Efficacy of inhaled Technosphere® insulin: a comparative review to injectable insulin

Brian Johnston
Pacific University

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Abstract

Background: Insulin therapy is often met with apprehension among diabetic patients due to the inconvenience and discomfort of injecting oneself. Past attempts to develop an inhaled insulin has been met with such obstacles as inefficiency, cost issues, and patient acceptance. Technosphere® insulin (MannKind Corporation, Valencia, CA) is a rapid acting inhalable insulin that is indicated for prandial use and is currently in phase III clinical trials. It is showing promising results and this systematic review aims to evaluate the efficacy of Technosphere insulin as compared to traditional injectable insulin.

Methods: An exhaustive search was conducted using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science with the key terms: Technosphere®, Afresa®, and Afrezza® for relevant studies. A search on the MannKind Corp. website was conducted for additional articles and data. Selected articles were assessed for quality using GRADE.

Results: Two studies met inclusion criteria and were included in this systematic review. The first study is a randomized controlled trial that demonstrated the use of prandial inhaled Technosphere insulin to be non-inferior to injectable biaspart insulin in terms of HbA1c lowering capacity. In addition, patients treated with Technosphere insulin experienced fewer hypoglycemic episodes, less weight gain, and increased patient satisfaction. The second study is a randomized controlled trial that compares the pharmacokinetic profile of Technosphere insulin to that of regular human insulin. Technosphere insulin was found to have a significantly higher maximum concentration (Cmax), faster onset of action (tmax), and a quicker elimination (t1/2) compared to that of regular human insulin.

Conclusion: Inhaled Technosphere insulin was shown to be non-inferior to injectable biaspart insulin in terms of HbA1c lowering capacity and has a pharmacokinetic profile similar to that of other rapid acting insulins. Technosphere insulin was also found to be associated with less weight gain, fewer hypoglycemic episodes, and greater patient satisfaction. Although not currently FDA approved, Technosphere insulin seems to be a viable alternative to prandial injectable insulin.

Keywords: Technosphere, Technosphere insulin, inhaled insulin, insulin therapy

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Efficacy of inhaled Technosphere® insulin: a comparative review to injectable insulin

Brian Johnston

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Faculty Advisor: James Ferguson, PA-C

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
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Table I: GRADE Quality of Assessment and Summary of Findings

List of Abbreviations

HbA1c.................................................................Glycated hemoglobin
PD.................................................................Pharmacodynamics
PK.................................................................Pharmacokinetics
SF.................................................................Short Form

List of Appendices

Appendix A................................................. Euglycemic glucose clamp procedure
Efficacy of inhaled Technosphere® insulin: a comparative review to injectable insulin

BACKGROUND

There is mounting evidence\textsuperscript{1,2} that tight glycemic control prevents and/or slows the progression of long-term complications such as retinopathy, neuropathy, and cardiovascular problems commonly seen in uncontrolled diabetic patients. However, the initiation of insulin therapy is often unnecessarily delayed by patient or physician due to concerns of inconvenience, risk of side effects, and a perception of increased disease severity.\textsuperscript{3} This consequently results in delayed treatment or non-compliance among patients, resulting in inadequate glycemic control. Theoretically, a less invasive form of insulin delivery could sway patients to begin insulin therapy sooner and increase compliance.

Pulmonary delivered insulin represents an alternative, less invasive route of administration that eliminates the need for repetitive subcutaneous injections. The concept of inhalable insulin therapy has been postulated for many years but has not successfully come to fruition due to cost issues, inefficiency, and lack of acceptance.\textsuperscript{4} An FDA approved inhalable insulin, Exubera® (Pfizer), was available for a short time in the US from August 2006-October 2007 before being discontinued by the manufacture due to lack of acceptance by patients and clinicians.\textsuperscript{5} A systematic review\textsuperscript{6} of Exubera found it to be non-inferior with a quicker onset than comparator injectable insulin but never gained wide acceptance because the hand held inhaler was bulky and difficult to use, it was expensive, and inefficient.\textsuperscript{5} Currently, there is no FDA approved inhalable insulin
available on the market but one formulation (Technosphere® insulin, in phase III clinical trials) is showing promising results.

Technosphere® Insulin (MannKind Corporation, Valencia, CA) is a rapid acting inhalable insulin intended for prandial dosing. The uniquely designed drug delivery platform allows for efficient pulmonary administration of insulin and demonstrates unique pharmacokinetic and pharmacodynamics properties. The Technosphere carrier is created when specialized delivery molecules self-assembly with powdered insulin into spherical microparticles that form a large surface area allowing for more efficient lung absorption. In addition to a more efficient insulin, the handheld inhaler is more compact and easier to use than the Exubera inhaler. Is inhaled Technosphere insulin as efficacious as subcutaneously injected insulin?

METHODS

An exhaustive database search of Medline-OVID, CINAHL, EBMR Multifile, and Web of Science search was conducted for English-language and human studies using the terms: Technosphere®, Afresa®, and Afrezza®. Additionally, a search on the Mannkind Corp. website was conducted for relevant articles and data. Studies comparing Technosphere insulin (Afresa/Afrezza) to traditional injectable insulin were chosen. Selected articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).
RESULTS

The initial result of the search yielded 148 articles for review. After screening relevant articles for primary data and human studies, a total of 2 articles met inclusion criteria. These articles included two randomized controlled trials.\(^8\),\(^10\) See table 1.

Rosenstock et al

This study\(^10\) was a non-inferiority study comparing Technosphere insulin to injectable biaspart insulin (70% insulin aspart protamine suspension and 30% insulin aspart of rDNA origin). Adult patients with type 2 diabetes and poor glycemic control (glycosylated hemoglobin [HbA1c] between 7.0% and 11.0%) despite insulin therapy were enrolled. This was an open-label study (due to different routes of administration) where a total of 677 patients were enrolled. 334 patients were randomly allocated to receive twice-daily prandial inhaled Technosphere insulin plus bedtime glargine and 343 received twice-daily prandial injectable biaspart insulin plus bedtime glargine over a 52-week period.\(^10\)

The primary endpoint being measured was the change in HbA1c over a 52-week period. Secondary endpoints being analyzed were weight gain, safety, and patient satisfaction. Upon the study’s completion, a total of 211 patients were analyzed in a “per-protocol population” in the inhaled insulin group and 237 patients in the biaspart insulin group. The per-protocol population included randomly allocated patients who had received at least one dose of study drug, had measurements of HbA1c at baseline and at least one time point after baseline, completed the study, and were deemed to be protocol compliant. The change in HbA1c from baseline in patients treated with inhaled insulin
averaged -0.68\% (SE 0.077, 95\% CI -0.83 to -0.53) and patients on biaspart insulin averaged a change of -0.76\% (SE 0.071, 95\% CI -0.90 to -0.62) from baseline.\textsuperscript{10}

Researchers determined Technosphere inhalable insulin to be non-inferior to injectable biaspart insulin with a difference of 0.07\% (SE 0.102, 95\% CI –0.13 to -0.27) between groups. Secondary endpoints also showed significantly less weight gain in the inhaled insulin group with a mean weight gain of 0.9kg (SD 0.3, 95\% CI 0.3-1.5) as compared to biaspart insulin with a mean weight gain of 2.5kg (SD 0.3, 95\% CI 1.9-3.0), with a treatment difference of -1.6kg (SD 0.4, 95\% CI -2.4 to -0.7, p=0.0002). There was a significant reduction in mild-to-moderate and severe episodes of hypoglycemia. Incidents of mild-to-moderate episodes of hypoglycemia occurred in 47.99\% (n=155) and 68.88\% (n=228) in the inhaled and injectable insulin groups respectively. Incidents of severe hypoglycemia occurred in 4.33\% (n=14) and 9.97\% (n=33) in inhaled and injectable insulin groups respectively. Lastly, from the short-form 36 (SF-36) quality of life and insulin treatment questionnaires, patient’s concerns about diabetes decreased significantly from baseline in the group on inhaled insulin (p=0.0083) but did not in the biaspart group; the between-group difference was not significant (p=0.1825).\textsuperscript{10}

