

Technosphere insulin: a new inhaled insulin

Introduction

Insulin has traditionally been an injectable preparation which is a common barrier to its use, and as a result, since the discovery of insulin in the 1920s, new strategies for its delivery by routes other than intravenous and subcutaneous (SC) injection have been investigated.¹ Many pharmaceutical companies doing research in the field to develop an inhalational preparation announced the termination of product development following the poor acceptance and risk of lung cancer of the first US FDA approved inhaled insulin product, Exubera. This formulation produced cough, dyspnoea, increased sputum, and epistaxis, and was contraindicated in patients with chronic obstructive pulmonary disease (COPD) and asthma.² MannKind Corporation has developed a powdered formulation of insulin with a higher percentage of absorption from the lungs. This product, Afrezza[®] (Technosphere[®] insulin), appears to have overcome some of the barriers that contributed to the withdrawal of Exubera and is currently under review by the FDA.³

Chemistry and formulation

Technosphere is a drug delivery system made up of microparticles of fumaryl diketopiperazine (FDKP) which forms microspheres (2–5 µm) via hydrogen bonds in a mildly acidic medium sufficient for inhalation.² During the precipitation process that is used to form microspheres in solution, peptides and proteins are introduced into the solution, which are then microencapsulated within the FDKP microspheres.⁴ Following microsphere formation Technosphere particles are freeze dried to form a powder suitable for inhalation. For instance, regular human insulin is incorporated into these microspheres, which is then lyophilised into dry powder for pulmonary administration. Once inhaled, these particles get dissolved in the neutral pH of the lung leading to quick absorption of microencapsulated peptides like insulin or proteins into the systemic circulation. This Technosphere technology has been

studied for felbamate in mice and parathyroid hormone in humans.^{5,6}

Pharmacokinetics

On inhalation, the pH in the lungs will cause dissolution of microspheres, releasing insulin. It rapidly reaches systemic circulation and attains maximum concentration in 15 minutes (T_{max}) which is much earlier compared to injectable insulin, and the C_{max} is also higher.^{1,7} The mechanism of insulin action remains the same once insulin is absorbed through the lung mucosa.¹ Technosphere insulin delivered by inhaler has a relative bioavailability of 21–25% compared to SC regular insulin and is also eliminated quickly.³ The $T_{1/2}$ of inhaled insulin is around 45 minutes.⁸ This rapid absorption and elimination resemble endogenous postprandial insulin release. Following inhalation, insulin and FDKP levels in lungs decline over time with values being 12%, 1.6%, and 0.3% of maximum at 4, 8 and 12 hours post-dose, respectively.^{1,9}

Clinical trials

Short term

A study by Rave *et al.* performed in 16 non-smoking subjects with type 2 diabetes mellitus (T2DM) showed that the peak blood glucose concentrations were significantly lower with Technosphere insulin than with regular insulin ($p=0.002$).¹⁰ Fasting blood glucose levels were similar with both formulations, but Technosphere insulin had beneficial effects on postprandial blood glucose (PPG) levels compared to regular human insulin. Another study by Rave *et al.* was done to assess onset of action of 48 units of inhaled Technosphere insulin in 13 participants with T2DM by measuring three-hour insulin exposure (AUC_{3h}) and was comparable to 14 units of regular insulin given SC.¹¹ The time taken for maximum effect was quick (79 vs 293 minutes; $p<0.0001$), and the percentage of glucose disposal during the initial three-hour postprandial period was higher with Technosphere insulin than with regular insulin (59% vs 27%). A prospective, double-blind, placebo-controlled, multicentre study

was performed in 227 T2DM subjects to define the dose-dependent effect of Technosphere insulin on HbA_{1c}, given three times daily with insulin glargine over 11 weeks of treatment.¹² HbA_{1c} was reduced by -0.4, -0.5, -0.5, and -0.6% for the 3.6, 7.3, 10.9, and 14.6 unit doses respectively, and this was found to be statistically significant when compared to placebo. In addition, a statistically significant dose-dependent decrease in peak PPG concentrations was observed when compared to baseline, except with 3.6 units. A 12-week, randomised, double-blind, parallel-group, placebo-controlled, multicentre study was carried out to compare the efficacy, safety and tolerability of Technosphere insulin vs Technosphere powder placebo in insulin-naïve patients with T2DM ($n=126$).¹³ A statistically significant decrease in HbA_{1c}, PPG and peak PPG levels from baseline was observed with Technosphere insulin at the end of 12 weeks ($p<0.0001$).

Long term

Rosenstock *et al.* compared a basal/bolus regimen consisting of Technosphere insulin plus insulin glargine ($n=323$), with premixed bipart 70/30 administered twice daily ($n=331$).¹⁴ A statistically significant decrease in fasting plasma glucose (FPG) ($p=0.0029$) and one-hour PPG ($p=0.0001$) was observed in the Technosphere group. Technosphere insulin reduced FPG consistently, which is remarkable since the insulin was completely depleted long before fasting glucose levels were measured in the morning. The percentages of patients with HbA_{1c} <7% (53mmol/mol) were similar in both of the groups and HbA_{1c} was reduced by -0.59 and -0.71% by Technosphere and bipart insulin, respectively. From the clinical trials, it is observed that Technosphere insulin is non-inferior to regular or other insulin preparations in reducing FPG and significantly decreases PPG and HbA_{1c} levels.¹⁴

