PATIENT-LEVEL ASSESSMENT OF COUGH WITH TECHNOSPHERE® INHALED INSULIN IN PATIENTS WITH T1DM

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INTRODUCTION

- Technosphere® inhaled insulin (TI) is a dry-powder formulation of regular human insulin adsorbed onto Technosphere microparticles for oral inhalation in patients with diabetes.
  - TI is delivered by the Gen2 inhaler device (**Figure 1**)
- Cough, generally reported to be mild-to-moderate, nonproductive, and decreasing in incidence over time, is a commonly reported side effect associated with inhaled insulins.[1,2]
- Cough, which was generally mild and transient, has been reported with TI in patients with both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus.[3]
- In a phase 3 study of inhaled TI versus injected insulin aspart in people with T1DM receiving basal insulin, glycated hemoglobin A_{1c} (A1C) reduction with TI was noninferior to that with injected insulin aspart, with less hypoglycemia and less weight gain.[4]

OBJECTIVE

- To describe the characteristics and changes in lung function of patients with T1DM reporting cough, and to compare the safety and efficacy outcomes in those who experienced cough compared to those who did not, in a phase 3 clinical trial of TI.

METHODS

Study Design and Patients

- This was a patient-level post hoc analysis of patients with T1DM receiving basal insulin, treated with TI during a 24-week, randomized, multicenter, phase 3 study.[4]
- Inclusion criteria for the study were:
  - nonsmoking (never smoked, or quit smoking for > 6 months)
  - adults (age > 18 years) with T1DM for ≥ 12 months
  - A1C 7.5-10.0%
  - body mass index (BMI) ≤ 38 kg/m^2
  - forced expiratory volume in 1 second ($FEV_{1.0}$) and forced vital capacity (FVC) ≥ 70% predicted[5]
  - stable insulin dose (< 2 IU/kg/day)
  - fasting plasma glucose < 220 mg/dL for 3 months before screening
- Exclusion criteria were:
  - significant pulmonary disease
  - significant abnormalities on chest X-ray
  - malignancy within 5 years
  - severe complications of diabetes
  - ≥ 2 severe hypoglycemic episodes within 6 months
- Patients with T1DM administered TI at the beginning of a meal or up to 20 minutes after starting a meal.
  - for the first 12 weeks of treatment, prandial doses were adjusted weekly to achieve targeted average 90-minute post-meal self-monitored blood glucose (SMBG) values of 110-160 mg/dL, with a supplemental dose (10 units of TI) at the time of the reading if a 90-minute post-meal SMBG value was ≥ 180 mg/dL
- Cough was a reported adverse event; details regarding cough were collected using a cough-specific case report form:
  - cough frequency, characteristics, start and end dates (whenever possible), and timing in relation to the study drug inhalation were recorded

Analysis Outcomes

- Patients with T1DM who reported ≥ 1 cough episode during the 24-week study were included in the "Cough" group; all other patients who never reported cough were included in the "No Cough" group.
- The characteristics of cough (intensity, duration, frequency, onset date of cough, and whether the cough was productive) were self-reported; the number of people who discontinued the study drug due to cough was also recorded.
- Efficacy and safety outcomes, including A1C and hypoglycemia (all events, confirmed, nocturnal, and severe events) were reported after the start of drug administration up until Week 24.
- Parameters of lung function ($FEV_{1.0}$, FVC, and $FEV_{1.0}$/FVC ratio) were reported at baseline and Week 24.

Statistical Analyses

- Descriptive analysis was conducted between the Cough and No Cough groups at baseline and Week 24.
  - Week 24 values were last observation carried forward or end of treatment for the patient
  - descriptive statistics included mean, standard deviation (SD), interquartile range (IQR), full range, and number and percent of patients
  - probabilities based on Student t-tests or χ^2 tests were used to highlight possible differences or lack of differences
  - annualized rates of hypoglycemias were estimated using negative binomial regression

Figure 1. The Gen2 Inhaler Device.

RESULTS

- 174 patients were included in the analysis, with cough reported by 31.6% (n = 55).
- Baseline characteristics are shown in **Table 1**.
  - there were no significant differences between the Cough and No Cough groups, apart from BMI, which was slightly higher in patients reporting cough but remained < 30 kg/m^2 in both groups

Cough Characteristics

- In those patients reporting cough, it was generally considered to be mild in intensity (72.7%; moderate 21.8%, severe 5.5%) and intermittent in frequency for a majority of patients (**Figure 2A** and **2B**).
- Cough was reported as nonproductive in the majority of patients (n = 45; 81.8%) and occurred within 10 minutes of inhalation of TI (n = 49; 89.1%).
- Cough was transient for many patients (mean [IQR] duration: 50 [9-126] days) (**Figure 2C**).
- The majority (61.8%) of cough events started in Week 1 of initiating TI and continued through the study only in a fraction of patients (**Figure 3**).
  - there was only 1 patient who reported cough initiating after Week 8
- 10 patients (5.7%) discontinued the study due to cough.

Table 1. Baseline Characteristics.

