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PULMONARY DELIVERY OF INSULIN: A REVIEW OF AFREZZA, TECHNOSPHERE FORMULATION AND COMPARATIVE LABELING WITH EXUBERA

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ABSTRACT

Compared to traditional subcutaneous injections, pulmonary delivery of insulin utilizing Technosphere-based formulations offers a needle-free, ultra-rapid prandial insulin option that more closely mimics physiological post-meal insulin production. Recombinant human insulin is adsorbed onto fumaryl diketopiperazine microparticles to form inhalable dry powder particles that dissolve quickly in the alveoli. Afrezza reaches peak plasma insulin concentrations in 12 to 15 minutes and lowers blood sugar for approximately 2.5 to 3 hours. When compared to rapid-acting injectable counterparts, pharmacokinetic and clamp tests demonstrate a faster onset, an earlier peak effect, and a quicker return to baseline, indicating better early postprandial glucose management and possibly less late hypoglycemia. When Afrezza is used in conjunction with basal insulin, clinical trials in patients with type 1 and type 2 diabetes show HbA1c reductions that are not inferior to injectable prandial insulin. Additionally, some analyses show tendencies toward reduced weight gain and fewer mild hypoglycemia episodes. Afrezza is positioned as a targeted alternative primarily for appropriately selected patients who are unwilling or unable to use injectable prandial insulin, but widespread adoption is limited by minor declines in FEV1, frequent mild cough, contraindication in chronic lung disease, mandatory spirometry, and cost and access constraints.

KEYWORDS: Technosphere insulin, fumaryl diketopiperazine, HbA1c, spirometry, diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a severe, long-term metabolic disease marked by aberrant gluconeogenesis and glycogenolysis, as well as hyperglycemia brought on by β cell malfunction.[1] One important hormone that controls metabolism and maintains normoglycemia and normolipidemia is insulin. In an outpatient situation, insulin can be given intravenously, intramuscularly, or, most frequently, subcutaneously.[2,3]

However, other alternative methods of administering insulin have been investigated and shown to be inadequate. The primary disadvantage of the insulin formulations now on the market is that they must be injected and do not replicate the physiological transport of insulin into the systemic circulation after meals. The two primary clinical categories of diabetes mellitus are type 1 and type 2. For patients with Type 1 diabetes to live, subcutaneous insulin must be given as either a continuous subcutaneous insulin infusion or several daily injections. With oral antidiabetic medications and lifestyle changes, many T2DM patients can initially attain glycaemic control.[1,4,5]

The Food and Drug Administration (FDA) authorized technosphere insulin (TI) for use in type 1 and type 2 diabetes in June 2014 under the brand name Afrezza (MannKind Corp., Valencia, CA). A dry powder of recombinant human insulin is called Afrezza.[6,7]

According to the 11th edition of the IDF Diabetes Atlas, around 11.1% of people worldwide (approximately 589 million adults between the ages of 20 and 79) had diabetes in 2024. By 2050, this number is expected to

rise to over 13% (approximately 853 million adults). According to IDF data, India ranks among the top nations in terms of the total number of adults with diabetes, making a significant contribution to the Atlas's global burden. The average yearly cost of treating type 2 diabetes and its consequences is estimated by Indian cost-of-illness studies to be between ₹15,500 and ₹17,000 per patient. Hospital admissions and complications drive costs to levels that are disastrous for many households.[8,9,10]

Exogenous insulin replacement, typically in the form of a basal-bolus regimen or continuous subcutaneous insulin infusion, is necessary for survival in type 1 diabetes due to nearly complete β cell loss. Because type 2 diabetes is a progressive condition, many patients who manage it with lifestyle changes and oral medications eventually experience severe β cell failure and need basal insulin. Prandial insulin is then added when fasting glucose levels improve but postprandial hyperglycemia still occurs. In particular, when HbA1c stays above target despite improved basal insulin and non-insulin treatments, clinical guidelines emphasize that adding prandial insulin to basal insulin improves overall glycaemic control and lowers glucose variability.[11,12]

