

Place of technosphere inhaled insulin in treatment of diabetes

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Abstract

Technosphere insulin (TI), Afrezza, is a powder form of short-acting regular insulin taken by oral inhalation with meals. Action of TI peaks after approximately 40-60 min and lasts for 2-3 h. TI is slightly less effective than subcutaneous insulin aspart, with mean hemoglobin A1c (HbA1c) reduction of 0.21% and 0.4%, respectively. When compared with technosphere inhaled placebo, the decrease in HbA1c levels was 0.8% and 0.4% with

TI and placebo, respectively. Compared with insulin aspart, TI is associated with lower risk of late post-prandial hypoglycemia and weight gain. Apart from hypoglycemia, cough is the most common adverse effect of TI reported by 24%-33% of patients *vs* 2% with insulin aspart. TI is contraindicated in patients with asthma and chronic obstructive pulmonary disease. While TI is an attractive option of prandial insulin, its use is limited by frequent occurrence of cough, need for periodic monitoring of pulmonary function, and lack of long-term safety data. Candidates for use of TI are patients having frequent hypoglycemia while using short-acting subcutaneous insulin, particularly late post-prandial hypoglycemia, patients with needle phobia, and those who cannot tolerate subcutaneous insulin due to skin reactions.

Key words: Afrezza; Efficacy; Safety; Technosphere insulin; Cough

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Core tip: Technosphere insulin is the only approved form of inhaled insulin. It is a short-acting insulin that can be taken with meals in patients with type 1 or type 2 diabetes. In this minireview, the author provides an appraisal of this new formulation of insulin to help determine its place in the management of diabetes.

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INTRODUCTION

In June 2014, the Food and Drug Administration (FDA) approved technosphere insulin (TI) under the trade name Afrezza (MannKind Corp., Valencia, CA) for use in

type 1 and type 2 diabetes^[1]. Afrezza is a dry powder of recombinant human insulin adsorbed onto an inert excipient of fumaryl diketopiperazine (FDKP) particles^[2]. In this powder, insulin and FDKP are present in a 1:9 ratio by dry weight^[3]. The median aerodynamic diameter of technosphere microparticles is 2-2.5 μm , suited for deposition in distal lungs^[3]. In initial studies, Afrezza was delivered by a device called MedTone. In 2010, the manufacturer produced a smaller and more efficient device called Gen2^[4]. The main purpose of this article is to identify the best candidates for the use TI based on its pharmacodynamics, efficacy and safety. More emphasis will be placed on data derived from clinical trials using the current Gen2 device of TI.

SEARCH METHODOLOGY

PubMed search was conducted until July 2016 to identify all humans studies related to efficacy and safety of TI published in the English, Spanish and French literature. The search included pertinent animal and *in-vitro* studies. Review articles, and prescribing information of afrezza are also reviewed. Search terms included "inhaled insulin", "diabetes mellitus", "technosphere", "pulmonary safety", "cough", "lung cancer".

ABSORPTION AND METABOLISM

Upon inhalation, a mean of approximately 60% of the emitted dose of TI reaches the lungs. The remainder 40% is swallowed and enters the gastrointestinal tract^[3]. The technosphere particles dissolve rapidly at the physiological pH of the lungs. This dissolution allows both insulin and the excipient FDKP to be independently absorbed across the alveolar wall to the systemic circulation with a time to maximum concentration (Tmax) of 15 and 10 min, respectively^[1,3]. The inhaled insulin and its carrier FDKP are rapidly cleared from the lungs. Thus, clearance half-life of insulin and FDKP from the bronchoalveolar lavage is approximately 1 h. By 12 h post-inhalation, their concentrations in the bronchoalveolar lavage are below or near the limit of quantification^[3]. After systemic absorption, the carrier FDKP is excreted unchanged in urine without any evidence of pharmacological activity^[5].

PHARMACOKINETICS AND PHARMACODYNAMICS

Bioavailability of TI (calculated based on actual insulin content of the TI cartridge) is approximately 20%-27% relative to subcutaneous regular insulin, and 33% relative to lispro^[6]. TI has rapid onset of action characterized by a sharp rise in serum concentrations reaching peak levels after 12-15 min^[7]. The median time to maximum effect in 12 patients with type 1 DM was shown to be 53 min (SD 74 min) compared to approximately 90-120 min with insulin lispro^[7]. In another study of 11 healthy volunteers, mean time for maximal effect of TI was 42-58 min for doses 25-100 units compared to 171 min with subcutaneous regular insulin given in a single dose of 10 units^[8].

Duration of action of TI is short and fades away by approximately 160 min or 2-3 h^[7,9]. Median terminal half-life of TI is 28-39 min (for doses 4-32 units) vs 145 min for subcutaneous regular insulin (15 units)^[7]. Based on the above pharmacodynamics, TI is considered an ultra-rapid insulin given at the start of a meal or within 20 min after starting a meal^[10].

EFFICACY OF TI

Effect on blood glucose concentrations

Reduction in post-prandial hyperglycemia is the main target action of TI. In one placebo-controlled trial of patients with type 2 diabetes, patients randomized to TI had 43% more reduction in maximal postprandial glucose levels compared with inhaled placebo^[11]. The study of Rosenstock *et al*^[12] shed the light on timing of action of TI. Thus, compared with biaspart insulin injected 15 min before meals, the inhalation of TI within 90 s of meal ingestion was associated with significant decrease in self-monitored blood glucose (SMBG) at 1 h after meals (171 mg/dL vs 209 mg/dL with biaspart). Yet, 2 h after meals, blood glucose concentrations were similar between biaspart and TI, and after 2 h, postprandial glucose levels became higher in patients randomized to TI than biaspart^[12]. The previous finding is in agreement with pharmacodynamics studies described above showing that peak action of TI occurs at approximately 1 h and fades away after 2 h^[6,7].

Effect on hemoglobin A1c levels

Overall, available data suggest that TI is slightly less effective than subcutaneous insulin. In one meta-analysis of 8 clinical trials of type 1 and type 2 diabetes, mean hemoglobin A1c (HbA1c) reduction with subcutaneous insulin was slightly greater than TI, with net statistically significant difference of 0.16% (95%CI: 0.06%-0.25%)^[13]. The same meta-analysis showed that mean HbA1c reduction compared to baseline was 0.55% (95%CI: 0.34%-0.78%) based on data compiled from 12 clinical trials using the older MedTone device and the current Gen-2 device^[13]. The efficacy of the TI Gen2 device was published in 2 trials summarized in Table 1^[9,10]. In one trial, the mean reduction in HbA1c levels among patients randomized to TI and aspart was 0.21% and 0.4%, respectively with a significant difference of 0.19% (95%CI: 0.02-0.36)^[10]. In the second study, TI was superior to placebo, as expected, with HbA1c reduction of 0.8% vs 0.4%, respectively^[9]. Although the MedTone device is no longer used, 2 randomized trials using this older device are presented in Table 2 because of their large size, and relatively long-duration (1-2 years)^[12,14]. Studies that directly compare the efficacy of the 2 devices are not available. However, their short-term safety was compared in single head to head trial discussed in the safety section below^[10].