The authors felt the study was limited by the fact that the design and the administration of the different insulins did not allow for masking. They also feel that greater reductions in HbA1c could have been achieved in both groups if insulin titration to glycemic targets was systematically enforced rather than allowing clinicians to treat patients to their perceived glycemic targets. The authors feel that further studies are needed to compare Technosphere insulin to different treatment regimens and additional safety data is needed on more diverse populations of patients.\textsuperscript{10}
This study\textsuperscript{8} was a randomized, open-label, four-way crossover study of 11 healthy volunteers evaluating pharmacokinetics (PK) and pharmacodynamics (PD) of inhaled Technosphere insulin and injectable regular human insulin. Inclusion criteria consisted of healthy, non-smoking male/female volunteers 18-40 years of age, with a body mass index of 18-27kg/m\textsuperscript{2}. Volunteers were excluded from the study if they had type 1 or type 2 diabetes, the presence of human insulin antibodies, or any tobacco or nicotine use in the past year. Three different doses of inhaled Technosphere insulin (25, 50, or 100 units) were compared to a single 10 units of regular human insulin. PK and PD were analyzed over a 360-minute period. To normalize basal insulin levels between treatment groups, a euglycemic glucose clamp procedure (see appendix) was utilized.\textsuperscript{8}

The primary endpoints being measured were the time to maximum insulin concentrations (t\textsubscript{max}), maximum insulin concentrations (C\textsubscript{max}), and half-life (t\textsubscript{1/2}). Subjects were randomly assigned to either receive inhaled Technosphere insulin or injectable regular human insulin. Insulin concentrations were analyzed at 120, 90, 60, and 30 minutes before dosing and 0, 1, 3, 7, 12, 20, 30, 45, 60, 90, 120, 180, 240, 300, and 360 minutes post dose.\textsuperscript{8}

Following the inhalation of 25, 50, or 100 units of Technosphere insulin, the t\textsubscript{max} occurred notably earlier than the t\textsubscript{max} of 10 units of regular human insulin. The t\textsubscript{max} for 25, 50, or 100 units of Technosphere insulin occurred respectively at 12 (SD ±6), 15 (SD ±5), and 17 minutes (SD ±5) as compared to the t\textsubscript{max} of injectable insulin at 134 minutes (SD ±87). Additionally, the C\textsubscript{max} following all three doses of Technosphere insulin were notably higher than the C\textsubscript{max} of injectable insulin. C\textsubscript{max} concentrations for 25, 50, or 100
units of Technosphere insulin were 54.6 (SD ±39), 105 (SD ±40), and 181µU/ml•min (SD ±181) respectively as compared to the $C_{\text{max}}$ for injectable regular human insulin measured at 26.9µU/ml•min (SD ±10). This was followed by significantly faster elimination of inhalable Technosphere insulin as demonstrated by the time to half-minimum serum concentration ($t_{1/2}$). The $t_{1/2}$ for 25, 50, or 100 units of Technosphere insulin was measured at 45.2 (SD ±11), 42.0 (SD ±7), and 49.7 minutes (SD ±5) respectively as compared to a $t_{1/2}$ of 284 minutes (SD ±59) for regular human insulin.8

This study demonstrated that the profile of inhalable Technosphere insulin in healthy, non-diabetic subjects had a faster $t_{\text{max}}$ and higher $C_{\text{max}}$ as compared to injectable regular human insulin with subsequent faster elimination. Inhalable Technosphere insulin reached $t_{\text{max}}$ as quickly as 12 minutes (25 U), whereas regular human insulin reached $t_{\text{max}}$ at 134 minutes, approximately 2hrs later. The $C_{\text{max}}$ was also shown to be much higher with inhaled insulin as compared to injectable regular human insulin (54.6 vs 26.9 µU/ml•min). Lastly, elimination occurred more rapidly with inhaled Technosphere insulin than with injectable regular human insulin as demonstrated by the $t_{1/2}$ of 42-50 minutes vs. 284 minutes respectively.8

**DISCUSSION**

The discomfort and inconvenience of injectable insulin is a problem that has yet to be successfully solved with a less invasive form of delivery. Although Technosphere insulin is not yet FDA approved, the previous two studies8,10 demonstrate that it is a feasible alternative to injectable insulin. The Rosenstock et al10 study demonstrated that inhaled Technosphere insulin has a similar HbA1c lowering capacity to that of injectable biaspart insulin (-0.68% vs -0.76% respectively). This study10 also found that patients
treated with inhalable Technosphere insulin experience significantly less weight gain, fewer hypoglycemic episodes, and greater patient satisfaction.

