

Clinical experience

Thrice-daily biphasic insulin aspart 30 may be another therapeutic option for Chinese patients with type 2 diabetes inadequately controlled with oral antidiabetic agents

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In subjects with type 2 diabetes inadequately controlled with oral antidiabetic agents (OADs), insulin therapy is usually started to improve glycaemic control after failure of diet, exercise and OADs.¹ Although there is no standard way to introduce insulin treatment, premixed formulations are a popular option. They offer an alternative to basal-bolus therapy and provide basal and prandial coverage with a single injection. Indeed, Koivisto et al² in 1999 reported that 39% of patients with type 2 diabetes worldwide used premixed insulin as part of their therapeutic regimen. The modern premixed insulins, such as biphasic insulin aspart 30 (BIAsp 30) are most frequently prescribed twice-daily (BID) in clinical practice. However, BID premixed insulin may not provide sufficient flexibility for all patients to achieve optimal glycaemic control and for some patients an additional injection, covering lunch, may be beneficial. In the 1-2-3 study, a stepwise comparison of once-, twice- and thrice-daily BIAsp 30 with OADs treatment in western patients with type 2 diabetes, a proportion of patients achieved improved glycaemic control with BIAsp 30 thrice-daily (TID) compared with BID treatment.³ The daily insulin doses of TID BIAsp 30 group in the 1-2-3 study were 0.58, 0.25 and 0.70 U/kg at pre-breakfast, pre-lunch and pre-dinner time respectively in subjects with mean body mass index (BMI) about 33.4 kg/m². The sample size included only 25 subjects even though the glycosylated hemoglobin 1c (HbA_{1c}) decrease of 1.8% was observed in the subjects with the treatments of BIAsp 30 plus OADs. Due to lack of dose titration experience in clinical practice, whether or not TID BIAsp 30 without OADs could be used in Chinese subjects with type 2 diabetes having relatively lower BMI^{4,5} was still unclear. Moreover, the incidence of hypoglycaemia, especially for nocturnal events, was another concern preventing TID BIAsp 30 from acceptance of TID treatment.

The aim of this study was a head-to-head comparison of BID versus TID BIAsp 30 dosing in Chinese insulin-naïve subjects with type 2 diabetes after at least six-month inadequately controlled by OAD treatment. The published data from the study by Yang et al⁶ demonstrated improved glycaemic control as assessed by HbA_{1c} levels, especially in patients with higher baseline

HbA_{1c} levels. In this report we investigated factors that may influence the difference in glycaemic control between treatment regimens as well as influences on weight gain and hypoglycaemic rate.

METHODS

Subjects

In this 24-week, parallel-group, randomised, treat-to-target and open-label study, the efficacy and safety of BID and TID BIAsp 30 were compared in 321 eligible insulin-naïve subjects (aged 18–75 years old, BMI \leq 32 kg/m², and poorly controlled on OAD therapy (FBG \geq 7.8 mmol/L, HbA_{1c} \geq 7.5%)) from clinics at eight hospitals in China. The eligible subjects were randomised into a ratio of 1:1 to receive BID (immediately before breakfast and dinner) or TID BIAsp 30 (immediately before breakfast, lunch and dinner) treatment following a 2-week screening period. Randomisation codes were stratified by centre and block randomisation was used to minimise treatment bias.

Material and procedures

BIAsp 30 was administered subcutaneously using

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NovoMix® 30 FlexPen®, a prefilled disposable pen device provided by Novo Nordisk (China) Pharmaceuticals Co., Ltd. The study protocol was approved by the Independent Ethics Committees for each participating centre and was performed in accordance with the Declaration of Helsinki⁷ and Guidelines on Good Clinical Practice.