The time-action profiles of conventional rapid-acting insulin mimics still do not accurately reflect the quick increase and fall of physiological postprandial insulin secretion, which contributes to post-meal hyperglycemia and late hypoglycemia. Conventional rapid-acting insulin analogues begin to work within ten to twenty minutes. Reviews of ultra quick acting analogues point out that while they enhance early postprandial hyperglycemia compared to older analogues, injection site pain and reactivity, the requirement for several daily injections, and patient resistance continue to be major obstacles to optimum use. Fear of injections, worries about hypoglycemia, weight gain, and complicated regimens are the main causes of poor adherence and persistence with insulin therapy, according to observational studies and adherence research.[13,14,15]

In 2006, the FDA and EMA authorized Exubera, the first commercial inhaled insulin, as a prandial insulin alternative for adults with type 1 and type 2 diabetes.[16,17] Exubera was first marketed as a needle-free substitute for subcutaneous injections with equivalent glycaemic effectiveness. It used recombinant human insulin produced as a dry powder for inhalation using a rather big, complicated inhaler apparatus. Despite this assurance, Exubera was taken off the market in 2007 due to low sales; investigations revealed a number of reasons, including the large inhaler, difficult dosage regimen, expensive price, stringent labeling, and ongoing worries regarding long-term pulmonary safety.[17,18] Exubera's withdrawal, according to commentators, decreased interest in the development of inhaled insulin and caused uncertainty among patients and prescribers, particularly with regard to lung safety and cost-effectiveness. Exubera's low bioavailability, additional cost per patient, and requirement for pulmonary function testing made it difficult to justify in routine practice, with the exception of patients with severe injection site problems or true needle phobia, according to regulatory documents and expert reviews, even though short-term efficacy and safety were acceptable.[18,19]

PULMONARY ROUTE AND TECHNOSPHERE FORMULATION

The FDA authorized Technosphere insulin, marketed as Afrezza, as a novel inhaled rapid-acting insulin for people with type 1 and type 2 diabetes in 2014, not withstanding Exubera's failure.[16,20] Drugs can enter the systemic circulation quickly thanks to the lung's extensive vascularization and enormous absorptive surface (about 100–140 m²).[21]

Even bigger molecules, such as insulin, can be readily absorbed when they reach the distal airways because the alveolar epithelium is incredibly thin and moderately permeable.[22] Peptide medications like insulin benefit from the alveoli's slower mucociliary clearance than bronchiolar areas, which gives inhaled particles more time to breakdown and be absorbed.[21] Inhaled dry powder formulations can solve the drawbacks of subcutaneous insulin (pain, needle anxiety, injection site issues) while still obtaining sufficient biological activity in experimental models, according to reviews on pulmonary insulin delivery.[23] In contrast to previous products, Afrezza uses a more compact, discrete inhaler and a new carrier technology (Technosphere particles based on fumaryl diketopiperazine) to enhance pharmacokinetics, lung deposition, and convenience of use.[16,24] Fumaryl diketopiperazine (FDKP) is a carrier used by Technosphere insulin (Afrezza) to create microparticles that can carry insulin to the alveoli when inhaled. Within the respirable size range that is appropriate for deposition in the distal lung.[25] FDKP self-assembles into porous microspheres with an aerodynamic diameter of roughly 2 to 2.5 µm. In order to produce a stable dry powder for inhalation, recombinant human insulin is adsorbed onto these FDKP particles in Afrezza, usually in a 1:9 ratio by dry weight. Approximately 60% of the Technosphere insulin dose that is exhaled enters the lungs after inhalation; the particles quickly disintegrate at physiological pH, enabling the separate absorption of FDKP and insulin across the alveolar wall.[26,27] Afrezza's ultra-rapid onset of action is supported by pharmacokinetic evaluations, which reveal that both insulin and FDKP reach their maximal plasma concentrations in roughly 10 to 15 minutes.[25,27] A recent assessment of "twenty years of inhaled insulin" details Afrezza is a member of the second generation of inhaled insulin technology, which seeks to overcome the safety and practical issues that plagued Exubera and provide ultra-rapid prandial insulin.[17]

PHARMACOKINETICS AND PHARMACODYNAMICS

A. Basic PK profile of Afrezza

Regular human insulin is present in Afrezza; it exhibits very rapid systemic absorption, reaching peak plasma insulin concentrations in 12 to 15 minutes after inhalation. When compared to subcutaneous ordinary human insulin, clamp experiments show an insulin T "max" of 12–15 minutes, an elimination half-life of 28–39 minutes, and an absolute bioavailability of about 21–30%. Compared to conventional insulin and rapid-acting analogues, Afrezza's glucose-lowering impact lasts for a shorter total of 2.5–3 hours.[6,16]

