly greater reduction in HbA_{1c}, as compared with met/pio alone. In patients with type 2 diabetes poorly controlled by 2 OADs, more achieved glycaemic targets using BIAsp 30+met/pio than using met/pio alone.

Keywords: HbA_{IC}, initiation of therapy, NovoLog Mix 70/30, NovoMix 30, Oral antidiabetic, thiazolidinedione, treat-to-target
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Correspondence:
Philip Raskin, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75390-8858, USA.
E-mail:
Philip.Raskin@UTSouthwestern.edu

Introduction

Long-term glycaemic control has beneficial effects on the incidence and progression of diabetes complications in patients with type 1 or type 2 diabetes, as demonstrated by the Diabetes Control and Complications Trial [1] and United Kingdom Prospective Diabetes Trial [2] respectively. The American Association of Clinical Endocrinologists (AACE) recommends a target glycosylated haemoglobin A1C (HbA_{1c}) of $\leq$6.5% while the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) have issued a joint statement that recommends at least <7.0% and as close to normal (<6.0%) as possible without significant hypoglycaemia [3].

Currently there are many treatment possibilities that allow patients with type 2 diabetes to achieve treatment goals. Oral antidiabetic (OAD) agents can be used to lower HbA_{1c} values, and combinations of two or more OADs are often used to try to bring patients to target HbA_{1c} goals. When patients are unable to achieve goals when treated with OADs, insulin may be added to the treatment regimen. Despite the availability of a variety of treatment regimens, a number of studies have shown that the majority of type 2 diabetes patients do not reach these HbA_{1c} goals [4–6]. Results from the National Health and Nutrition Examination Survey 1999–2002 (NHANES 1999–2002) showed that only 37% of all type 2 diabetes patients have an HbA_{1c} <7.0%, and 20% have an HbA_{1c} >9.0%, despite the fact that over 80% are treated with OADs, insulin or both [7]. Although most type 2 diabetes patients are not achieving HbA_{1c} targets, only 27% are treated with insulin [6]. Recently, the ADA and EASD have recommended that, after metformin failure, diabetes patients should add insulin as the most effective treatment regimen [3].

In this treat-to-target clinical trial (ACTION: Achieving Control Through Insulin plus Oral ageNts), subjects who were unable to achieve HbA_{1c} targets with OADs were randomized to treatment with optimized metformin and pioglitazone (met/pio) or optimized met/pio plus twice-daily biphasic insulin aspart (BIAsp 30). The biphasic insulin analogue NovoMix® 30 (BIAsp 30) is a formulation of insulin aspart containing 30% soluble insulin aspart (fast acting) and 70% insulin aspart crystallized with protamine (intermediate acting or basal). When injected at mealtime, BIAsp 30 results in improved postprandial glucose levels as compared with biphasic human insulin 70/30 [8,9], as well as providing basal insulin coverage.

Research Design and Methods

This was a 34-week, randomized, multi-centre, open-label, parallel-group, treat-to-target study with a 2-week run-in and an 8-week met/pio optimization period. Subjects were randomized to treatment with twice-daily BIAsp 30 before breakfast and the evening meal + metformin + pioglitazone (BIAsp 30+met/pio), or metformin + pioglitazone (met/pio). Subjects were stratified based on insulin secretagogue use and fasting plasma glucose (FPG) (<9.4 and $\geq$9.4 mmol/l). The study was conducted at 73 centres in the USA, in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines [10]. All subjects provided written informed consent prior to receiving study medication.

Subjects

The study randomized 200 insulin-naive subjects with type 2 diabetes mellitus who were $\geq$18 years of age and had a body mass index $\leq$42 kg/m^2 and an HbA_{1c} value $\geq$7.5% and $\leq$12% at screening (before met/pio optimization). All subjects were previously treated with two OADs [insulin secretagogues, thiazolidinediones (TZDs) ($\geq$50% maximum approved dose) or metformin ($\geq$1000 mg/day)] for at least 6 weeks prior to the trial.

Treatments

During the 8-week OAD-optimization period, metformin was increased 500 mg weekly to the target dose of 2500 mg/day, and pioglitazone was dosed at 30 mg/day (for subjects taking $\leq$30 mg pioglitazone or <8 mg rosiglitazone) or 45 mg/day (subjects taking >30 mg pioglitazone or 8 mg rosiglitazone). Subjects discontinued insulin secretagogues at the fourth week. Met and pio doses remained constant throughout the trial. Subjects with three consecutive FPG values <6.7 mmol/l or >12.2 mmol/l at the end of the optimization period were considered run-in failures and were not randomized into the study.

Insulin therapy was initiated with a 6-unit dose, subcutaneously injected before both breakfast and the evening meal. BIAsp 30 (NovoMix® 30; Novo Nordisk, Bagsvaerd, Denmark) was administered within 15 min of meal initiation using the FlexPen® insulin delivery device.

Insulin doses were titrated every 3–4 days to achieve target FPG and pre-evening meal plasma glucose (PG) values of 4.4–6.1 mmol/l. The pre-evening meal dose was titrated based on FPG values, and the pre-breakfast dose was titrated based on pre-evening meal values. Dose titration was based on values from the preceding 3 days

(measured with OneTouch® Ultra blood glucose metre calibrated to PG; Lifescan, Milpitas, CA, USA). Insulin dose was adjusted based on PG readings (table 1), unless hypoglycaemia was occurring. Each increase in the total daily dose was not to exceed 10 units or 10% of the current total daily dose, whichever was greater.

Efficacy Assessments

The primary end-point was the reduction in HbA_{1c} values from baseline to the end of the study. Values for HbA_{1c}, FPG and eight-point (immediately before and 90 min after breakfast, lunch and evening meal, at bedtime and at 03:00 hours) self-monitored PG (SMPG) profiles were obtained at randomization and at study weeks 12 and 24.

Safety Assessments

Safety was assessed by physical examination findings, clinical laboratory evaluations and reporting of adverse events and hypoglycaemic episodes. Minor hypoglycaemic episodes were defined as PG values of <3.1 mmol/l with or without symptoms that were self-treated. Major hypoglycaemia was an episode with neurological symptoms consistent with hypoglycaemia that required assistance from a third party and had either a PG value <3.1 mmol/l or reversal of symptoms after food intake, glucagon injection or intravenous glucose.

Statistical Analysis

The analysis of data was performed on the intent-to-treat (ITT) population, defined as the set of subjects who took at least one dose of the study medications after randomization and had at least one post-baseline efficacy assessment. End-of-study values represent mean values for last observation carried forward. An ANCOVA model was used, with HbA_{1c} change-from-baseline to end-of-study as the dependent variable, treatment as fixed effect, and HbA_{1c} at baseline, mean FPG stratum (FPG <9.4 mmol/l vs. ≥9.4 mmol/l at baseline) and insulin secretagogue stratum as covariates. The results were summarized with 95% confidence intervals and p-values. Mean rates of hypoglycaemia were compared using a Poisson regression model. Values are expressed as mean ± s.d. unless otherwise noted.

Table 1 Insulin pre-breakfast and pre-evening meal titration

Average plasma glucose (three readings*) (mmol/l)	Adjustment
<4.4	−3 U
4.4–6.1	No adjustment
6.2–7.8	+3 U
7.8–10.0	+6 U
>10.0	+9 U

*Fasting plasma glucose and pre-evening meal plasma glucose, measured by the subject; at least two values should be available.

Results

Subjects

A total of 305 subjects were enrolled into the 8-week OAD-optimization run-in period. One hundred and five subjects withdrew during the run-in period or failed to meet the randomization criteria (FPG 6.7–12.2 mmol/l) at the end of the run-in period. The remaining 200 were randomized to treatment with BIAsp 30+met/pio or met/pio. Baseline demographic characteristics were similar between treatment groups (table 2). Most subjects (n = 151, 75.5%) completed the study. Forty-nine subjects discontinued the study: 22 subjects from the BIAsp 30+met/pio group and 27 from the met/pio group (table 2). The ITT population (subjects who had baseline measurements and at least one additional data point) included 93 subjects in the BIAsp 30+met/pio group and 88 subjects in the met/pio group.

Efficacy

At the end of the study, 76% of subjects treated with BIAsp 30 reached the HbA_{1c} goal of <7.0%, as compared with 24% treated with only met/pio (figure 1). A majority of subjects treated with BIAsp 30 achieved HbA_{1c} values ≤6.5%, and 33% had values ≤6.0% (figure 1). Even in subjects with baseline HbA_{1c} values ≤7.5%, only 39.3% (11 of 28) of optimized met/pio-treated subjects achieved an end-of-study HbA_{1c} <7.0%, as compared with 96.8% (30 of 31) of those adding insulin to the regimen.

There were no subjects with a baseline HbA_{1c} value >9.0% who achieved target HbA_{1c} values after treatment with optimized met/pio only. However, after treatment with BIAsp 30+met/pio, 60% achieved <7.0% and 33% achieved ≤6.5%. Half of the 42 subjects with baseline HbA_{1c} values >8.0% achieved the HbA_{1c} target of ≤6.5% with BIAsp 30+met/pio treatment, as compared with 3 of 39 subjects (8%) with met/pio treatment. Similarly, the HbA_{1c} target of <7.0% was reached by 28 of 42 subjects (67%) with BIAsp 30+met/pio treatment and 6 of 39 (15%) with met/pio treatment.

The mean HbA_{1c} values at the end of the study were 6.5% ± 1.0 for the BIAsp 30+met/pio group, as

Table 2 Characteristics of randomized population and subject disposition

	BIAsp 30	Met/pio
Subjects randomized	102	98
Age (years), mean ± s.d.	53.4 ± 10.1	54.2 ± 10.1
Gender (%): M/F	46/54	38/62
Ethnicity (%): C/B/H/A/O	52/12/33/3/0	44/10/37/4/5
Body mass index (kg/m^2), mean ± s.d.	32.4 ± 5.2	33.4 ± 5.7
Previous treatment, n (%)		
Metformin + TZD	19 (19)	23 (23)
Metformin + secretagogues	76 (75)	71 (72)
TZD + secretagogues	7 (7)	4 (4)
Diabetes duration (years), mean ± s.d.	9.2 ± 6.2	8.3 ± 5.6
HbA_{1c} (%), mean ± s.d.		
All subjects	8.1 ± 1.0	8.1 ± 1.0
Completed study, n (%)	80 (78.4)	71 (72.4)
Discontinuation from study, n (%)*	22 (21.6)	27 (27.6)
For adverse event, n (%)	3 (2.9)	4 (4.1)
For non-compliance, n (%)	8 (7.8)	4 (4.1)
For ineffective therapy, n (%)	1 (1.0)	12 (12.2)
For 'other', n (%)	10 (9.8)	7 (7.1)

A, Asian; B, Black; BIAsp 30, biphasic insulin aspart 30; C, Caucasian; F, female; H, Hispanic; M, male; met/pio, metformin and pioglitazone; O, other, TZD, thiazolidinedione.

*Adverse event withdrawals in the BIAsp 30 group were unrelated to treatment: pyelonephritis, arrhythmia and blood creatinine increased. Adverse event withdrawals in the OAD group were unrelated to treatment: angina pectoris, hyperglycaemia, coronary artery disease and myalgia. Reasons for 'other' included: lost to follow-up, failure to return and subject withdrawing consent.

compared with 7.8% ± 1.2 for the met/pio group ($p < 0.0001$). The mean reduction in HbA_{1c} for subjects treated with insulin was significantly greater than for subjects in the met/pio group (−1.5% ± 1.1 vs. −0.2% ± 0.9, respectively, $p < 0.0001$). The HbA_{1c} reduction from baseline was significant for both treatment groups.

By the end of the study, FPG values were significantly reduced in the BIAsp 30+met/pio group, but not the met/pio group (−2.45 ± 2.77 vs. +0.06 ± 2.42 mmol/l, respectively, $p < 0.001$ between treatment groups). Starting FPG values were similar at baseline (9.62 ± 2.21 vs. 9.07 ± 1.97 mmol/l, BIAsp 30+met/pio vs. met/pio, respectively, $p > 0.05$). The final mean FPG value was significantly lower in the BIAsp 30+met/pio group (7.21 ± 2.78 vs. 9.01 ± 2.27 mmol/l, BIAsp 30+met/pio vs. met/pio, respectively, $p < 0.001$). Target FPG (4.4–6.1 mmol/l) was achieved by 37 and 2% of the subjects in the BIAsp 30+met/pio and met/pio groups, respectively, at the end of the study.