All subjects discontinued their previous OADs at randomisation and no wash-out period of OADs was used. Starting doses for BIAsp 30 were based on fasting plasma glucose (FPG) at randomisation. For patients randomised to BID BIAsp 30 group, the total daily dose was assigned equally to the pre-breakfast and pre-dinner dose (50% : 50%). In the TID BIAsp 30 group, the initial daily dose ratio at breakfast, lunch and dinner was 25% : 25% : 50%. The insulin dose was adjusted based on the mean pre-meal self-monitored blood glucose (SMBG) to achieve pre-meal blood glucose targets of 4.4–6.1 mmol/L⁸ (Table 1). Subjects performed pre-meal SMBGs on three consecutive days prior to each of the 19 patient contacts during the 24-week trial. Patients were provided with standard meals on office visits to compare 2-hour post-breakfast plasma glucose (2hr PPG) between the treatments. During the trial, the subjects received food intake and lifestyle suggestions from investigators. At each lab visit, FPG and 2hr PPG testing was performed. Patients were required to fast prior to each lab visit. At the baseline, the 12th week and the 24th week, HbA_{1c} was analysed at the central lab. This study was designed as an open-labeled trial due to different numbers of daily subcutaneous administration with trial drugs.

Table 1. Guideline for insulin dose titration

Mean pre-meal BGs (mmol/L)	Titration
<4.4	-2 units
4.4–	0
6.2–	+2 units
7.8–	+4 units
>10.0	+6 units

Efficacy parameters

The change in HbA_{1c} after 24-week treatment was the primary endpoint. The change in HbA_{1c} after 12 weeks, FPG, 2hr PPG and percentages of subjects who achieved HbA_{1c} targets (American Diabetes Association (ADA) <7%⁹ and International Diabetes Federation (IDF) ≤6.5%¹⁰) at the end of treatment were also recorded as secondary endpoints.

Safety parameters

The change in weight and insulin dose from baseline to 24 weeks was evaluated. The relationship between weight change and baseline HbA_{1c} value, and that between weight change and baseline BMI were evaluated. The episodes of hypoglycemia (including major, minor and nocturnal hypoglycemia) were recorded during the study. Major hypoglycaemia was defined as an episode with neurological symptoms consistent with hypoglycaemia that could not be self-treated by the patient. Minor hypoglycaemia was an episode that was self-treated with

the confirmed blood glucose (BG) reading <2.8 mmol/L. Rate of hypoglycaemia was analysed by duration of treatment and by the time of a day. Adverse events were reported throughout the whole study. Weight was assessed at the beginning and the end of the study.

Statistical analyses

A total of 321 subjects were randomised assuming a drop-out rate of 20%, allowing a power of 80% to detect that TID BIAsp 30 was non-inferior to BID BIAsp 30 (α=0.025, β=0.2). Analyses for primary and secondary endpoints were performed on the intention-to-treat (ITT) population.

The estimated treatment difference in HbA_{1c} (HbA_{1c} in TID group minus that in BID group), the 95% confidence interval (CI) and the P value were obtained from an analysis of covariance (ANCOVA) model, with treatment and centre as factors and HbA_{1c} at baseline as a covariate. Percentages of subjects who achieved HbA_{1c} targets at the end of the study were analysed by a Logistic regression approach with treatment, center and baseline HbA_{1c} as explanatory variables. The changes in SMBG values were analysed for treatment difference using the ANCOVA model, with treatment and center as factors and the value of HbA_{1c} at baseline as a covariate. The multiple stepwise linear regression method was applied to analyse the relationship between the change of body weight and gender, age, insulin dose and HbA_{1c}. The change of body weight was response variable. Entry significance level (sle) and stay significance level (sls) were set to be 0.1. The Poisson regression model was used for the analysis of hypoglycaemia. Computations for the statistical methods were performed using the computer software package SAS® (version 9.1, SAS Institute Inc., USA). All statistical analyses were two-sided and performed at the 5% significance level.

RESULTS

Of 321 randomised subjects (BID BIAsp 30, n=160; TID BIAsp 30, n=161), 305 completed the study (BID BIAsp 30, n=148; TID BIAsp 30, n=157). Eight patients in the BID BIAsp 30 group withdrew due to non-compliance with the protocol, three due to adverse events and one due to ineffective therapy. In the TID group, two subjects withdrew due to adverse events, one for non-compliance and one for not wanting to inject insulin. Baseline characteristics were comparable between treatment groups (Table 2).