	Cough (n = 55)	No Cough (n = 119)	*P* Value
Age in years, mean (SD)	38.5 (13.6)	36.3 (11.9)	0.2793
Female, n (%)	31 (56.4)	66 (55.5)	0.9116
BMI in kg/m^2, mean (SD)	27.5 (4.4)	25.1 (4.3)	0.0011
Height in cm, mean (SD)	168 (7.7)	170 (13.7)	0.2482
Body weight in kg, mean (SD)	77.9 (15.1)	74.1 (15.5)	0.1282
A1C, %, mean (SD)	7.95 (0.81)	7.95 (0.66)	0.9599
Average TI dose in U/kg, mean (SD)			
At breakfast	0.37 (0.18)	0.50 (1.74)	0.6078
At lunch	0.41 (0.22)	0.57 (2.15)	0.6231
At dinner	0.45 (0.22)	0.61 (2.42)	0.6394

Figure 2. Cough Characteristics in Patients With T1DM Treated With TI (n = 55): Intensity (A); Frequency (B); and Duration (C).

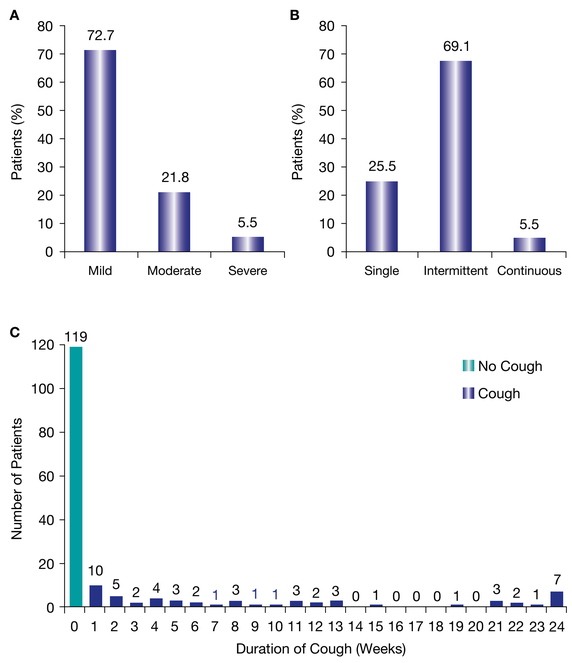
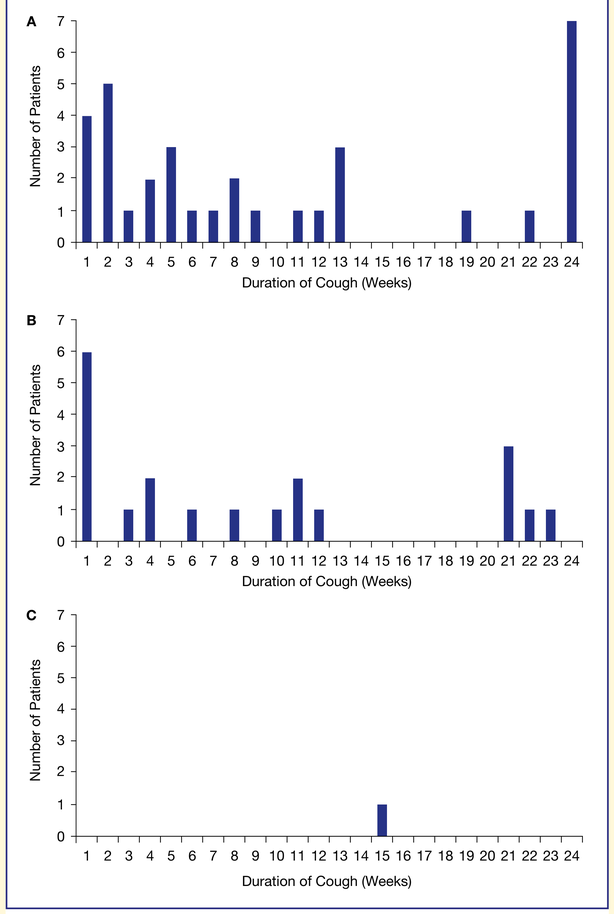


Figure 3. Duration of Cough for Patients With T1DM Who First Reported Cough During: Week 1 (A); Weeks 2-8 (B); or After Week 8 (C).



Efficacy and Safety

- There was no significant difference in A1C between the Cough and No Cough groups at either baseline or end of treatment (**Figure 4**), or in change from baseline (mean [SD] change: –0.05% [0.67] vs –0.20% [0.72], respectively; *P* = 0.2183).
- There were no significant differences in incidence or rates of hypoglycemia between the groups (**Figure 5**).
- The average TI dose at each meal at the end of the study (Week 24) did not differ between the Cough and No Cough groups.