The BIAsp 30+met/pio group had improvements from baseline at all eight daily time points in the SMPG profile, while the met/pio group had significant improvements

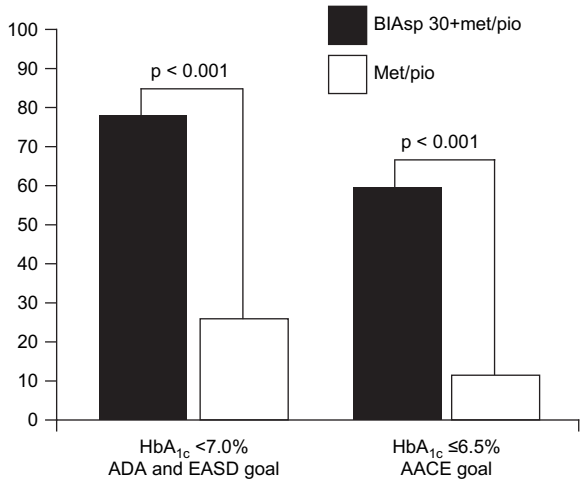

Fig. 1 Per cent of subjects that reached HbA_{1c} targets. AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; BIAsp 30, biphasic insulin aspart 30; EASD, European Association for the Study of Diabetes; met/pio, metformin and pioglitazone.

after breakfast and after lunch (figure 2). At the end of the study, all time points in the eight-point SMPG were significantly less for the BIAsp 30+met/pio group than the respective time points for the met/pio group (figure 2).

By the end of the OAD optimization period, the daily doses of met and pio were similar in both treatment groups (met: 2446 ± 156 vs. 2439 ± 194 mg and pio: 32.5 ± 5.6 vs. 31.7 ± 4.8 mg for BIAsp 30 vs. OAD, respectively). Daily BIAsp 30 dose by weight was 0.60 ± 0.35 U/kg (pre-breakfast: 0.32 ± 0.20 U/kg; pre-evening meal: 0.28 ± 0.18 U/kg).

Safety

The overall rate of minor hypoglycaemia (PG < 3.1 mmol/l) was greater in the BIAsp 30+met/pio group than in the met/pio group (8.3 vs. 0.1 episodes per patient year, respectively, $p < 0.05$). Forty-eight per cent of subjects in the BIAsp 30 group had no minor hypoglycaemic events, while 97% of subjects in the OAD group had no minor hypoglycaemic events ($p < 0.05$). Eight subjects (7.8%) in the BIAsp 30 group accounted for over half of the minor hypoglycaemic events (183 of the 342 events). In addition, three of these eight subjects reported the four major hypoglycaemic episodes, which occurred during this trial. No subjects discontinued treatment because of hypoglycaemic episodes.

The number and type of reported adverse events were similar for the two treatment groups and were not unexpected for the trial population. Mean body weight increased in both the treatment groups by the end of the

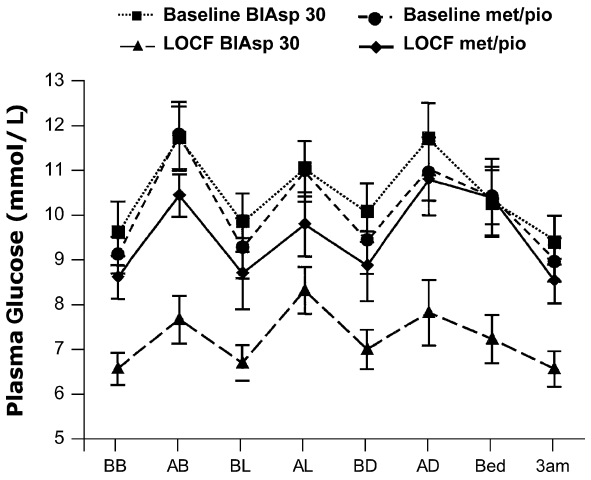

Fig. 2 Eight-point blood glucose measurements. Eight-point self-monitored PG readings before breakfast, lunch, and evening meal [BB, BL and BE] and 90 min after breakfast, lunch and evening meal [AB, AL and AE]; at bedtime [Bed]; and at 03:00 hours. All time points show a statistically significant difference ($p < 0.05$) between treatment groups at the end of the study (LOCF). Error bars represent two Standard error. LOCF, last observation carried forward.

study (BIAsp 30: 4.6 ± 4.3 kg vs. met/pio: 0.8 ± 3.2 kg; $p < 0.0001$ between groups). Peripheral oedema was reported by 9 and 12% of subjects in the BIAsp 30 and met/pio groups respectively.

