

REVIEW

Inhaled insulins: the present and future of diabetes therapy

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ABSTRACT

It is well established that intensive insulin regimens reduce the risk of diabetes-related complications. However, multiple daily injections have an important impact on treatment burden and compliance. Various non-invasive formulations of insulin have been researched and the first inhaled insulin formulation, Exubera* (insulin human [rDNA origin] Inhalation Powder), was approved in the United States and European Union for the treatment of adults with type 1 or type 2 diabetes in January 2006. Comprehensive studies with Exubera have shown comparable efficacy to regular subcutaneous mealtime insulin in type 1 and type 2 diabetes, and superior efficacy to oral antidiabetic agents (OAs) in patients with

type 2 diabetes with glycosylated hemoglobin (HbA_{1c}) > 8%. Furthermore, Exubera shows a good safety profile and improved patient satisfaction versus comparators. The key limitation of this review is that few publications are available for other inhaled insulin formulations. Although their data also suggest favorable efficacy and safety profiles, it is currently unknown whether the key findings are specific to one formulation or a class effect. Therefore, more detailed investigations are expected in the future. In the meantime, we could speculate that inhaled insulins may improve patient acceptance of insulin-based therapeutic regimens, and thereby improve glycemic control and long-term diabetic outcomes.

Introduction

Studies have established that uncontrolled type 1 or type 2 diabetes are strongly associated with an increased risk of micro- and macrovascular diabetic complications (Figure 1) and intensive insulin therapy to optimize glycemic control can help reduce the risk of these complications^{1,2}. Exogenous insulin has been given by subcutaneous (SC) injection since 1921. Since then, many different formulations have been produced in an attempt to match insulin action to insulin need. However, the appropriate use of adequate strategies of insulin-based therapeutic regimens have been hampered because of the limited compliance of patients and, too often, of physicians³⁻⁵. As a result, substantial numbers of patients do not achieve current treatment goals and continue to live at risk of complications^{6,7}. Alternative

insulin delivery options, which bypass the need for SC injection, may encourage the initiation and intensification of insulin-based therapeutic regimens, and therefore help improve long-term diabetes outcomes⁸.

Of all the alternative routes of insulin delivery that have been investigated, the pulmonary route is the most promising. There are several inhaled insulin products under development, all of which should be administered before meals for control of postprandial hyperglycemia. These include inhaled human insulin, Exubera* (insulin human [rDNA origin] Inhalation Powder), AERx insulin diabetes management system (iDMS) developed by Novo-Nordisk and Aradigm, Technosphere pulmonary insulin system developed by MannKind, AIR inhaler with human insulin inhalation

* Pfizer Inc, New York, NY, USA; Nektar Therapeutics, San Carlos, CA, USA

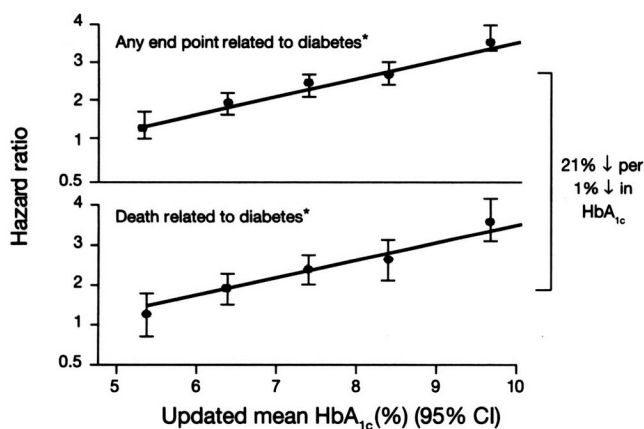


Figure 1. Correlation between HbA_{1c} levels and risk of diabetes-related complications (data from the UKPDS trial). With permission from UKPDS publication². * $p < 0.0001$; reference category (hazard ratio 1.0 = HbA_{1c} < 6% with log linear scales). HbA_{1c} = glycosylated hemoglobin; CI = confidence interval

powder (HIIP) developed by Lilly and Alkermes, and an inhaled insulin developed by KOS Pharmaceuticals^{9,10}. In terms of development, Exubera is the most advanced, and was recently approved in the United States and European Union for the treatment of adults with type 1 or type 2 diabetes. Other inhaled insulins are currently in Phase 2 or Phase 3 clinical development. This article reviews the published efficacy, safety and patient-reported outcome data of inhaled insulins in patients with type 1 or type 2 diabetes.

Efficacy

The treatment of type 1 diabetes predominantly requires the provision of exogenous insulin to match physiological needs. Thus, depending on patients' requirements, insulin is administered as part of conventional (involving three to four daily insulin injections as split into three mealtime doses of short-acting insulin and one dose of long-acting insulin) or intensive (up to five daily insulin injections as outlined above but with an additional dose of long-acting insulin) regimens.

Type 1 diabetes

The efficacy and safety profile of Exubera has been investigated as part of both conventional (using regular insulin plus neutral protamine Hagedorn [NPH] insulin)¹¹ and intensive insulin regimens (using regular and short-acting insulins plus NPH) in patients with type 1 diabetes^{12–14}. In all studies, Exubera achieved and maintained glycemic control comparable to SC insulin, as evidenced by a similar decline from (suboptimal)

baseline in glycosylated hemoglobin (HbA_{1c}) and a similar proportion of patients achieving a target HbA_{1c} < 7%^{11–14}. A recent abstract published on a 12-week study with the AIR (HIIP) inhaler also demonstrated equivalent changes in HbA_{1c} with AIR (HIIP) taken in combination with glargine compared with a SC lispro or regular insulin plus glargine regimen¹⁵. In spite of the fact that inhaled insulins are administered with meals, all studies have pointed out a greater reduction in fasting plasma glucose levels compared with SC insulin comparators^{11,12,14,16}. The reasons for this are not completely clear, but initial animal studies suggest that insulin inhalation results in a unique action on non-hepatic glucose clearance¹⁶. Compared with SC insulin, some studies suggest that treatment of Exubera was associated with a trend for less weight gain^{11,12}. For example, in one study where patients received either Exubera plus twice-daily NPH or an SC insulin regimen comprised of four daily injections (two of regular human insulin during meals versus two NPH), the adjusted treatment group difference in change from baseline in body weight was –0.19 kg (95% confidence interval [CI] –0.91 to 0.53)¹². