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Review Article

The Role of Inhaled Insulin in the Management of Type 2 Diabetes

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Abstract

Type 2 diabetes continues to place a major burden on the health care system of the United States and world-wide. Many patients with type 2 diabetes have decreased insulin production which requires exogenous insulin therapy in order to manage their disease. Despite this need, there is often a reluctance to initiate insulin therapy from both providers and patients. One reason for this reluctance may be a fear of needles or of administering injections. Delivering insulin through the lungs has been studied for decades, with the first inhaled insulin product coming to market in 2006. This product's launch was considered unsuccessful, and the product was discontinued by the manufacturer the following year. New inhaled insulin, Technosphere® insulin, was approved for use in type 1 and type 2 diabetes in 2014. This product was shown superior to placebo and non-inferior to pre-mixed bi-phasic subcutaneous insulin in patients with type 2 diabetes and may offer an alternative to patients who are averse to giving subcutaneous injections.

INTRODUCTION

Diabetes and its complications continue to pose a major burden to the United States (US) and the world. In 1995, the world-wide prevalence of diabetes in adults was estimated at approximately 4%, and it was predicted that this would increase to 5.4% by the year 2025 [1]. In the US, 29.1 million people are estimated to have diabetes, with approximately 8 million of these cases remaining undiagnosed [2]. This comprises roughly 9.3% of the US adult population, with another estimated 37% of adults showing clinical signs of prediabetes. The economic impact of this disease in the US is estimated at 245 billion dollars a year [2].

Type 2 diabetes (T2D) accounts for over 90% of the total prevalence of the disease, and is characterized by increased insulin resistance by skeletal muscle, adipose and liver cells, and decreased insulin secretion by the pancreatic beta cells, both of which lead to elevated blood glucose levels, or hyperglycemia [3]. Initially, this disease can be managed with lifestyle modifications (healthy diet, moderate exercise, and weight loss) together with one or more oral antihyperglycemic agents (OAAs), but due to its chronic, progressive nature, additional therapies are often required. The continuous loss of beta cells often leads to the need for exogenous insulin therapy in T2D patients. National clinical guidelines recommend basal insulin therapy as a possible 2nd line option for T2D treatment, with insulin intensification suggested for those patients who do not meet hemoglobin A1C (A1C) goals [4,5]. Guidelines from the American Diabetes Association (ADA) suggest that insulin therapy may be superior to other treatment options in managing T2D, particularly as a 3rd line agent or in patients with very high A1C values (>9%) [4]. Insulin therapy allows for some flexibility with therapy, as the patient can adjust their insulin dose based on food choices, glycemic targets, and the amount of activity they have performed [6,7]. Unfortunately, there is often resistance to initiating insulin therapy from both patients and providers, which may delay or inhibit insulin's use [8-10]. This resistance may be due to misconceptions or misunderstandings about insulin, or fear and anxiety about needles and self-administering injections [10,11]. For decades, the delivery of insulin has been restricted to administration through subcutaneous injections or delivered by continuous infusion through the use of a pump device. Much research has focused on identifying alternative, less invasive methods to deliver insulin into the body. This article reviews the evidence for pulmonary insulin delivery, with a focus on Technosphere® insulin, approved as inhaled insulin in the US in 2014.

Development of Inhaled Insulin

Pulmonary delivery of insulin has been investigated for years, assisted by technological advances in drug delivery for the treatment of asthma. Expert opinion identifies inhaled insulin as one of the most advantageous non-invasive delivery routes [12]. Research exploring inhaled insulin dates back to shortly after insulin was discovered, in 1924 [13]. Initial absorption challenges faced with delivering insulin through the lungs were

overcome through advancements in inhaler technologies in the 1990s [14]. This led to a number of companies exploring inhaled insulin products, with the first inhaled insulin becoming approved in both the US and in Europe under the trade name of Exubera® in 2006. While shown to be effective, this product was not very successful on the market, however, and was removed from the market voluntarily by Pfizer in October 2007 due to low sales [15]. There was quite a bit of speculation as to why this first inhaled insulin was unsuccessful in its market launch. Sales had been predicted at approximately two billion dollars, but the product only yielded around 12 million through the first three quarters of 2007 [15]. There were criticisms about the inhaler device being large, cumbersome, and hard to clean, the marketing strategy being possibly flawed, and difficulties in the dosing conversion, as the inhaled insulin was produced and marketed in milligrams, not units [15,16]. Clinical guidelines at the time also did not support wide spread use, citing that the cost-effectiveness of the product had not been shown, and reserving it for specific populations of patients where there may be needle phobias or other concerns [15,16]. The poor success shown by Exubera® resulted in the discontinuation of research on another inhaled insulin product that was being developed by Eli Lilly [16]. This left one company, Mannkind Corporation, who continued research and development on their inhaled insulin product, Technosphere® insulin. This product, Technosphere® insulin, was approved for use in the United States in 2014.

Technosphere insulin- Pharmacokinetics

Technosphere® insulin (TI) is a powdered formulation of human, recombinant DNA insulin. The product demonstrates very rapid absorption through the lungs due to a proprietary carrier molecule, fumary like to piperazine (FDKP), which encapsulates the insulin into microspheres [17]. Once inhaled into the lungs, the neutral pH causes the particles to dissolve and release the insulin for absorption into circulation. Pharmacokinetic studies demonstrated time to maximum concentrations (T_{max}) of TI being achieved in approximately 12 to 15 minutes, compared to around 40 minutes with a subcutaneous rapid acting insulin analog (RAIA) [18,19] (Figure 1). This early absorption has been shown to suppress endogenous glucose production more quickly than other insulin preparations [18]. The maximum concentration (C_{max}) of insulin following TI inhalation was also shown to be higher than that of injected insulin [20]. Bioavailability for the product varied, possibly due to patients' inhaler technique, but was shown to be approximately 21% to 35%, compared with regular subcutaneous (SC) insulin [201,21]. There is also evidence that the product clears more quickly than injected insulin, evaluated by a shorter time to reach the half-minimum serum concentration when compared with regular SC insulin [20].

Technosphere insulin- Efficacy and Safety

Efficacy: Ten Phase 3 studies have been conducted to evaluate the efficacy and safety of TI. Early Phase 3 studies were limited by short study durations, inadequate dose titrations, and utilization of the MedTone inhaler device, which was later replaced by the current TI Gen2 inhaler. The application for approval to the FDA focused primarily on four Phase 3 studies, which had treatment

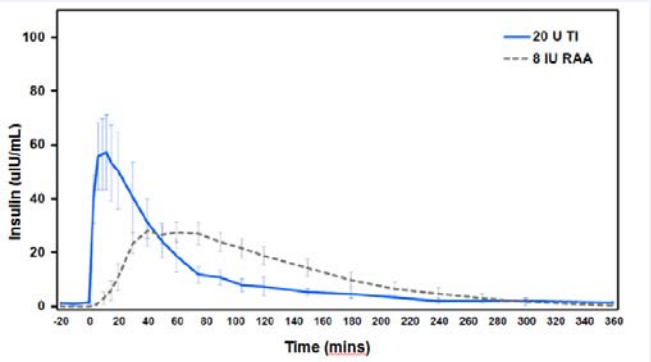

Figure 1 Mean (SE) baseline-corrected TI concentration-time profile compared to a subcutaneously-injected RAIA.

Figure 2 Picture of the Gen2 Technosphere® insulin inhaler device.

durations of 16 weeks or longer and appropriate dose titration protocols [22]. Two were performed in patients with T1D (Studies 009 and 171) [23,24] and two in patients with T2D (Studies 102 and 175) [25,26].

Study 175 was a 24-week, double-blind, placebo-controlled, superiority study in 353 patients with T2D [19,26]. Subjects were insulin naïve, inadequately controlled on OAD therapy, with baseline A1C levels 7.5-10%. Subjects continued background OAD therapy at stable doses and were randomized to either inhaled TI or inhaled placebo using the Gen2 inhaler device. Insulin and placebo doses were titrated during the first 12 weeks of the study using a pre-specified titration protocol and were kept stable for the last 12 weeks of the study. After 24 weeks of therapy, the mean reduction in A1C from baseline was significantly greater in the TI group compared to the placebo group (-0.82% vs. -0.42%, $p<0.001$) [19]. In addition, more patients achieved an A1C≤7% in the TI group compared to the placebo group (32.3% vs. 15.3%, $p<0.0005$) [19]. The TI group showed a mean weight gain of 0.49kg during the study compared to a 1.13kg weight loss in the inhaled placebo group. The study has not been published so data is restricted to what is available with the prescribing information.

