REDUCED HYPOGLYCEMIA IS OBSERVED WITH INHALED INSULIN VERSUS SUBCUTANEOUS INSULIN ASPART IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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INTRODUCTION

- Technosphere® Insulin Inhalation Powder (TI) is a dry powder formulation of recombinant human insulin adsorbed onto Technosphere microparticles for oral inhalation in patients with diabetes mellitus.
- TI has been shown to have a more rapid absorption and elimination profile compared with subcutaneous regular human insulin.[1]
- The AFFINITY 1 Study (ClinicalTrials.gov Identifier: NCT01445951) was a randomized, open-label, noninferiority study of 24 weeks' duration comparing prandial TI versus subcutaneous insulin aspart added to basal insulin in patients with type 1 diabetes mellitus (T1DM).[2]
- In the AFFINITY 1 Study, TI was shown to be noninferior to subcutaneous insulin aspart with regards to improvement in glycated hemoglobin A_{1c} (A1C) levels.[2]
- Lower hypoglycemia event rates were also observed with TI compared with insulin aspart.[2]

OBJECTIVES

- To conduct a post hoc analysis of hypoglycemia rates from the AFFINITY 1 Study and investigate the impact of supplemental dosing of TI and insulin aspart on rates of hypoglycemia.
- To investigate hypoglycemia rates in the titration and maintenance phases of the study.

METHODS

Study Design and Patients

- This was a post hoc analysis conducted in a modified safety population of the AFFINITY 1 Study (those patients with T1DM who received ≥ 1 dose of TI or insulin aspart, and who also had baseline A1C data available; N = 339).
- Annualized hypoglycemia rates were determined in the modified safety population, patients taking ≥ 1 post-meal supplemental dose (TI, n = 111; insulin aspart, n = 91), and patients not taking a supplemental dose (TI, n = 61; insulin aspart, n = 76).
  - patients in the TI group were instructed to administer 1 supplemental dose (a fixed dose of 10 Units TI) if their 90-minute postprandial blood glucose (BG) measurement was ≥ 180 mg/dL; those patients who achieved a 90-minute postprandial BG measurement of ≥ 110 to < 160 mg/dL and who also had 2 of 3 pre-next-meal BG measurements ≥ 160 mg/dL were instructed to regularly use a supplemental dose 90 minutes after their meals
  - patients in the insulin aspart group were not instructed to administer supplemental doses on the basis of their postprandial BG values; however, correction doses were allowed by protocol
- The impact of supplemental dosing frequency on hypoglycemia was also investigated.
  - any hypoglycemic event that occurred ≥ 1 hour after the supplemental dose and also on the same day as the supplemental dose was included in the analysis
  - patients included in the analyses were distributed equally among 3 groups depending on the number of supplemental doses they received: 1-5, 6-20, and 21-60 supplemental doses during the study
  - patients receiving > 60 supplemental doses during the study (11.0% vs 6.6% in the TI and insulin aspart treatment arms, respectively; $P = 0.1489$) comprised too small a sample size, and thus were not included in the analyses of the impact of supplemental dosing frequency on hypoglycemia; no statistically significant difference was observed in the number of patients taking > 60 supplemental doses between treatments groups
- Hypoglycemia rates during study weeks 0-12 (titration phase) and study weeks 12-24 (maintenance phase) were also assessed.
  - during the titration phase, prandial doses in each group were adjusted weekly; patients randomized to TI targeted average 90-minute post-meal BG levels between 110 and 160 mg/dL and patients randomized to insulin aspart targeted average pre-next-meal BG values between 100 and 120 mg/dL

Endpoints

- Hypoglycemia was defined as
  - total: all hypoglycemic events (any symptomatic or asymptomatic hypoglycemic event)
  - confirmed: any hypoglycemic event with a BG value ≤ 49 mg/dL
  - nocturnal: any hypoglycemic event occurring between midnight and 06:00 AM
  - severe: any hypoglycemic event for which the patient required assistance

Statistical Analyses

- Descriptive statistics were used to compare baseline characteristics of patients treated with TI and insulin aspart.
- Continuous variables were compared using Student t-tests and categorical variables were compared using χ^2 tests.
- Annualized hypoglycemia event rates were determined (total number of hypoglycemic events divided by total exposure) and adjusted for baseline A1C level; negative binomial regression was used to compare results between TI and insulin aspart.

RESULTS

Patients and Baseline Characteristics

- Baseline characteristics of the 339 patients included in the post hoc analysis are shown in Table 1.
- There was no statistically significant difference in the mean number of supplemental doses taken between the TI and insulin aspart treatment arms (34.1 vs 26.6 doses, respectively; $P = 0.1907$).

Table 1. Baseline Patient Characteristics (Modified Safety Population; N = 339).