B. PD characteristics and clamp data

Afrezza has a faster onset and an earlier peak glucose-lowering impact than subcutaneous rapid-acting insulin analogs, according to pharmacodynamic evaluations conducted under euglycaemic clamp settings. Technosphere insulin's significantly accelerated prandial profile was demonstrated in a comparative clamp trial, where the time to peak glucose infusion rate was roughly 53 minutes, compared to 108 minutes for a rapid-acting analogue and 3–4 hours for conventional human insulin. Effective management of early postprandial glucose excursions is made possible by this quick "in and out" movement, which may also lessen late postprandial hypoglycemia.[6,16,28]

C. Comparison with subcutaneous rapid-acting analogues

Afrezza recovers to near baseline in around three hours as opposed to more than five hours for many analogues, and it reaches peak plasma concentrations more quickly (12–15 minutes v/s roughly 45–60 minutes) than SC rapid-acting analogues. Technosphere insulin has a higher early insulin availability in the first 1-2 hours after dosage, but a lower overall exposure per unit than subcutaneous lispro, according to PK/PD studies.[16, 29]

CLINICAL EFFICACY

A. Clinical efficacy in Type 1 diabetes

In persons with type 1 diabetes, Technosphere insulin plus basal insulin was compared to injectable quick acting insulin aspart plus basal insulin in a 24-week randomized trial. The results demonstrated comparable HbA1c reductions, satisfying the non-inferiority criterion.[30] According to a post hoc analysis from the AFFINITY 1 cohort, patients who received Technosphere insulin had a 30% decrease in level 1 hypoglycemia across a range of final HbA1c values, resulting in clinically non-inferior glycaemic management.[31] Another randomized study comparing insulin lispro and Technosphere insulin revealed similar HbA1c levels, but the Technosphere group experienced considerably lower early postmeal glucose and fewer cases of mild to moderate hypoglycemia.[32]

B. Clinical efficacy in Type 2 diabetes

A double blind, placebo controlled experiment showed that adding Technosphere insulin significantly decreased HbA1c and post-meal glucose excursions when compared to Technosphere placebo powder in insulin-naïve persons with type 2 diabetes that was not properly controlled on oral medications.[33] According to the study's findings, Technosphere insulin was well accepted and may develop into "an important treatment option" for people with type 2 diabetes who require prandial insulin but are hesitant to begin receiving injections. According to the study's findings, Technosphere insulin was well accepted and may develop into "an important treatment option" for people with type 2 diabetes who require prandial insulin but are hesitant to begin receiving injections.[34] When combined with basal insulin or current oral medication, inhaled insulin significantly improves postprandial control and total glycaemia in people with type 2 diabetes, according to subsequent analyses and reviews.[28, 33]

C. Systematic review and overall interpretation

Technosphere inhaled insulin was linked to a lower incidence of severe hypoglycemia and less weight gain, but overall, its glycaemic efficacy was marginally lower than that of subcutaneous insulin, according to a systematic review and meta analysis of the drug in individuals with type 1 and type 2 diabetes. The authors came to the conclusion that Technosphere insulin should mainly be used in persons without lung disease who would otherwise put off starting or increasing their insulin due to a reluctance to use injections, awaiting additional long-term safety evidence.[28,34]

SAFETY AND LIMITATIONS

A. Pulmonary Safety

According to a pooled analysis of 13 phase 2/3 trials, Technosphere insulin's short-term treatment-emergent respiratory incidents and overall lung safety outcomes were comparable to those of comparative insulin and placebo. Small drops in FEV1 were noted, though: during a 24-week period, the mean FEV1 reduction with Technosphere insulin was about -0.07 to -0.08 L, whereas the mean reduction with insulin as part was approximately -0.03 L, resulting in an absolute difference of approximately -0.04 to -0.05 L. According to safety evaluations, cough is the most common respiratory adverse event, affecting between 24–33% of users. It is typically dry, occurs soon after inhalation, and is usually mild; a small percentage of patients discontinue treatment because of cough.[25, 27, 32]