Discussion

Improved glycaemic control has been found to decrease many of the complications related to diabetes, such as cardiac events [11] and the development and progression of retinopathy, nephropathy and neuropathy [12]. Despite such evidence, less than 40% of diagnosed type 2 diabetes patients have HbA_{1c} values less than 7.0% [6], the current EASD/ADA target. This study demonstrates that a majority of type 2 diabetes patients can achieve HbA_{1c} targets by adding insulin to a regimen of two OADs.

This study has shown that titrating the premixed insulin analogue BIAsp 30, in addition to an optimized treatment regimen of met/pio, enabled 59% of subjects to reach HbA_{1c} values ≤6.5% and 76% to reach <7.0%, as compared with 12 and 24%, respectively, for treatment with optimized met/pio alone. In addition, BIAsp 30+met/pio treatment enabled more subjects with poorly controlled type 2 diabetes (i.e. HbA_{1c} >8.0%) to reach treatment goals. While 60% of subjects with baseline HbA_{1c} values >9.0% treated with BIAsp 30+met/pio were able to achieve the EASD/ADA target of <7.0%, there were no subjects treated with optimized OADs only who were able to reach this target.

The large percentage of subjects achieving target HbA_{1c} values after initiating treatment with a premixed insulin analogue in the current study confirms the results of prior studies. It has previously been demonstrated that initiating insulin therapy twice daily with an insulin analogue mix is significantly more effective than once-daily basal insulin.[13,14] The INITIATE (INITiation of Insulin to reach A1c TargEt) study was a direct, head-to-head comparison of BIAsp 30 with the basal insulin analogue glargine. Treatment with BIAsp 30 + metformin ± TZDs resulted in a significantly greater HbA_{1c} reduction than treatment with insulin glargine +met ± TZDs (−2.79% ± 0.11 vs. −2.36% ± 0.11, $p < 0.05$) [13]. Additionally, significantly more subjects reached HbA_{1c} targets with BIAsp 30 treatment than with insulin glargine ($HbA_{1c} < 7.0\%$: 66 vs. 40%, $p < 0.001$; $HbA_{1c} \leq 6.5\%$: 42 vs. 28%, $p < 0.05$). Unlike the current clinical trial, OADs were not optimized in the INITIATE study.

The 1-2-3 Study has shown that treatment with BIAsp 30 was effective when dosed once, twice or three times daily [15]. Addition of once-daily BIAsp 30 before the evening meal achieved HbA_{1c} ≤6.5% in 21% of patients, and HbA_{1c} <7.0% in 41%. The addition of a second injection of BIAsp 30 enabled subjects to achieve these glycaemic goals in 52 and 70% of subjects respectively. With three daily injections, 60% of patients achieved HbA_{1c} ≤6.5% and 77% achieved HbA_{1c} <7.0%. Unlike the current study, these subjects were not all insulin-naïve and OADs were not optimized.

In the current study, subjects initiating insulin therapy with twice-daily BIAsp 30 had significant improvement in overall glycaemic control as measured by lower end-of-study HbA_{1c} values, FPG values and eight-point SMPG values, in addition to the large number of subjects achieving HbA_{1c} goals. Slightly less peripheral oedema was reported in the BIAsp 30+met/pio group as compared to the met/pio group, which is contrary to results from previous studies [16, 17].

The mean rate of hypoglycaemia for subjects treated with BIAsp 30+met/pio was significantly greater than the rate for subjects treated with met/pio therapy alone. Although there was a greater rate of hypoglycaemia in the BIAsp 30+met/pio group, almost half of the subjects treated with BIAsp 30 (48%) reported no hypoglycaemic events. Moreover, almost all of the hypoglycaemic events were minor and self-treated. The increased rate of hypoglycaemia was not unexpected, as initiation of insulin therapy is often accompanied by an increase in the rate of

minor hypoglycaemia, because patients have to learn how to use insulin and be diligent about eating meals when they administer insulin. Education about insulin administration is particularly important when initiating an insulin mix that contains a rapid-acting component. Patients that are initiating insulin therapy should receive training programs to help prevent, recognize and manage their hypoglycaemic episodes as intensive glycaemic control is associated with an increased risk of hypoglycaemia.

In conclusion, this study demonstrates that in a population with type 2 diabetes that was poorly controlled by two oral agents, the addition of BIAsp 30 to met/pio leads to significant improvements in HbA_{1c} and FPG. The addition of BIAsp 30 to oral agents could allow a majority of type 2 DM patients achieve the recommended EASD/ADA and AACE glycaemic targets.

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