Study 102 was a 52-week, open-label, non-inferiority study that randomized 618 patients with T2D to TI plus insulin glargine or a biphasic, pre-mixed rapid acting insulin analog (BPR 70/30) containing 70% insulin as part protamine suspension and 30% insulin as part [25]. The TI was delivered using an earlier inhaler device (MedTone) than the currently approved TI product which uses the Gen2 inhaler device. Enrollment criteria specified that

subjects needed to be inadequately controlled on insulin with or without OAD therapy; with baseline A1C levels 7-11%. Subjects that were randomized to TI plus insulin glargine received about half of their total daily dose as insulin glargine and half of their total daily dose as TI distributed across main meals and titrated incrementally based on self-monitoring blood glucose (SMBG). For subjects randomized to twice daily BPR 70/30, doses were adjusted based on fasting plasma glucose and glucose levels before dinner. All insulin doses were made at the discretion of the investigators.

After 52 weeks of therapy, the mean reduction in A1C from baseline was similar between groups. The TI plus insulin glargine group achieved a reduction of -0.68%, which was non-inferior to the BPR 70/30 group which achieved a reduction of -0.76% [25]. The between group difference was 0.07% (95% CI -0.13 to 0.27) which met the pre-defined criteria for non-inferiority (upper 95% CI less than 0.4). The proportion of patients achieving an A1C≤7% was also similar between subjects receiving TI plus insulin glargine and those on BPR 70/30 (22% vs. 27%, p=0.2793). Changes in fasting glucose and post-prandial glucose values were also similar between groups. Weight gain was significantly lower in subjects receiving TI plus basal insulin compared to those receiving BPR 70/30 (0.9kg vs. 2.5kg, p=0.0002) [25].

Safety: Similar to other insulin agents, hypoglycemia is the most common adverse effect (AE) seen with TI [19]. Rates of hypoglycemia in Phase 3 studies in T2D subjects are in Table 1. Rates of both severe and non-severe hypoglycemia were more common in patients with T2D taking TI compared to those taking inhaled placebo [19]. In the active comparator study, both severe and non-severe hypoglycemia events were less common in patients taking TI plus insulin glargine compared to patients taking BPR 70/30 [25].

Due to the inhaled route of delivery and concerns regarding the pulmonary safety of TI, subjects with active pulmonary disease, current smokers, and those with a history of chronic obstructive pulmonary disease (COPD) or asthma were excluded from Phase 3 studies. Pulmonary safety, including pulmonary function tests (PFTs) were evaluated consistently across all trials. The most common adverse effects associated with TI, other than hypoglycemia, were cough, throat pain and throat irritation [19] (Table 2). Overall, pooled respiratory AEs were higher in patients taking TI (45.2%) compared to patients taking inhaled placebo (35.9%) and patients taking comparator agents (31.0%) [22]. Respiratory AEs leading to treatment discontinuation were similar between TI and inhaled placebo (4.6% vs. 2.4%) but higher than non-inhaled comparators (0.1%). In the Phase 3 clinical trials, cough occurred in about one quarter of patients receiving TI. The cough is likely due to the dry powder inhalation formulation and has been described as dry and transient, occurring most frequently in the first weeks of therapy.

Pooled data of clinical trials which excluded patients with chronic lung disease showed a small decline in FEV_1 in patients taking TI [19]. The initial decline occurred in the first 3 months and persisted over the duration of the studies, but did not appear to worsen with continued use up to 2 years [19]. Mean differences in FEV_1 decline between the TI and comparator groups were -0.040 L at 3 months, -0.043 L at 6 months, -0.036 L at 9 months, -0.038 L at 12 months, -0.045 L at 18 months and -0.045 L at 24 months [22]. To put this in perspective, a 20% decrease of FEV_1 would amount to approximately -0.5 L, depending on patient-specific factors.

Table 1: Technosphere Insulin: Common Adverse Reactions (excluding hypoglycemia) in Patients with T2D.