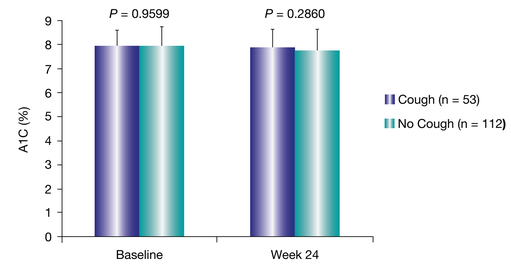
Lung Function

- Patients who reported cough had significantly lower $FEV_{1.0}$ and FVC at baseline and at the end of treatment compared with those who did not report cough (**Table 2**).
- Predicted values were also numerically lower for those who reported cough, resulting in mean percent of predicted values ranging between 92% and 98% for the 2 groups (**Table 2**).
- There was, however, no significant difference in $FEV_{1.0}$/FVC ratio between groups at baseline and end of treatment (**Table 2**).
- There were no significant differences in the changes in lung function ($FEV_{1.0}$, FVC, or $FEV_{1.0}$/FVC) from baseline to Week 24 between those who reported cough and those who did not (**Table 2**).

LIMITATIONS

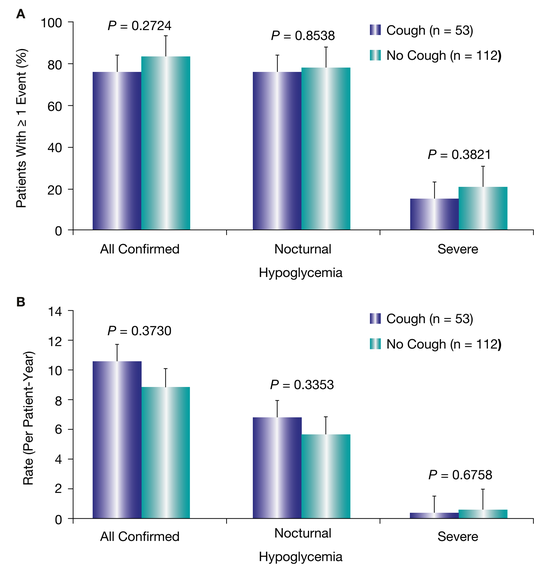
- These results are from a clinical study of adults with T1DM and may not be applicable to other populations.
- This study is limited due to the small number of participants and thus the small number of patients who experienced cough, and the self-reported nature of some cough characteristics.

Figure 4. A1C at Baseline and Week 24 in Patients With T1DM With and Without Cough (n = 165).[a]



Error bars show SD.
[a] Only patients with both baseline and follow-up values were included.

Figure 5. Hypoglycemia in Patients With T1DM With and Without Cough (n = 165)[a]: Incidence (A) and Rate (B).



Error bars show SE.
[a] Only patients with both baseline and follow-up values were included.

Table 2. Lung Function in Patients With and Without Cough.

	Cough (n = 55)	No Cough (n = 119)	*P* Value
Baseline, mean (SD)			
$FEV_{1.0}$, L	3.217 (0.725)	3.590 (0.861)	0.0058
Predicted $FEV_{1.0}$, L	3.416 (0.671)	3.660 (0.797)	0.0504
FVC, L	3.857 (0.789)	4.412 (1.098)	0.0009
Predicted FVC, L	4.193 (0.812)	4.493 (1.010)	0.0550
$FEV_{1.0}$/FVC, %	83.2 (5.49)	81.8 (5.85)	0.1302
End of treatment, mean (SD)			
$FEV_{1.0}$, L	3.163 (0.715)	3.527 (0.863)	0.0071
FVC, L	3.824 (0.792)	4.367 (1.096)	0.0012
$FEV_{1.0}$/FVC, %	82.6 (5.25)	81.1 (5.97)	0.1219
Change from baseline, mean (SD)			
$FEV_{1.0}$, L	–0.075 (0.176)	–0.072 (0.142)	0.9037
FVC, L	–0.044 (0.191)	–0.052 (0.165)	0.7996
$FEV_{1.0}$/FVC, %	–0.98 (2.84)	–0.78 (2.60)	0.7076

CONCLUSIONS

- Overall, there were few differences in the baseline characteristics of patients with T1DM treated with TI who reported cough and those who did not.
  - patients who reported cough had lower $FEV_{1.0}$ and FVC values at baseline and end of treatment, but with mean percent of predicted values ranging between 92% and 94% and no significant difference in $FEV_{1.0}$/FVC ratio between groups
- In those patients reporting cough, it was generally reported to be transient, starting within the first week of treatment, occurring within 10 minutes of inhalation of TI, and was generally considered as mild, intermittent, and nonproductive.
  - cough was the leading cause of discontinuation in the phase 3 study; 5.7% of patients discontinued due to cough[4]
- The changes from baseline in $FEV_{1.0}$, FVC, and $FEV_{1.0}$/FVC ratio were similar in patients who experienced cough and those who did not after 24 weeks of treatment with TI.
- The pattern and characteristics of cough associated with TI are similar to the cough reported with other inhaled insulin dry-powder formulations; this cough probably represents transient airway irritation during dry-powder inhalation.[3]
- In patients with T1DM treated with TI plus basal insulin, cough was not associated with differences in efficacy in terms of A1C or the incidence of hypoglycemic events.

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