Total and Severe Hypoglycemia Is Reduced With Use of Inhaled Technosphere® Insulin (AFREZZA®) Relative to Insulin Aspart in Type 1 Diabetes

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Background/Objectives

BACKGROUND

- Hypoglycemia and fear of hypoglycemia prevent many individuals living with diabetes from intensifying insulin therapy and achieving glycemic targets[1,2]
- Longer-acting (basal) and ultra-short-acting insulins may limit hypoglycemia risk[3]
- Ultra-rapid-acting mealtime insulin can improve early post-meal glucose control and limit the risk of post-meal hypoglycemia[4]
- Phase 3 study in type 1 diabetes (T1D; AFFINITY 1) demonstrated that prandial inhaled Technosphere® Insulin (TI) provides glycemic control that is noninferior to prandial insulin aspart[5]
- Lower rates of hypoglycemia were seen with TI, particularly 2 to 5 hours after meals and in those achieving HbA_{1c} <7.0%,[5] and the incidence of severe hypoglycemia was lower in TI users (18.4% vs 29.2%; *P*=0.0156)

OBJECTIVE

- We performed a detailed, post hoc regression analysis to evaluate overall and severe hypoglycemic event rates based on the HbA_{1c} level achieved in patients treated with TI vs subcutaneous insulin aspart

Study Design/Methods

METHODS

- Post hoc analysis was performed on a representative subset of the AFFINITY 1 (24-week treat-to-target study in T1D: NCT01445951) cohort[5] for whom an end-of-treatment value for HbA_{1c} was known (Table 1)
- Hypoglycemia was defined as any self-monitored blood glucose <70 mg/dL or symptomatic events that corrected with carbohydrate ingestion. Severe hypoglycemia was defined in the usual fashion[6]
  - Frequency of hypoglycemia was modeled as a negative binomial distribution with mean μ and reciprocal dispersion factor v
  - The logarithm of μ, ln(μ), was modeled as a linear function of the continuous variable HbA_{1c} and indicator variables representing treatment, basal insulin, and region (Figure 1)
  - Hypoglycemia incidence and events were tabulated and evaluated using χ^2 statistics (Table 2)

Table 1. Population Comparison: Original vs Post Hoc Analysis

Mean HbA_{1c} (%)	Insulin aspart	TI	Treatment difference
Original analysis (MMRM)			
N	170	174	
Baseline	7.92	7.94	
End of treatment	7.52	7.73	
Adjusted mean change	−0.40	−0.21	0.19
95% CI	−0.52, −0.28	−0.33, −0.09	0.02, 0.36
Post hoc analysis (ANCOVA)			
N	147*	129	
Baseline	7.88	7.97	
End of treatment	7.47	7.76	
Mean change	−0.40	−0.21	0.20
95% CI	−0.53, −0.28	−0.34, −0.08	0.02, 0.38

*Baseline values for 3 patients randomized to aspart were not recorded.

Results

Figure 1. Hypoglycemic event rates as a function of HbA_{1c}.

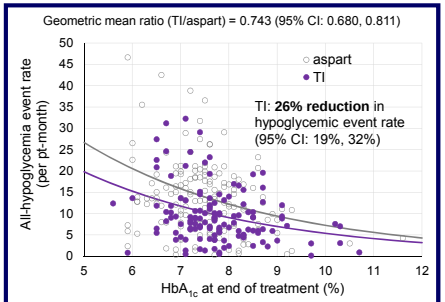

Figure 2. Comparison of estimated hypoglycemia rates vs achieved HbA_{1c}.

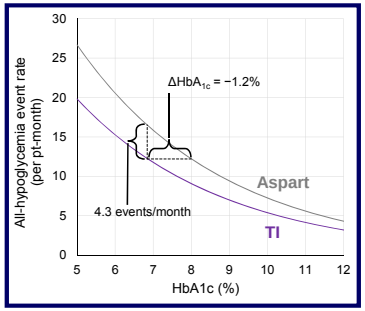

Table 2. Summary of Hypoglycemia Incidence and Events

	Parameter	Aspart	TI	*P* value
	N	150	129	
All hypoglycemia	Incidence, n (%)	150 (100)	129 (100)	1
	Events	11,723	6983	<0.001
	Events per patient	78.2	54.1	
Severe hypoglycemia	Incidence, n (%)	47 (31.3)	28 (21.7)	0.071
	Events	127	59	0.114
	Events per patient reporting at least 1 severe hypoglycemic event	2.7	2.1	

Summary

- Use of TI vs aspart was associated with significantly lower rates of hypoglycemia
- At any given HbA_{1c} level, overall rates of hypoglycemia with TI were reduced ~26%
- Achieved HbA_{1c} does not account for the differences observed in hypoglycemia
- TI allows for greater HbA_{1c} reduction with lower rates of hypoglycemia (Figure 2)
  - HbA_{1c} could be reduced by 1.2% at a hypoglycemia rate of 12.2 events/month
  - Total events could be reduced by 4 per patient-month at an HbA_{1c} of ~6.8%

Conclusions

- Use of the ultra-rapid-acting inhaled insulin (TI) significantly lowers the rate of hypoglycemia in type 1 diabetes while providing noninferior glycemic control
- Use of TI in a multidose insulin regimen may permit treatment intensification to be achieved with less hypoglycemia
- Switching to TI may also benefit patients already at goal by reducing the frequency of hypoglycemic events

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