New data on Technosphere insulin indicate that the treatment confers no discernible risk for increased cardiovascular (CV) events, according to two studies presented at the American

Diabetes Association 71st Scientific Sessions.^{15,16} Another study addressed the issue of patient satisfaction. In this 16-week, randomised, multicentre study, T1DM adults were given meal-time Technosphere insulin in combination with insulin glargine, or insulin lispro in combination with insulin glargine. Participants were then given the Inhaled Insulin Treatment Questionnaire. The survey revealed similar perceptions for both inhaled and injected treatments. However, insulin perception subscales for convenience, comfort and ease of regimen adherence showed a significant difference, favouring the Technosphere insulin plus glargine group.¹⁷

Adverse effects

Technosphere insulin has been well tolerated by healthy volunteers as well as by people with diabetes. The most common adverse effects were hypoglycaemia and cough.^{1,3,12} Episodes of coughing were more frequent in the first week of treatment and declined by six weeks. Inhaled insulin has the potential to produce amyloid deposits in the lungs.¹⁸

In the study by Rosenstock *et al.*, a small insignificant, asymptomatic change in pulmonary functions (FEV₁, FVC, DLCO [carbon monoxide diffusing lung capacity]) was observed in the Technosphere insulin group and was reversible after three months on cessation.¹⁴ The subjects in the Technosphere insulin group gained less weight than those in the premixed bipart group at 52 weeks when compared to baseline (+0.9 vs +2.5kg, respectively; $p=0.0002$).¹⁴ Similarly, the occurrence of both mild to moderate hypoglycaemia (47.99 vs 68.88%, $p<0.0001$) and severe hypoglycaemia (4.33 vs 9.97%, $p<0.0066$) was significantly less with Technosphere insulin compared to insulin bipart.¹⁴ Weight gain was not seen after 12 weeks of Technosphere insulin added to oral antidiabetic drugs.¹³

Drug interactions

There is an increased risk of hypoglycaemia when concurrently used with oral antidiabetic drugs.

Dose and dosage forms

The Technosphere insulin inhalation powder is available as a cartridge which is inserted into an inhaler and

Key points

- Technosphere insulin is a new inhaled insulin preparation which mimics normal prandial insulin release. It decreases PPG levels and has good glycaemic control with significantly lesser hypoglycaemia
- Current data show that this formulation has no impact on pulmonary function
- Long-term safety studies with regard to pulmonary function and risk for development of lung carcinoma need to be monitored
- The FDA is currently reviewing Technosphere insulin for use in both type 1 and type 2 diabetes

inhaled by mouth one minute before food.¹⁹ The cartridges are pre-metred with 15 units or 30 units of insulin (the MedTone™ device was used in clinical trials).²⁰ Recently, MannKind has applied for FDA approval of its second generation inhaler device named Dreamboat™ which uses a 10 unit dose of inhaler powder.²¹ This may cut device cost. Technosphere insulin 15 units is equivalent to 3.8 units of SC rapid-acting insulin analogue.³ The inhalation device is small, compact, and easy to use, store and carry as compared to Exubera insulin. The procedure for loading the insulin powder to administer the Technosphere insulin is simple when compared with previous devices.²⁰ Type 1 diabetes mellitus (T1DM) patients can use insulin glargine or insulin detemir, as basal insulin, once-daily in conjunction with bolus Technosphere insulin to reduce prandial insulin requirement.

Advantages and limitations

Technosphere insulin has been shown to be a unique insulin formulation with rapid onset and relatively short duration of action, and is equally efficacious with minimal weight gain and occurrence of hypoglycaemic events being less compared to SC regular human and rapid-acting insulins. Three studies in patients with T1DM and T2DM reported treatment satisfaction with this formulation.² Technosphere insulin closely mimics the physiological insulin release and hence would be ideal for T2DM patients, particularly those who are unwilling to initiate treatment with SC insulin due

to self-administration phobia. The absorption of insulin from this formulation is not significantly altered in patients with COPD or in smokers, and has no impact on pulmonary function over one year of use.

Recent update

The MedTone device was used to administer Technosphere insulin and phase III clinical trials were conducted. Later on, MannKind switched to Dreamboat as it is smaller in size and used a 10 unit dose of inhaled powder compared to MedTone's 15 unit dose. This reduced the device cost with lesser incidence of cough; reduction in lung function was comparatively less which was reversible and clinically insignificant.²¹ MannKind's complete response letter to the FDA in January 2011 has shown pharmacoequivalence with both of the devices. Presently, the company is conducting phase III trials using Dreamboat but the FDA has requested them to compare the two devices with respect to *in vitro* performance and clinical pharmacology data. The FDA has also requested additional information regarding performance characteristics, usage, handling, shipment and storage of Dreamboat, an update on the safety of Technosphere insulin, proposed user training and changes in the proposed labelling of the device, blister pack, foil wrap and cartons. MannKind has planned to include a patient cohort using the MedTone inhaler as an arm to already undergoing phase III Dreamboat trials to provide data to the FDA.²²

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Declaration of interests

This article was written by the authors with their own interest in Technosphere insulin. Mannkind Corporation has not been involved in the article and the authors have not received any kind of help including financial support from the company.

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New technology

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