	Placebo (n=290)	TI (n=1991)	Non-placebo comparator (n=1363)
Cough	19.7%	25.6%	5.4%
Throat pain or irritation	3.8%	4.4%	0.9%
Headache	2.8%	3.1%	1.8%
Diarrhea	1.4%	2.7%	2.2%
Productive cough	1.0%	2.2%	0.9%
Fatigue	0.7%	2.0%	0.6%
Nausea	0.3%	2.0%	1.0%

TI= Technosphere Insulin

Table 2: Incidence of Hypoglycemia in Phase 3 TI T2D Studies.

Study	Treatment Arms	Severe hypoglycemia	Non-severe Hypoglycemia
Trial 175	TI Placebo	5.1% 1.7%	67% 30%
Trial 102 (Rosenstock et al)	TI + insulin glargine BPR 70/30	4.3% 10%	48% 69%

BPR= Biphasic Pre-mixed Rapid-Acting Insulin; TI= Technosphere Insulin

There are some data evaluating TI in patients with underlying lung disease. A Phase 1, single-dose trial was conducted in 20 patients with COPD, matched to 20 control patients to assess the effects of a single dose of TI on lung function. Patients with COPD experienced a rapid decline in FEV_1 that resolved gradually over 8 hours [22].

Similarly, a phase 1, single-dose study was conducted in 17 patients with asthma, matched to 13 healthy control patients to assess the effects of TI on lung function. After withholding bronchodilator therapy, patients were given 1 dose of TI. Patients with asthma experienced a mean decline in FEV_1 of 12% after 15 minutes; those without asthma experienced a mean decline of 3.4% after 15 minutes. Five patients with asthma (29%) developed bronchoconstriction, wheezing, or an asthma exacerbation after receiving TI. Administering salmeterol prior to the TI dose resulted in no decline in FEV_1 [22]. Finally, to evaluate the effects of smoking on TI treatment, a Phase 1, single-dose, euglycemic clamp study was conducted in 12 T2D patients who smoked and 12 non-smoking T2D patients as controls. The non-smoking group reached T_{max} more quickly compared to the smoking group (12 vs. 20 minutes, p=0.010) but there were no significant differences in C_{max} or AUC between groups [22].

In clinical trials of TI, two cases of lung cancer were observed in patients taking TI while no cases were observed in patients taking comparators. In both cases, the patient had a history of heavy tobacco use. Two additional cases of lung cancer were

reported after completing of the clinical trial in non-smoking patients who had received TI [19].

Due to the risk of acute bronchospasm, TI is contraindicated in patients with chronic lung disease including COPD or asthma. TI is not recommended in patients who smoke or have smoked in the previous six months. PFTs should be conducted at baseline prior to initiating TI, after 6 months of use, and annually thereafter [19]. Patients who encounter an FEV_1 decline of ≥ 20% from baseline should consider discontinuation [19]. The long term efficacy and safety of TI in patients with chronic lung disease has not been established.

Patient Perspectives

Patient perceptions regarding inhaled insulin therapy are important considerations, due to documented barriers with the use of subcutaneously injected insulin, and due to the failure of the first inhaled insulin product to succeed on the US market. There have been a number of studies demonstrating better patient satisfaction with inhaled insulin compared to subcutaneous injections [27-29], with one study reaching a preference of 8:1 in favor of inhaled insulin [29].

An open-labeled, parallel-group, randomized, controlled, 12-week trial compared patients using either a mixed SC insulin (2-3 injections/day) (n=25) or inhaled insulin (Exubera®) used before meals with basal ultralente injected subcutaneously at night (n=26) [28]. The Patient Satisfaction with Insulin Therapy Questionnaire was used to evaluate patient perceptions, and was completed by 47 patients (22 in the inhaled group, 25 in the SC injection group). The mean overall satisfaction improvement was significantly greater ($p<0.05$) in the inhaled insulin group (31%; 95% CI 14-50) compared with the SC insulin group (13%, 95% CI 7-19) [28].

Peyrot and colleagues presented data evaluating health-related quality of life (HR-QOL) through the use of the standardized short-form 36 (SF-36) and Insulin Treatment Questionnaire in T2D patients [30]. Patients were randomized to receive either TI (n=177), metformin with a secret agogue (n=162), or a combination of TI with metformin and secret agogue (n=169) [30]. The authors reported an increase in treatment satisfaction after 12 weeks in both the TI arm ($p=0.003$) and the TI plus oral therapies arm ($p<0.0001$), compared with baseline ratings. These changes were statistically better than those reported in the metformin + secret agogue group ($p=0.0116$ for TI alone, $p=0.0009$ for TI with oral agents) [30].

Another study used a standardized HR-QOL questionnaire to ask 532 T2D patients about potential additional drug therapy options [31]. Initially, patients compared the option of SC insulin with alternative OAA options. During this phase, patients rejected the option of insulin 83% of the time. As a second phase, researchers added inhaled insulin as a potential option, and this dropped patients' resistance to insulin therapy down to 57%. The paper concluded that while insulin therapy acceptance with T2D is low, that adding alternative delivery options may improve patient acceptance [31].

An internet survey was distributed to 1094 T2D patients in the US, where patients were instructed to rank potential advantages that inhaled insulin may have over SC injected insulin [32]. Patients ranked "avoiding post-prandial hyperglycemia" and less "discomfort and inconvenience" as benefits most strongly related to evaluating and considering inhaled insulin therapy [32].

Place in Therapy

TI is rapid-acting inhaled insulin indicated for use in adult patients with either T1D or T2D to improve glucose control. Published efficacy and safety data in patients with T2D is limited, but indicate that TI lowers A1C significantly more than inhaled placebo and is non-inferior, when used with basal insulin, to biphasic, pre-mixed insulin. Pharmacokinetic studies show that TI has a faster onset and shorter duration of action compared to rapid-acting, subcutaneous insulin. This rapid-on, rapid-off PK profile could theoretically lead to better postprandial glucose profiles with less pronounced hyperglycemia and lower rates of delayed hypoglycemia [33]. More studies are needed to determine if these PK advantages translate to differences in clinically meaningful outcomes. Particularly, a head-to-head study comparing TI to rapid-acting insulin in the T2D patient population is needed.

One advantage of TI over current prandial insulin options is the inhaled route of delivery. TI may be a reasonable alternative to rapid acting insulins in patients who are resistant to self-administered subcutaneous injections. However, considering the available data, it is unclear where TI will fit within clinical treatment guidelines. Currently, in T2D treatment guidelines, prandial insulin is reserved for patients who have not achieved adequate glycemic control despite treatment with OADs and maximization of basal insulin [4,5]. This suggests that those patients that are resistant to subcutaneous injections would likely still require basal insulin delivered by injection prior to initiating prandial insulin. Although TI could eliminate the need for injections prior to meals and reduce the number of total injections per day, it would likely not eliminate injections completely. It has been observed that for inhaled insulin to truly be a successful alternative to injections, formulation changes need to be implemented to allow for both basal and bolus insulin delivery [12].

While typically viewed advantageously over injectable insulin, the inhaled route of delivery carries its own potential barriers and disadvantages. Proper use of the inhaler device, including inhaler technique, correct dosing and correct utilization of dose cartridges requires adequate training and patient understanding. The average wholesale price of initial doses of TI (4 units before each meal) is $271.27 for a 30-day supply, which is comparable to rapid-acting insulin analogs [34]. Cost implications for patients, however, will ultimately come down to formulary decision makers. The additional costs of routine PFTs as well as the availability of conducting these tests are important considerations and could prove to be significant barriers to TI therapy.

It has been observed that one key aspect to this product's success is the manufacturer's on-going support and marketing to both consumers and providers [35]. Survey data suggest that providers would consider this alternative method of insulin delivery, but reserve it for specific patient populations. More

extensive pediatric safety and efficacy data would improve the uptake of inhaled insulin in this population.

CONCLUSION

TI offers a new rapid-acting insulin option with a novel delivery that targets post-prandial glucose and does not require subcutaneous injection. It has demonstrated superior effectiveness in lowering A1C compared to placebo and non-inferiority, when used in combination with basal insulin, compared to premixed, biphasic SC insulin. Pharmacokinetic studies suggest that TI may provide faster onset of action and shorter duration of action compared to rapid-acting insulin, which could potentially improve the postprandial glucose profile. However, this has not been demonstrated yet in a head-to-head trial in patients with T2D. TI may be a reasonable alternative to prandial insulin in patients who are resistant to administering injections.

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