EFFECTS OF INHALED TECHNOSPHERE INSULIN (TI) ON THE PULMONARY FUNCTION OF PATIENTS WITH T1D AND T2D

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Abstract

TI is a novel inhaled rapid-acting insulin (RAI) approved for use in the US. Management of spirometry may be a barrier to TI use, and there are concerns regarding declines in pulmonary function. This analysis explored spirometry data from clinical trials of TI. Spirometry results were assessed using pooled analyses of 7 TI studies (duration 6-24 months). We included 1,842 patients with T1D (mean age 39 years; 51% male) and 2,281 with T2D (mean age 56 years; 56% male) using TI or comparator (RAI, standard of care, placebo). Baseline mean (SD) forced expiratory volume in 1 second (FEV_1) values were 3.49 (0.787) L and 3.01 (0.714) L for patients with T1D and T2D, respectively. FEV_1 in both TI and comparator groups declined from baseline to 3 months in patients with T1D (TI = –0.063 L, comparator = –0.019 L; p = 0.1414) and T2D (TI = –0.084 L, comparator = –0.043 L; p = 0.1431) (**Figure**). After 3 months, the decline in FEV_1 at each timepoint was comparable between TI and comparator groups. These reductions were a small percentage of the FEV_1 and not influenced by significant outliers. In 2 studies where FEV_1 was measured after discontinuation, there was no difference between groups after 1 month. Our data, pooled from 7 clinical trials, demonstrate that TI's effects on pulmonary function are small and develop during the first 3 months of use. After that, TI and comparator groups demonstrate comparable physiologic declines for up to 24 months.

*since submitting the abstract an MMRM model including additional patients and data beyond 12 months were run, which resulted in alterations in the original 3 months change from baseline estimates for FEV_1

Introduction

- Technosphere® insulin inhalation powder (TI) is a novel inhaled human insulin approved in the US for use as a rapid-acting insulin (RAI) to improve glycemic control in adult patients with diabetes.
- In people with type 1 or type 2 diabetes (T1D and T2D, respectively), TI has been shown to provide a comparable degree of glycemic control with that achieved using premixed insulin or an RAI in combination with basal insulin.[1-4]
- Small, rapidly developing, non-progressive, and reversible declines in pulmonary function have been seen in people treated with TI;[1,3,5,6] these declines have also been observed with other inhaled insulins.[7]
- Concerns regarding changes in pulmonary function have led to a recommendation for pulmonary function testing (PFT) in all patients prior to initiating treatment with TI and at additional intervals during therapy.

Objective

To provide clinicians with a more detailed understanding of the timing and extent of pulmonary function changes associated with TI.

Methodology

Study Selection

- Patient-level data were pooled from 7 prospective Phase 3 randomized controlled trials with a duration of > 6 months that were conducted in adults with T1D or T2D who initiated TI.[1-6,8]
- All patients who were randomized, treated, and had PFT data at baseline and at least 1 follow-up timepoint were considered eligible for inclusion.
- For inclusion in this analysis, PFT in these trials had to be conducted according to the 2005 American Thoracic Society/European Respiratory Society test quality recommendations.

Endpoints and Statistical Analyses

- For the purposes of these analyses, patients receiving any intervention other than TI were considered as a comparator group; this included treatment with RAI, premix insulin, standard of care, and placebo.
- Descriptive statistics were used to describe pulmonary function (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC] and FEV_1/FVC ratio) at baseline and at selected timepoints.
- A mixed-model, repeated-measures (MMRM) analysis with baseline FEV_1, height, age, gender, and visit by treatment was used to assess change from baseline for FEV_1. Slopes from the MMRM analyses between 3 and 24 months were also compared between groups.

Results

Patients and Baseline Demographics

- Overall, 4,271 patients using either TI or a comparator were included in this analysis: 1,842 with T1D and 2,429 with T2D. Baseline characteristics are shown in **Table 1**.
- Baseline mean (SD) FEV1 values were 3.48 (0.782) L for people with T1D and 2.97 (0.707) L for people with T2D:
  - In patients with T1D, mean (SD) baseline FEV_1 values were 3.48 (0.766) for TI and 3.51 (0.810) for comparator.
  - In patients with T2D, mean (SD) baseline FEV_1 values were 2.99 (0.688) for TI and 3.01 (0.747) for comparator.

