Improved Time-in-Range (TIR) on Continuous Glucose Monitor (CGM) with Technosphere Inhaled Insulin (TI) compared to insulin Aspart in Patients with T1D—STAT Study

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Background

- The majority of adults with type 1 diabetes (T1D) are not at optimal glycemic control
- Hyperglycemia is associated with increased risk of diabetic complications and mortality
- Post-prandial hyperglycemia and late post-prandial hypoglycemia are common problems due to insulin stacking with rapid-acting insulin analogs
- Technosphere insulin (TI, Afrezza® Mannkind Corporation, Westlake Village, CA) is a dry powder formulation of regular human insulin adsorbed onto Technosphere microparticles for oral inhalation (Figure 1)
- TI has a faster onset and shorter duration of action that allows more rapid post-prandial insulin action

Study Objective

•In this pilot investigator-led, collaborative open-label multi-center randomized pilot clinical trial, we evaluated the efficacy of TI for post-prandial glucose control (PPBG) measured by time-in-range (TIR) on continuous glucose monitor (CGM) and post-prandial glucose excursions (PPGE) over a 4-week treatment period.

Methods and Materials

Study Participants: Adults 18-70 years old with T1D for at least 6 months and HbA1c 6.5-10.0% (48.0-86.0 mmol/mol) participated at 5 clinical centers in the US between June 2017 and December 2017.
Inclusion Criteria: Nonsmoking adults, BMI ≤ 35 kg/m^2, forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FEV_1) ≥ 70% predicted, on multiple daily injections (MDI), with stable insulin dose ≥ 3 months, and use of insulin degludec or glargine as a basal insulin.
Withdrawal Criteria: A decrease ≥ 20% of FEV_1 was a withdrawal criteria, but no patients met this criteria.

Randomization: Patients were randomized 1:1 to TI or insulin aspart, stratified by screening HbA_{1c} (≤ 8% or > 8%).
Insulin Dosing: Patients randomized to insulin aspart continued the same bolus dose as used prior to randomization; Patients randomized to TI converted to a starting pre-meal TI dose according to a conversion table based on the label (Table 1). Patients in the TI group were advised to take additional inhalations at 1 and 2 hours after meals based on PPBG per protocol (Table 1).
Compliance: At least 80% compliance with TI doses was considered 'compliant', and a per protocol analysis was conducted to examine compliant use of TI vs. insulin aspart.

Figure 1 Technosphere Insulin Inhaler

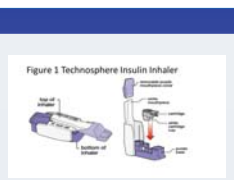


Figure 2

Table 1 TI Dose Conversion and Correction

TI Dose Conversion		TI Dose Correction		
Injected mealtime insulin	**TI dose**	**Sensor Glucose**	**1-hr**	**2-hr**
Up to 4 units	4 units	≤ 150 mg/dl	-	-
5-8 units	8 units	151-200 mg/dl	4 units	-
9-12 units	12 units			
13-16 units	16 units	≥ 201 mg/dl	8 units	4 units*
17-20 units	20 units			

* 2-hour correction used only if sensor glucose is ≥ 201 mg/dl and not decreased by ≥ 50 mg/dl between 1 and 2 hours

Visits (Fig. 2): Patients were screened and then randomized up to one week later; In-Clinic visits were at 2 and 4 weeks, and phone visits at 1, 3 and 5 weeks and 1 week after completion of study

Results

Use of TI Improved PPBG and PPGE (Table 4, Figure 4, 6 and 8)
TIR was significantly increased in Compliant patients (Figure 3)
There was no increase in time in hypoglycemia (Table 4)
TI use also decreased Glucose Variability (Figure 5)

Table 2 Characteristics of patients at baseline	Aspart (n=34)	TI (n=26)	p-value
Age (years)	42 ± 14	41 ± 16	0.83
Diabetes duration (years)	19 ± 13	20 ± 11	0.79
Screening HbA1c (%)	8.0 ± 1.2	7.7 ± 0.9	0.19
Weight (kg)	85.9 ± 26.5	85.5 ± 21.7	0.94
Body mass index (kg/m2)	28.7 ± 9.8	27.8 ± 7.5	0.65
Systolic BP (mmHg)	120 ± 14	127 ± 14	0.06
Diastolic BP (mmHg)	77 ± 8	77 ± 8	0.65
Forced expiratory volume-one second (FEV_1)	3.3 ± 1.1	3.4 ± 0.9	0.69
Daily total basal dose (U/Day)	22.7 ± 8.2	27.9 ± 15.0	0.12
Daily total bolus dose (U/Day)	21.3 ± 8.1	21.8 ± 12.1	0.86

Table 3 CGM parameters by treatment group	Aspart (n=34)	TI (n=26)	p-value
Mean sensor glucose (mg/dl)	173.1 ± 5.2	171.1 ± 6.7	0.80
Final HbA1c (%)	7.8 ± 1.0	7.6 ± 0.8	0.60
HbA1c change	-0.25 ± 0.31	-0.02 ± 0.36	0.01*
Glucose SD (mg/dl)	63.2 ± 2.2	58.5 ± 2.9	0.14
% Time in range (70-180 mg/dl)	54.5 ± 2.6	56.2 ± 3.4	0.63
% Time in hyperglycemia (>180 mg/dl)	40.7 ± 3.0	40.5 ± 3.8	0.96
% Time hypoglycemia (<70 mg/dl)	3.6 ± 0.8	2.0 ± 1.0	0.16
% Time in hypoglycemia (<60 mg/dl)	1.72 ± 0.50	0.69 ± 0.63	0.14
% Time in hypoglycemia (<50 mg/dl)	0.66 ± 0.25	0.24 ± 0.31	0.22

Table 4 CGM parameters by compliance	Aspart (n=34)	TI - Non-Compliant (n=7)	TI - Compliant (n=15)	p-value
Mean sensor glucose (mg/dl)	172.3 ± 2.4	183.4 ± 5.4§	163.7 ± 3.6*	0.009
Glucose SD (mg/dl)	64.4 ± 1.1	67.0 ± 2.4§	56.0 ± 1.6*	<0.001
% Time in range (70-180 mg/dl)	54.7 ± 1.3	47.6 ± 2.8*§	61.1 ± 1.9*	<0.001
% Time in hyperglycemia (>180 mg/dl)	40.1 ± 1.4	48.3 ± 3.1*§	35.4 ± 2.1	0.003
%Time in hypoglycemia (<70 mg/dl)	3.91 ± 0.35	2.76 ± 0.76	2.30 ± 0.51*	0.03
% Time in hypoglycemia (<60 mg/dl)	1.96 ± 1.48	1.44 ± 0.48	0.80 ± 0.32*	0.01
% Time in hypoglycemia (<50 mg/dl)	0.79 ± 0.12	0.61 ± 0.26	0.32 ± 0.18*	0.08

Figure 3 TIR by treatment group and compliance

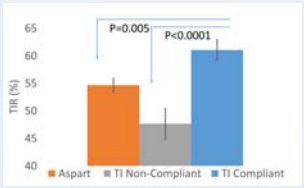


Figure 4 Post-prandial glucose excursion 1-4 hours by group and compliance

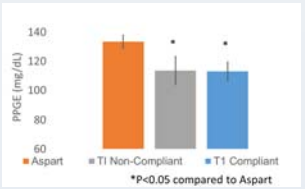


Figure 5 Daytime and nighttime Glucose SD by treatment group and compliance

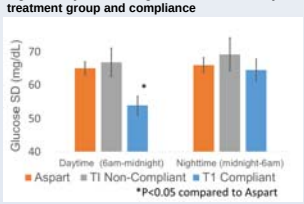


Figure 6 Post-prandial glucose excursion 1-4 hours by meal

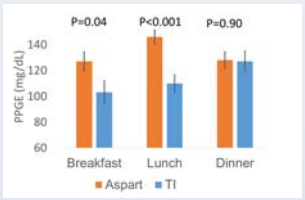


Figure 7 PP glucose by treatment group and compliance

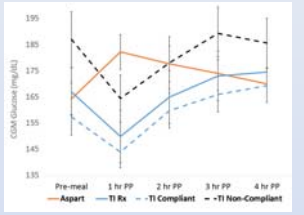


Figure 8 Two Hour PP glucose AUC by treatment group and compliance

Figure 9 TIR by treatment and time of day

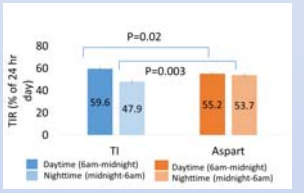
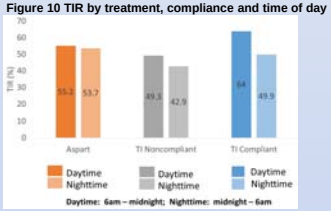


Figure 10 TIR by treatment, compliance and time of day



Summary of Results

In summary, TI improved PPG as well as all day glucose time-in-range with additional post-prandial TI dose as needed. Further, TI decreased daytime glucose variability and reduced time spent in hypoglycemia.

Conclusion

The faster action with shorter duration profile of TI when compared to rapid-acting insulin analogs may provide a flexible approach for patients to optimize post-prandial glucose control without increasing risk of hypoglycemia.

Acknowledgements

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