Table 2. Baseline characteristics of the ITT population

Characteristics	Groups	
	BID BIAsp 30	TID BIAsp 30
Number of subjects (randomised /completed)	160/148	161/157
Age (years)	54.4±9.1	55.3±8.8
Sex ratio (male/female)	1.22	0.96
BMI (kg/m ²)	24.3±3.2	24.3±3.1
Duration of diagnosed diabetes (years)	7.7±5.1	8.0±4.8
HbA _{1c} baseline (%)	9.52±1.44	9.55±1.50
FPG baseline (mmol/L)	11.54±2.73	11.82±3.08

Efficacy

HbA_{1c}

After the 24-week treatment, the reduction in HbA_{1c} from baseline was significantly greater in the TID BIAsp30 group than that in the BID BIAsp 30 group (mean difference: -0.33%, 95% CI: -0.53, -0.13, $P < 0.01$). Mean end-of-trial HbA_{1c} values were 7.01% and 6.68% in the BID and TID groups, respectively. A significantly greater proportion of patients in the TID BIAsp 30 group than in the BID BIAsp 30 group achieved HbA_{1c} targets; 41.6% of patients on TID BIAsp 30 achieved a target of <6.5% compared with 30.6% of patients in the BID BIAsp 30 group ($P < 0.05$). At an HbA_{1c} target of <7% the respective percentages were 65.8% and 51.3% ($P < 0.01$).

SMBG values

Reductions in pre-breakfast and pre-dinner SMBG values from baseline were significantly greater in the TID BIAsp 30 group than in the BID BIAsp 30 group. The estimated treatment difference for pre-breakfast SMBG (TID BIAsp 30 minus BID BIAsp 30) was -0.351 mmol/L (95% CI: -0.604, -0.098; $P = 0.0067$). For pre-dinner SMBG the estimated treatment difference was -0.91 mmol/L (95% CI: -1.262, -0.560; $P < 0.0001$).

Safety

Insulin dose

Total daily insulin dose was not different between treatment groups at the end of the study (BID, (0.82±0.28) U/kg; TID, (0.86±0.34) U/kg, $P = 0.19$). Pre-breakfast and pre-dinner doses were similar in the BID group ((0.40±0.15) and (0.41±0.15) U/kg, respectively). In the TID group, the insulin doses were (0.29±0.15) U/kg, (0.22±0.11) U/kg and (0.36±0.14) U/kg respectively.

Analyses of changes in body weights

During treatment there was a similar increase in weight of patients treated with TID BIAsp 30 ((4.0±0.27) kg) and BID BIAsp 30 ((3.9±0.28) kg) ($P = 0.788$). Multiple linear regression analysis of change in weight with gender, age, total daily insulin dose, baseline HbA_{1c}, and end of treatment HbA_{1c} as covariates, showed that age (standardized estimate (SE), -0.1306; $P = 0.0195$) and baseline HbA_{1c} (SE, 0.1967; $P = 0.0005$) were significantly correlated with weight change (Table 3). Further analysis showed that weight gain decreased along with increasing BMI at baseline. For patients with baseline BMI ≤23 kg/m², weight gain was 4.8 kg in BID group and was 5.0 kg in TID group. The weight gain was 3.6 kg and 3.3 kg in the BID and TID group respectively for the patients with BMI between 23 kg/m² to 25 kg/m² at baseline. For the ones with BMI above 25 kg/m² before the trial, weight gain was 3.3 kg in BID group and was 3.5 kg in TID group after the trial. Mean BMI at baseline was 25.0 kg/m² in patients with HbA_{1c} levels between 7% and 9%, 23.4 kg/m² in patients with HbA_{1c} between 9% and 11%, 23.8 kg/m² in patients with HbA_{1c} between 11% and 13%, and was 22.3 kg/m² in patients with baseline HbA_{1c} >13%. The higher HbA_{1c} at baseline was