The Rave et al\textsuperscript{8} study demonstrated that Technosphere insulin was characterized by rapid absorption and faster elimination than injectable regular human insulin. Technosphere insulin reached a maximum insulin concentration in \( \sim 15 \) minutes as compared to regular human insulin which reached \( C_{\text{max}} \) after 284 minutes. This rapid onset of action is comparable to intravenous insulin, and Technosphere insulin represents the first formulation that approaches the physiological early insulin release during meals.\textsuperscript{11} This translates to a formulation that displays an onset of action faster than that of other rapid-acting insulin analogs such as lispro, aspart, or glulisine.\textsuperscript{11} Lastly, inhalable insulin was eliminated at a much faster rate than injectable insulin as demonstrate by the \( t_{1/2} \). Inhaled Technosphere insulin reached \( t_{1/2} \) in \( \sim 45 \) minutes whereas injectable regular human insulin reached \( t_{1/2} \) in 284 minutes.

There were several limitations found when evaluating the quality of evidence. The biggest being a risk for publican bias due to the fact that both studies\textsuperscript{8, 10} were funded by the company (Mannkind) that manufactures Technosphere insulin. Another problem was the lack of blinding in the Rosenstock et al\textsuperscript{10} study which could have been solved by using a double dummy method. However, the primary endpoint (HbA1c) is a relatively objective measurement and the lack of blinding does not weaken the study significantly. The lack of blinding did however, allow researches to evaluate patient satisfaction by not subjecting all patients to injectable insulin. Furthermore, this study\textsuperscript{10} used a per-protocol analysis that excluded a significant amount of patients that resulted in data that was biased towards a greater HbA1c lowering capacity for Technosphere insulin. In terms of
clinical relevance, the major endpoints ($t_{\text{max}}$, $C_{\text{max}}, t_{1/2}$) in the Rave et al.$^8$ study were
assumed to be not as significant as a change in HbA1c that was measured in the
Rosenstock et al.$^{10}$ study. Lastly, the precision in the Rave et al.$^8$ study was quite low as
demonstrated by large standard deviations and a small sample size. Due to these
limitations, the overall quality of evidence was determined to be low to very low.

The amount of studies directly comparing inhalable Technosphere insulin directly
to subcutaneously injected insulin is limited. Currently, the Rosenstock et al.$^{10}$ study is the
only study comparing the efficacy of inhalable Technosphere insulin directly to a rapid
acting injectable insulin. Further studies involving long-term comparisons of
Technosphere insulin to other rapid acting insulin analogs in terms of efficacy,
tolerability, cost effectiveness, and safety are needed to determine the clinical application
of this novel drug.

**CONCLUSION**

Although inhaled Technosphere insulin was not found to be superior to injectable
insulin in terms of efficacy, Technosphere has other benefits that make it more attractive
than injectable insulin. Patient satisfaction was markedly higher in participants that were
treated with Technosphere as compared to traditional injectable insulin. This is likely due
to the elimination of repetitive subcutaneous injections, less weight gain, and fewer
hypoglycemic episodes. In theory, these benefits may translate into increased patient
compliance and timely initiation of insulin therapy. Ultimately, resulting in improved
glycemic control and preventing or slowing long-term complications seen in uncontrolled
diabetes.
References


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ᵃThe authors conducted a per-protocol analysis and there was a lack of blinding.
ᵇStudy was funded by MannKind corporation.
ᶜPrimary outcomes are indirectly related to patient outcome.
ᵈSample size was small and standard deviation intervals were quite large.
Appendix A

At 4-6 hours before administration of the study drug, an individual intravenous insulin infusion was administered by means of a precision pump in order to adjust the subject’s blood glucose to a target level of 120 ±18 mg/dl. One hour prior to study drug administration, the insulin infusion rate was lowered to a minimum level where blood glucose remained stable within the target range. All insulin infusion was stopped completely at the time of study drug administration.8