SAFETY PROFILE OF TI

Hypoglycemia

In clinical trials of TI-Gen 2, non-severe hypoglycemia

Table 1 Clinical trials of technosphere insulin using Gen2 device

Ref.	Rosenstock <i>et al</i> ^[9]	Bode <i>et al</i> ^[10]
Design	Randomized, double-blind, placebo-controlled, 24 wk-duration	Randomized, open-label, 24 wk-duration
Type of diabetes	Type 2	Type 1
Intervention	TI (<i>n</i> = 177) <i>vs</i> placebo (<i>n</i> = 177), both groups were on oral agents	TI (<i>n</i> = 174) <i>vs</i> prandial aspart (<i>n</i> = 170). Both groups received basal insulin (NPH or detemir, or glargine)
Mean HbA1c levels at baseline	8.26%	7.93%
Reduction in HbA1c <i>vs</i> baseline	-0.8% with TI and -0.4% with placebo	-0.21% with TI <i>vs</i> -0.4% with aspart
Reduction in mean HbA1c with TI <i>vs</i> comparator	-0.4% <i>vs</i> placebo (95%CI: -0.57 to -0.23)	0.19% <i>vs</i> aspart (95%CI: 0.02 to 0.36)
Proportions of patients reaching HbA1c ≤ 7%	38% with TI <i>vs</i> 19% with placebo (<i>P</i> = 0.0005)	18% with TI <i>vs</i> 31% with aspart (<i>P</i> = 0.01)
Proportions reporting adverse effects	61% TI <i>vs</i> 51.1% placebo	58% TI <i>vs</i> 43% aspart
Proportions of patients reporting hypoglycemia	67.8% TI <i>vs</i> 30.7% placebo (<i>P</i> < 0.0001)	96% TI <i>vs</i> 99.4% aspart (<i>P</i> = 0.06)
Proportions of patients reporting cough	23.7% TI <i>vs</i> 19.9% placebo (difference not statistically significant)	31.6% TI <i>vs</i> 2.3% aspart <i>P</i> < 0.05
Withdrawal due to cough	1.1% with TI <i>vs</i> 3.4% with placebo	5.7% with TI <i>vs</i> 0% with aspart
Change in mean weight	+ 0.5 kg TI <i>vs</i> -1.1 kg placebo (<i>P</i> < 0.0001)	-0.4 kg with TI <i>vs</i> +0.9 kg aspart (<i>P</i> = 0.01)
Change in mean FEV1 (L)	- 0.13 L with TI <i>vs</i> -0.04 L with placebo	-0.07 L with TI <i>vs</i> -0.04 L with aspart
Withdrawal due to adverse effects	4% with TI <i>vs</i> 5.1% placebo	9.2% with TI <i>vs</i> 0% aspart

FEV1: Forced expiratory volume in 1 s; TI: Technosphere insulin; HbA1c: Hemoglobin A1c.

Table 2 Clinical trials of technosphere insulin using the Med-Tone device

Ref.	Raskin <i>et al</i> ^[14]	Rosensens <i>et al</i> ^[12]
Design	Randomized, open label, 2 yr-duration, pulmonary safety trial	Randomized, open-label, 52-wk duration
Type of diabetes	Types 1 and 2	Type 2
Groups of subjects and intervention	TI (<i>n</i> = 938), usual diabetes care (<i>n</i> = 951), control subjects without diabetes (<i>n</i> = 164)	Glargine qhs + prandial TI (<i>n</i> = 334) <i>vs</i> ¹ biaspart insulin bid (<i>n</i> = 343)
Proportions of patients with adverse effects	79% TI <i>vs</i> 71% usual care	84% TI <i>vs</i> 89% biaspart
Mean HbA1c at baseline	8.7%	8.7%
Reduction in HbA1c <i>vs</i> baseline	-0.59% with TI and -0.50% with usual care	-0.68% with TI/glargine <i>vs</i> -0.76% with biaspart
Reduction in HbA1c with TI <i>vs</i> comparator	0.09% (not significant)	0.07% (not significant)
Proportions of patients reporting hypoglycemia	39.5% TI <i>vs</i> 39.1% usual care	48% glargine/TI <i>vs</i> 69% biaspart. OR 0.4 (95%CI: 0.3-0.5)
Proportions of patients reporting cough	27.8% TI <i>vs</i> 4.4% usual care	33% glargine/TI <i>vs</i> 6% biaspart
Withdrawal due to cough	4.7% TI <i>vs</i> 0% usual care	2% glargine/TI <i>vs</i> 0% biaspart
Change in mean weight	Not reported	+ 0.9 kg glargine/TI <i>vs</i> +2.5 kg biaspart. Mean difference 1.6 kg (95%CI: -2.4 to -0.7)
Decline in mean FEV1 (liters)	More decline in TI group <i>vs</i> usual care. Mean difference 0.037 (95%CI: 0.017-0.06)	-0.13 glargine/TI <i>vs</i> -0.09 biaspart (difference not significant)
Withdrawal due to adverse effects	11% TI <i>vs</i> 0.6% usual care	9% glargine/TI <i>vs</i> 4% biaspart