Table 1. Baseline Characteristics

Characteristic	Total (N = 4,271)	T1D (n = 1,842)	T2D (n = 2,429)
Mean age, years (SD)	48 (14)	39 (13)	56 (9)
Female, n (%)	1,902 (46.1)	905 (49.1)	997 (43.7)
White race, n (%)	3,514 (85.2)	1,698 (92.2)	1,816 (79.6)
Therapy, n (%)			
TI	2,293 (53.7)	1,014 (55.0)	1,279 (52.6)
RAI	1,611 (37.7)	828 (45.0)	783 (32.2)
Standard of care	219 (5.1)	0 (0.0)	219 (9.1)
Placebo	148 (3.5)	0 (0.0)	148 (6.1)

SD, standard deviation.

Results

Changes in Pulmonary Function

- The least-square (LS) mean changes in pulmonary function parameters from baseline to 24 months assessed by MMRM analysis are shown in **Table 2** and the **Figure**.
- There are small drops in FEV_1 between baseline and 3 months and between baseline and 24 months, with greater reductions in the TI groups (**Table 2**).
- The difference between TI and comparators is non-progressive, and from 3 to 24 months, the 2 lines are roughly parallel (**Figure**).
- Analyses of the slopes from 3 months to 24 months show a similar reduction in FEV_1 with both TI and comparator treatment in patients with both T1D (p = 0.200) and T2D (p = 0.991).

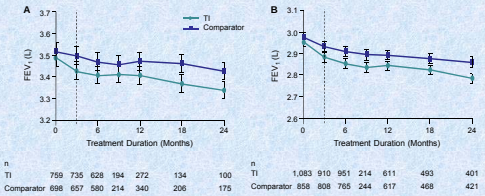
Table 2. Change in Pulmonary Function Measures From Baseline Derived by MMRM Analysis

	3 Months			24 Months		
T1D						
Variable	TI LS mean (SE) change	Comparator LS mean (SE) change	p Value	TI LS mean (SE) change	Comparator LS mean (SE) change	p value
FEV_1, L	−0.062 (0.010)	−0.019 (0.010)	0.024	−0.149 (0.016)	−0.087 (0.013)	0.041
FVC, L	−0.041 (0.009)	−0.021 (0.010)	0.186	−0.113 (0.017)	−0.074 (0.014)	0.155
FEV_1/FVC ratio	−0.372 (3582)	0.091 (0.363)	0.007	−0.899 (0.368)	−0.229 (0.370)	0.006
T2D						
	3 Months			24 Months		
	TI LS mean (SE) change	Comparator LS mean (SE) change	p Value	TI LS mean (SE) change	Comparator LS mean (SE) change	p value
FEV_1, L	−0.077 (0.006)	−0.042 (0.007)	0.066	−0.077 (0.006)	−0.087 (0.014)	0.041
FVC, L	−0.083 (0.015)	−0.051 (0.016)	0.068	−0.189 (0.017)	−0.130 (0.018)	0.057
FEV_1/FVC ratio	−0.231 (0.553)	0.095 (0.561)	0.222	−0.721 (0.560)	−0.070 (0.566)	0.083

Values derived from a MMRM model adjusted for age, sex, and baseline height and including the treatment group-by-visit-by-diabetic type interaction.
SE, standard error.

- These reductions in FEV_1 represent a small percentage of the FEV_1, and were not influenced by significant outliers.
- From baseline to 24 months, the distribution of change from baseline FEV_1 among patients were comparable in the TI and comparator groups (data not shown).
- In the 3 studies of patients with T1D and T2D where FEV_1 was measured 4 weeks after discontinuation of TI therapy, pulmonary function increased in the TI group (mean FEV_1 [SE] +0.037 [0.007] L) and decreased in the comparator group (−0.017 [0.007] L).

Figure. FEV_1 Over 24 Months in People With T1D (A) or T2D (B) Treated With TI or Comparator



Data represent LS means ±SE.
MMRM analyses were used; FEV1, age, height, and gender as covariates.

DISCUSSION

- This pooled analysis of 7 studies showed slightly greater declines in pulmonary function (FEV_1) in those treated with TI compared with comparator treatments during the first 3 months (approximately 30-40 mL difference).
- After 3 months, the change in pulmonary function was similar to comparators up to 24 months.
- FEV_1 reductions were small in both TI and comparator groups; they represented a small fraction of pulmonary capacity, and the observed treatment group difference disappeared within 1 month of cessation of TI therapy.

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