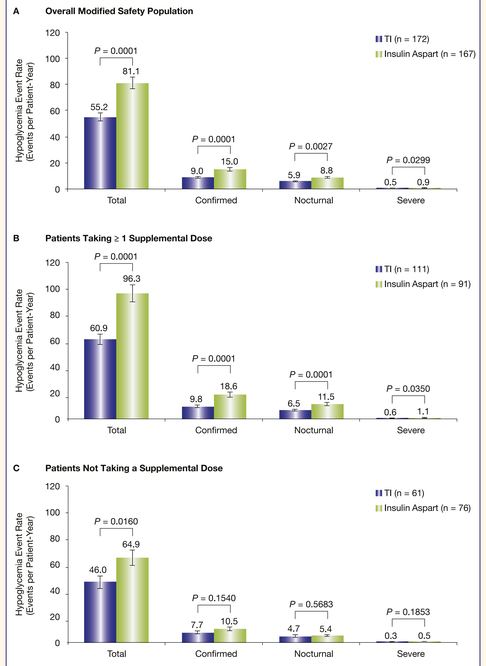
Characteristic	TI (n = 172)	Insulin Aspart (n = 167)	*P* Value
Age in years	36.9 (12.4)	39.2 (12.5)	0.0871
Male, n (%)	75 (43.6)	72 (43.1)	0.9275
Body mass index, kg/m²	25.9 (4.4)	25.2 (4.1)	0.1292
Weight, kg	75.2 (15.5)	72.4 (15.3)	0.0893
A1C, %	7.98 (0.77)	7.88 (0.75)	0.2431
T1DM duration, years	15.9 (10.1)	16.7 (10.0)	0.5055

Data represent mean (standard deviation) unless otherwise specified.

Hypoglycemia in the AFFINITY 1 Study

- Lower hypoglycemia events rates were seen for TI versus insulin aspart in the modified safety population (Figure 1A).
  - the differences observed were statistically significant for all types of hypoglycemia assessed (total, 55.2 vs 81.1 events per patient-year, $P = 0.0001$; confirmed, 9.0 vs 15.0 events per patient-year, $P = 0.0001$; nocturnal, 5.9 vs 8.8 events per patient-year, $P = 0.0027$; and severe 0.5 vs 0.9 events per patient-year, $P = 0.0299$)
- Similarly, in patients taking ≥ 1 supplemental dose, a lower hypoglycemia event rate was observed in patients treated with TI compared with insulin aspart (Figure 1B).
  - the differences observed were statistically significant for all types of hypoglycemia assessed (total, 60.9 vs 96.3 events per patient-year, $P = 0.0001$; confirmed, 9.8 vs 18.6 events per patient-year, $P = 0.0001$; nocturnal, 6.5 vs 11.5 events per patient-year, $P = 0.0001$; and severe, 0.6 vs 1.1 events per patient-year, $P = 0.0350$)

Figure 1. Hypoglycemia Event Rates in the Overall Modified Safety Population (A), Patients Taking ≥ 1 Supplemental Dose (B), and Patients Not Taking a Supplemental Dose (C).



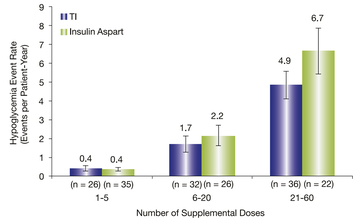
Error bars represent SE.
SE, standard error.

- In patients not taking a supplemental dose, lower rates of hypoglycemia were observed in patients treated with TI compared with insulin aspart, but the difference was statistically significant only for total hypoglycemia (46.0 vs 64.9 events per patient-year; $P = 0.0160$) (Figure 1C).

Impact of Supplemental Dosing Frequency on Hypoglycemia

- Within both the TI and the insulin aspart treatment arms, a statistically significant increase in the total hypoglycemia rate ≥ 1 hour after supplemental dosing was observed in patients who had a higher supplemental dose frequency (Figure 2).
  - 0.4 versus 1.7 versus 4.9 events per patient-year for patients receiving 1-5, 6-20, and 21-60 supplemental doses in the TI treatment arm, respectively (all $P < 0.01$)

Figure 2. Total Hypoglycemia Event Rates in the TI and Insulin Aspart Treatment Groups According to Number of Supplemental Doses Taken.[a,b]



[a]No statistically significant differences were observed in rates of total hypoglycemia between the TI and insulin aspart treatment arms in each supplemental dosing frequency category ($P = 0.7749$, $P = 0.4908$, and $P = 0.1907$ for patients receiving 1-5, 6-20, and 21-60 supplemental doses, respectively).
[b]All within treatment arm comparisons of total hypoglycemia rates across supplemental dosing frequency categories were statistically significant ($P = 0.0001$); for the comparison between 0-5 and 6-20 supplemental doses in the TI arm, the *P* value was 0.0059.

- 0.4 versus 2.2 versus 6.7 events per patient-year for patients receiving 1-5, 6-20, and 21-60 supplemental doses in the insulin aspart treatment arm, respectively (all $P = 0.0001$)
- There was no statistically significant difference observed in rates of hypoglycemia between the TI and insulin aspart treatment arms in each of the supplemental dosing frequency categories.