Table 3. Analysis of weight change by multiple linear regression

Models	Independent Variables	Standardized estimate	P values
Model 1*	Age	-0.1419	0.0127
Model 2†	Age	-0.1415	0.0128
Model 3‡	Age	-0.1306	0.0195
	HbA _{1c} baseline	0.1967	0.0005

Dependent variable: weight change; sle=0.1, sls=0.1. Model 1*: Weight change was adjusted for gender, age, total daily dose per weight. Model 2†: Weight change was adjusted for gender, weight, age, total daily dose per weight, HbA_{1c} at end of trial. Model 3‡: Weight change was adjusted for gender, age, total daily dose per weight, HbA_{1c} at baseline, HbA_{1c} at end of trial.

associated with increasing weight gain. For the patients with HbA_{1c} above 11% at baseline, the body weight gain was 5.7 kg and 5.4 kg in the BID group and TID group respectively. Body weight gain of patients with baseline value of HbA_{1c} between 9% and 11% was 3.8 kg and 3.9 kg. And for the ones with HbA_{1c} between 7% and 9%, the gain was 3.4 kg and 3.6 kg.

Hypoglycaemia

Overall, treatment emergent hypoglycaemic events were reported by 86 (54%) patients in the BID BIAsp 30 group (431 events) and by 69 (43%) patients in the TID BIAsp 30 group (271 events). Minor hypoglycaemic episodes (blood glucose <2.8 mmol/L) were experienced by 37 (23%) of subjects in the BID BIAsp 30 group (91 events) and 30 (19%) of patients in the TID BIAsp 30 group (65 events). Major hypoglycaemic episodes were experienced by one person (one event) in the BID BIAsp 30 group and three people (five events, one of which was nocturnal) in the TID BIAsp 30 group. The rates (episodes per subject year) of overall major and minor hypoglycaemia were 1.28 in BID group and 0.96 in TID group ($P = 0.32$). For minor hypoglycaemia, rates of 1.27 episodes per subject year in the BID BIAsp 30 group, and 0.89 episodes per subject year in the TID BIAsp 30 group were recorded ($P = 0.24$). In subjects who achieved an HbA_{1c} target <7%, patients on TID BIAsp 30 had a significantly lower risk of major and minor hypoglycaemia than those on BID BIAsp 30 ($RR = 0.41$; $P < 0.05$). Indeed, 43.9% of subjects in the BID group and 47.2% of subjects in the TID group who achieved this HbA_{1c} target had no hypoglycaemia.

Except during the first four weeks of treatment, the rate of hypoglycaemic episodes (major and minor) was not increased in the TID group relative to the BID group (Figure). Evaluation of the occurrence of hypoglycaemia by time of day showed similar overall treatment number with the exception of the period 10:00–12:00 a.m. after administration when the number of events for patients in the BID BIAsp 30 group was twice that for patients in the TID BIAsp 30 group (44 events vs 22 events).

DISCUSSION

In the present study administration of both the BID and TID regimens improved glycaemic control in insulin-naïve patients. Although our study showed that there was no significant difference between treatment groups in PPG after breakfast,⁶ compared with BID

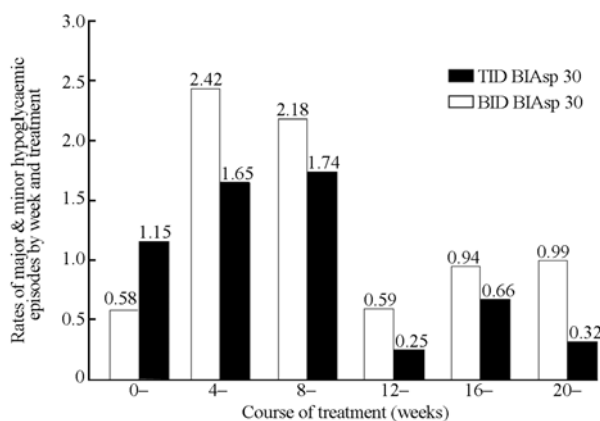


Figure. The rates of hypoglycaemia by course of treatment and treatment group.

BIAsp 30, use of TID BIAsp 30 was associated with significantly greater reductions in FPG and pre-dinner SMBG levels. In the TID BIAsp 30 regimen, the daily insulin dose was spread evenly between three meals rather than just two. This addition of an extra BIAsp 30 injection could, potentially, be advantageous for patients who usually eat a heavy lunch as it would provide additional prandial insulin coverage. Because insulin doses were modified by pre-meal BGs, TID treatment could improve fasting and pre-meal BGs.

The higher pre-breakfast and pre-dinner SMBG levels with BID BIAsp 30 indicated that this insulin premix regimen may be less effective for suppressing hepatic glucose production during the pre-dinner and the night in comparison with the thrice-daily regimen. Since total daily insulin was not different between the two insulin regimens, this difference likely reflected the difference in dosing frequency. Thus the lower pre-meal levels in patients on the TID regimen may explain the difference in HbA_{1c} reduction between the TID and BID regimens. Most blood glucose lowering therapies exacerbate weight gain. Moreover, weight gain is a well-known problem in patients with type 2 diabetes, especially in patients who are overweight at treatment start. Patients coming from such poor glycaemic control often experience some weight gain when they achieve good control.¹¹ In the United Kingdom Prospective Diabetes Study (UKPDS), increased weight gain was associated with improved glycaemic control and intensification of treatment.¹¹ In our study, weight gain with insulin treatment was strongly correlated with age and glycaemic control before the trial (baseline HbA_{1c}) by analysis of multiple linear regression. The insulin dose was not independently correlated with weight gain in all models. Therefore, glycaemic improvement was supposed to be a major reason of weight changes. Thus, weight gain was greatest in patients with the highest HbA_{1c} levels at treatment start. This could be predicted as weight gain with insulin therapy is attributed, at least in part to conservation of ingested calories as improved glycaemic control returns patients to glycaemic levels that are below the renal threshold. Hence patients in very poor baseline control

might gain the most weight by returning to below the renal threshold on insulin initiation.

The overall occurrence of hypoglycaemia was not different between TID and BID insulin treatment regimens. An increased rate of hypoglycaemia was reported in the TID group during the first four weeks of the study but thereafter rates were not different between the two regimens. The first four weeks was likely the period of intensive dose adjustment and it could therefore be expected that hypoglycaemia could be more problematic during this period. It could be explained by instable matching between insulin usage and meal time due to enrollment of insulin-naïve subjects. Since rates of hypoglycaemia were not different between treatment groups in the latter part of the study, when insulin doses were stabilized for each patient after investigators and patients understood insulin titration and how to avoid hypoglycaemia, this provides reassurance that the increased dosing frequency in the TID regimen and improvement of glycaemic control does not induce and increase risk of hypoglycaemia. The rapid absorption profile of IAsp thus appears to allow for the increased mealtime dosing without increasing the risk for postprandial hypoglycaemia. When the occurrence of hypoglycaemia was evaluated by time of day, a lower number of hypoglycaemia was observed at 10:00–12:00 a.m. in patients receiving the TID regimen than those on the BID regimen. This suggests that by spreading the dose more evenly throughout the day, with lower doses at each injection, there is less risk of hypoglycaemia, without compromising glycaemia. The ratio of insulin doses was 0.29 : 0.22 : 0.36 with TID BIAsp 30 without any OADs, which could be effective for decreasing FPG and PPG without increasing hypoglycaemia, especially for nocturnal hypoglycaemia.

The limitation of this study was its open label design. Although the inclusion and exclusion criteria may limit extrapolation of the study findings to other populations with type 2 diabetes, the baseline characteristics of the patients in this trial were representative of a typical Chinese patient with type 2 diabetes.

In conclusion, in Chinese subjects with type 2 diabetes in poor glycaemic control on OAD therapy, discontinuation of oral therapy and introduction of both BID and TID BIAsp 30 regimens were effective and safe. A TID regimen may further optimize control in Chinese patients who benefit from additional insulin at lunchtime. Furthermore, this regimen may delay the need for patients to progress to a more intensive basal-bolus treatment intervention.

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