B. Contraindications and warnings

Afrezza has an FDA boxed warning and is contraindicated in patients with chronic lung illness due to reports of abrupt bronchospasm in patients with asthma and COPD. Before beginning Afrezza, the prescribing literature advises a thorough respiratory history, physical examination, and baseline spirometry (FEV1), with follow-up lung function tests conducted

during the course of treatment. Although there were few lung cancer cases reported at the time of regulatory evaluation and no obvious causal link had been established, long-term surveillance for lung malignancy was still required. [35, 36, 37]

C. Other limitations and practical issues

The most significant systemic side effect is still hypoglycemia, although rates are often comparable to or less severe than with rapid-acting subcutaneous analogues, with some analyses indicating less weight gain and hypoglycemia. Afrezza's primary drawbacks, according to reviews, include its restriction in individuals with lung illness, the requirement for routine spirometry, coughing, and problems with cost and accessibility when compared to traditional insulin.[27, 28, 33]

Table 1: Comparison Of Exubera And Afrezza.

Parameter	Exubera	Afrezza
Approval year (FDA)	Approved January 2006 as the first inhaled insulin for adults with type 1 and type 2 diabetes.	Approved June 27, 2014 as an ultra-rapid-acting inhaled insulin to improve postprandial glycaemic control in adults with diabetes.[6,38,39]
Company / sponsor	Developed by Pfizer in collaboration with Nektar Therapeutics.	Developed by MannKind Corporation; marketed with various partners over time.[6,40]
Formulation	Dry-powder formulation of recombinant human insulin for oral inhalation; insulin particles blended with excipients such as sodium citrate and mannitol.	Technosphere insulin (TI): recombinant human insulin adsorbed onto fumaryl diketopiperazine (FDKP) microparticles, usually at a 1:9 insulin:FDKP ratio.[6,41]
Device	Large, multi-component pulmonary inhaler requiring assembly; produced a “standing cloud” of insulin powder before inhalation.	Small, breath-powered, disposable cartridge inhaler (Afrezza Inhalation System), designed for simple, quick use.[42]
Nominal dose forms	Blister packs with 1 mg and 3 mg unit-dose blisters of insulin powder; dose expressed in mg, requiring conversion from subcutaneous units.	Cartridges containing 4, 8 and 12 “Afrezza units” of TI; dosing approximated to subcutaneous insulin units (e.g., 4 Afrezza units ≈ 3 units SC).[43]
Onset of action	Insulin absorbed more rapidly than subcutaneous regular insulin; peak effect ~2 hours after inhalation, onset described as “rapid” but slower than Afrezza.	Median time to peak plasma insulin concentration 12–15 minutes; pharmacodynamic effect begins within minutes and is faster than any approved subcutaneous insulin analogue.[44]
Duration of action	Duration of glucose-lowering effect around 6 hours after inhalation.	Duration of action approximately 2.5–3 hours, with earlier return toward baseline compared with rapid-acting analogues and regular insulin.[45]
Indications at approval	Adjunctive treatment for adults (≥18 years) with type 1 or type 2 diabetes; intended to be used with longer-acting insulins or oral agents.	To improve glycaemic control in adult patients with type 1 and type 2 diabetes; used as mealtime (prandial) insulin in combination with basal insulin or oral agents.[6,38,39]
Pulmonary labeling	Not recommended in patients with underlying lung disease such as asthma or COPD; required pulmonary function testing and noted small non-progressive declines in FEV1 and DLCO.	Boxed warning for risk of acute bronchospasm in chronic lung disease; contraindicated in asthma and COPD; mandatory baseline and periodic spirometry (FEV1).[39, 46]
Market status	Withdrawn from the market in 2007 due to poor sales and concerns about device complexity, dosing, cost and long-term safety.	Remains on the market (with changing commercial partners), with restricted use and ongoing post-marketing safety monitoring. [39, 46, 47]

CONCLUSION

Compared to traditional subcutaneous formulations, inhaled Technosphere insulin offers a needle-free, ultra-rapid alternative that more closely resembles physiological postprandial insulin production, marking a significant advancement in prandial insulin therapy. With efficient early postprandial glucose lowering, a tendency toward decreased hypoglycemia and weight gain in some analyses, and clinical trials in both type 1 and type 2 diabetes, Afrezza can achieve glycaemic control comparable to injectable rapid acting analogues. However, its usage is limited by pulmonary safety

concerns, such as cough, slight drops in FEV1, contraindications in chronic lung illness, and the requirement for baseline and recurring spirometry, in addition to financial and accessibility concerns.

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