¹Biaspart insulin is pre-mixed insulin composed of 70% insulin protamine suspension + 30% insulin aspart. FEV1: Forced expiratory volume in 1 s; TI: Technosphere insulin; HbA1c: Hemoglobin A1c.

was defined as SMBG < 70 mg/dL and/or presence of symptoms of hypoglycemia, whereas severe hypoglycemia was an event that required assistance of another person^[9,10]. Compared with insulin aspart, incidence of all hypoglycemia was numerically lower in patients randomized to TI-Gen2, 96.0% and 99.4%, respectively (*P* = 0.062), and incidence of severe hypoglycemia was significantly lower with TI Gen2-treatment than with aspart, 18.4% and 29.2%, respectively^[10]. Importantly, the timing of hypoglycemic events reported in patients treated with TI was consistent with its short duration of action. Hence, hypoglycemic event rates (events/patient-months) within 2 h after meals were similar in patients randomized to TI and insulin aspart. Meanwhile, 2-5 h after meals, those rates were 2-3 times less with the use of TI compared with insulin aspart^[10]. On the other hand, when compared with inhaled placebo, the incidence of all

hypoglycemia was higher with TI-Gen 2 therapy (67.8%) compared with placebo (30.7%), (*P* < 0.0001), and incidence of severe hypoglycemia was 5.1% with TI *vs* 1.7% with placebo (*P* = 0.09)^[9].

Cough and throat symptoms

Cough is the most common non-hypoglycemic adverse effect of TI reported by 24%-33% of patients randomized to TI compared to 2%-6% of patients randomized to subcutaneous insulin or usual diabetes care^[9,10,13,14]. Cough induced by TI is characterized by several features. First, it is generally mild, described as severe in approximately 1% of patients^[10]; second, it occurs within 10 min of inhalation^[9]; third, the percentage of patients reporting cough is highest in the first week after treatment, then decreases gradually with time^[10]; fourth, cough is reversible, and resolves within 1-2 d after drug discon-

tinuation^[9]; fifth, the occurrence of cough did not seem to be related to changes in pulmonary function as discussed below^[14]; sixth, proportions of patients who reported cough was slightly higher in patients taking TI vs technosphere inhaled placebo powder: 23.7% (42 of 177) vs 19.9% (35 of 176), respectively^[9]. The latter observation suggests that cough is mainly due to the inhaled excipient powder (FDKP), and that the insulin component contributes to a lesser extent to the development of cough. The exact mechanism of cough is unclear, and is probably due to stimulation of cough reflex by dry powder inhalation^[9]. Unfortunately, frequency of cough associated with the use of the current Gen2 device is markedly greater than the older MedTone device, 31.6% and 22.5%, respectively^[9]. This finding was attributed to the high amount of powder being inhaled in a single inhalation with Gen2, whereas with MedTone, the amount of powder inhaled per dose was distributed over 2 inhalations^[9].

Throat pain or irritation occurred in 4.4% of patients with type 2 DM ($n = 1991$) compared with 0.9% of patients using comparator (non-inhaled) therapy ($n = 1363$)^[7].

Effect of TI on pulmonary function tests

The effect of TI delivered by MedTone device on pulmonary function was studied in a large randomized trial composed of 3 groups of subjects followed for 2 years: Patients with type 1 or type 2 diabetes receiving TI ($n = 730$), patients with type 1 or type 2 diabetes receiving usual care ($n = 824$), and a smaller group of subjects without diabetes not taking any medications ($n = 145$) (Table 2)^[14]. After 3 mo, the authors recorded an initial decline among the 3 patient groups in all parameters of pulmonary functions studied including the forced expiratory volume in 1 second (FEV1) with the largest decline occurring in the TI-treated group. The difference in decline in FEV1 from baseline to 24 mo between the TI-treated group and usual care group was small but statistically significant: 0.037 liters (95%CI: 0.014 to 0.060)^[14]. However, after 3 mo, the rate of change in respiratory parameters was not statistically different between patient groups. This suggests that worsening of pulmonary function in patients treated with TI occurred early in the first 3 month, and do not progress further up to 2 years of follow-up. The manufacturer recommends that pulmonary function tests (e.g., spirometry) should be assessed before treatment initiation, after 6 mo of therapy and annually thereafter^[7]. If there is reduction of 20% or more in FEV1 compared to pre-treatment values, consideration should be given for drug-discontinuation^[7]. Although Raskin *et al*^[14] did not found a relationship between the changes in pulmonary function and the occurrence of cough, the manufacturer recommends more frequent monitoring of pulmonary function in patients with any pulmonary symptoms such as persistent cough, wheezing and breathing difficulties, and to discontinue the drug if symptoms persist^[7]. Available data are insufficient regarding reversibility of pulmonary function abnormalities after discontinuation of long-term use of TI^[7]. However, in a 24-wk trial, the