Hypoglycemia in the Titration and Maintenance Phases of the AFFINITY 1 Study

- In the modified safety population, within the TI treatment arm, there was no statistically significant difference in the rate of hypoglycemia (all types) during the titration phase compared with the maintenance phase (Table 2).
- In the modified safety population, within the insulin aspart treatment arm, higher rates of total and confirmed hypoglycemia were observed during the titration phase compared with the maintenance phase; these differences were statistically significant (total, 90.5 vs 75.2 events per patient-year, $P = 0.0308$; and confirmed, 17.5 vs 13.1 events per patient-year, $P = 0.0297$) (Table 2).
- In patients taking a supplemental dose, within both treatment arms, there was no statistically significant difference in the rate of hypoglycemia (all types) during the titration phase versus the maintenance phase (Table 2).
- In patients not taking a supplemental dose, within the TI treatment arm, there was no statistically significant difference in the rate of hypoglycemia (all types) during the titration phase compared with the maintenance phase (Table 2).
- In patients not taking a supplemental dose, within the insulin aspart treatment arm, higher rates of total and confirmed hypoglycemia were observed during the titration phase versus the maintenance phase; these differences were statistically significant (total, 79.8 vs 57.2 events per patient-year, $P = 0.0064$; and confirmed, 14.1 vs 8.4 events per patient-year, $P = 0.0056$) (Table 2).

LIMITATIONS

- This study methodology was a non pre specified post hoc analysis.
- Correction for multiple comparisons is warranted.
- However, the data reported here do provide more detail and demonstrate consistency regarding the hypoglycemia benefits observed with TI compared with insulin aspart.

Table 2. Hypoglycemia Event Rates During the Titration and Maintenance Phases of the Study.

	Hypoglycemia, Events per Patient-Year (SE)				
	Titration Phase	*P* Value (Between Treatment Arms)	Maintenance Phase	*P* Value (Between Treatment Arms)	*P* Value (Within Treatment Arm)
Overall modified safety population					
Total TI	57.9 (3.5)		56.2 (3.8)		0.7550
Total insulin aspart	90.5 (5.4)	0.0001	75.2 (4.6)	0.0028	0.0308
Confirmed TI	9.7 (1.0)		8.8 (1.0)		0.5373
Confirmed insulin aspart	17.5 (1.6)	0.0001	13.1 (1.3)	0.0083	0.0297
Nocturnal TI	6.2 (0.7)		5.9 (0.7)		0.7710
Nocturnal insulin aspart	9.4 (0.9)	0.0031	8.3 (0.8)	0.0296	0.3737
Severe TI	0.6 (0.1)		0.4 (0.1)		0.2203
Severe insulin aspart	0.9 (0.2)	0.2259	0.9 (0.2)	0.0197	0.8131
Patient taking a supplemental dose					
Total TI	62.0 (3.9)		64.3 (4.8)		0.7066
Total insulin aspart	102.1 (7.9)	0.0001	95.8 (7.7)	0.0003	0.5660
Confirmed TI	10.1 (1.2)		10.6 (1.5)		0.7970
Confirmed insulin aspart	21.1 (2.6)	0.0001	18.5 (2.4)	0.0037	0.4462
Nocturnal TI	7.0 (0.9)		6.8 (1.0)		0.8974
Nocturnal insulin aspart	12.5 (1.5)	0.0001	11.6 (1.5)	0.0064	0.6767
Severe TI	0.6 (0.2)		0.6 (0.2)		0.9722
Severe insulin aspart	1.3 (0.4)	0.0866	1.1 (0.4)	0.1667	0.6311
Patient not taking a supplemental dose					
Total TI	50.7 (6.1)		46.8 (5.7)		0.6355
Total insulin aspart	79.8 (6.8)	0.0001	57.2 (5.0)	0.2034	0.0064
Confirmed TI	8.9 (1.7)		6.7 (1.3)		0.2924
Confirmed insulin aspart	14.1 (1.8)	0.0381	8.4 (1.1)	0.3280	0.0056
Nocturnal TI	4.9 (0.9)		4.9 (0.9)		0.9788
Nocturnal insulin aspart	6.5 (0.9)	0.2148	5.4 (0.8)	0.6921	0.3471
Severe TI	0.6 (0.3)		0.1 (0.1)		0.0604
Severe insulin aspart	0.5 (0.2)	0.7419	0.7 (0.2)	0.0154	0.5461

CONCLUSIONS

- These data show that there was a consistently lower hypoglycemia rate in patients with T1DM treated with TI versus insulin aspart, including in those patients taking supplemental doses.
- This lower hypoglycemia rate persisted during both the titration and maintenance phases of the study.
- The more rapid-acting profile of TI was not associated with a statistically significant increase in supplemental dosing compared with insulin aspart.

REFERENCES

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