authors documented reversibility of FEV1 4 wk after discontinuation of TI^[10]. The exact mechanisms of decline in pulmonary function after TI inhalation are unclear. Animal studies showed that the previous form of inhaled insulin (Exubera) forms amyloid aggregates in lungs of mice and may induce mitochondrial dysfunction leading to a significant reduction in pulmonary air flow^[15].

Effect on weight

The effect of TI on weight gain was less pronounced compared with subcutaneous insulin formulations. Thus, when TI was compared with twice daily premixed bipart, mean weight gain after 52 wk was 0.9 kg and 2.5 kg, respectively^[12]. Moreover, the use of TI was associated with mean weight loss of 0.4 kg as opposed to a mean weight gain of 0.9 kg among patient randomized to prandial insulin aspart^[10]. One meta-analysis has shown that TI was associated with less weight gain than subcutaneous insulin with a net difference of -1.1 kg (95%CI: -2.1 to -1.6 kg)^[14]. Meanwhile, an average weight gain of 0.5 kg was recorded in patients randomized to TI vs a weight loss of 1.1 kg in patients randomized to placebo^[9]. The reasons for low propensity of TI to cause weight gain are not entirely clear. Possible causes include its somewhat inferior efficacy and lower risk of causing late post-prandial hypoglycemia compared to subcutaneous insulin. The latter advantage might lead some patients to avoid "overeating" in an attempt to prevent hypoglycemia.

Diabetic ketoacidosis

In clinical trials of TI, no reports of ketoacidosis were reported^[9-12,14]. However, a meta-analysis that examined regulatory documents reported a nearly 5 times higher incidence of DKA among patients treated with TI compared with prandial short-acting insulin^[13]. Likewise, the manufacturer reports higher frequency of DKA in trials of type 1 diabetes among patients using TI vs subjects receiving comparators: 0.43% ($n = 13$) and 0.14% ($n = 3$), respectively^[7]. The reasons for this increase in DKA with TI are not understood, but could be partly attributed to its ultra-short duration of action of TI creating times of day with relative insulin deficiency.

Lung cancer

In patients exposed to TI in clinical trials, the manufacturer reported 2 cases of lung cancer (2 cases in 2750 patient-years of exposure) both having prior history of heavy tobacco abuse^[7]. Two other cases (both squamous cell carcinoma) occurred in non-smokers after clinical trial completion. Thus, 4 cases of lung cancer were reported in patients exposed to TI vs none in control group^[7]. Although the number of affected patients is too small to draw a valid conclusion, lung cancer is certainly a major concern of inhaled insulin, particularly that lung cancer rates were found to be increased in association with the previous inhaled insulin Exubera^[16]. The long-term local effects of TI and its carrier on pulmonary cell are unknown. *In vitro* studies of lung cell line (Calu-3) showed that TI did not affect insulin transport, cell viability, and plasma membrane integrity^[17]. Meanwhile,

Table 3 Candidate patients for technosphere insulin

Patients with type 1 diabetes who are taking basal insulin once daily, but prefers to take their prandial insulin in the inhaled formulation
Patients with type 2 diabetes uncontrolled on oral agents, and are reluctant to start subcutaneous insulin due to needle phobia or other reasons
Patients already on subcutaneous prandial insulin who develop frequent late post-prandial hypoglycemia (4-5 h after meals)
Any patient who develops skin reactions to insulin subcutaneous injections such as lipoatrophy or lipohypertrophy
In combination of automated artificial pancreas to provide rapid insulin delivery right after meals ^[20]

Table 4 Advantages and limitations of technosphere insulin

Advantages
Relatively easy and non-painful administration
Flexible timing of administration either inhaled directly before meals or within 20 min after finishing a meal ^[10]
Hypoglycemia is less frequent than subcutaneous insulin, particularly late postprandial hypoglycemia
Weight gain is slightly less pronounced than subcutaneous insulin
Limitations
Frequent cough (24%-33% of patients)
Available only as prandial short-acting insulin. Hence, long-acting basal subcutaneous insulin should be added in patients with type 1 diabetes
Slightly less effective than subcutaneous insulin
Need for baseline and then serial pulmonary function testing
Safer to switch to subcutaneous insulin in case of upper or lower respiratory infections to avoid exacerbation of the disease and possible unreliable pulmonary absorption
No data available for pediatric and pregnant populations
Limited strength options and difficult fine titration of doses
Lack of long-term safety data
High cost, e.g., average price of ninety 4-unit cartridges and 2 inhalers is \$271 ^[21]

insulin is a growth factor that binds to insulin receptors and if present in high concentrations, can bind to IGF-I receptors in lungs. This binding could potentially induce new-onset pulmonary cancer or accelerate growth of pre-existing malignant cells. Indeed, isolated human bronchial carcinoma cells (H292) were shown to express insulin receptors 4-5 times higher than normal bronchial epithelial cells^[18]. In fact, the FDA requested the manufacturer to conduct a clinical trial with sufficient power to examine this issue.

Patients with pulmonary diseases and smokers

TI is contraindicated in any chronic pulmonary disease such as asthma or chronic obstructive pulmonary disease (COPD)^[7]. Indeed, acute bronchospasm and wheezing were observed in 29% (5 of 17) of patients with asthma following inhalation of TI compared with none of 13 individuals without asthma^[7]. Moreover, in asthmatic patients, a substantial mean reduction in FEV1 of 400 mL was recorded 15 min after a single dose of TI^[7]. Similarly, in a small group of patients with COPD ($n = 8$), a mean decline in FEV1 of 200 mL was observed 18 min after TI inhalation^[7]. These acute and severe reactions to TI among patients with asthma and COPD could be the result of airway irritation upon contact with the inhaled insulin and/or the excipient. Interestingly, no significant differences in pharmacokinetics (time to maximum concentration, peak plasma insulin concentrations, and plasma insulin exposure) were found between patients with COPD and healthy subjects after a single dose of TI^[19]. In case of common cold or flu, some workers recommend switching to subcutaneous insulin until the disease resolves^[4]. It is not recommended that patients who smoke use TI^[7].

PLACE OF INHALED INSULIN TI IN DIABETES THERAPY

Based on available data, the use of TI is most appropriate in the following selected groups of patients (Table 3). First, patients with type 1 diabetes who are taking basal insulin once daily, but prefers to take their prandial insulin in the inhaled formulation; second, patients with type 2 diabetes uncontrolled on oral agents, and are reluctant to start subcutaneous insulin due to needle phobia or other reasons; third, patients already on subcutaneous prandial insulin who develop frequent late post-prandial hypoglycemia (4-5 h after meals); fourth, patients who develop skin reactions to insulin subcutaneous injections such as lipoatrophy or lipohypertrophy. Another potential place of TI that is under investigations includes its use in combination of automated artificial pancreas to provide rapid insulin delivery right after meals^[20].

CONCLUSION

Despite its limitations, TI represents a useful addition to the treatment of diabetes. Its easy non-invasive way of administration is a major advantage to patients who do not like injections. Although TI is slightly less effective than the subcutaneous insulin analog aspart, this is balanced by its lower risk of causing late postprandial hypoglycemia and weight gain. Cough remains a major limiting factor of TI occurring mainly in early treatment. Long-term clinical trials of adequate power along with post-marketing (phase IV) studies are needed to clarify the long-term safety of TI and its relationship to lung cancer. Advantages and limitations of TI are summarized in Table 4.

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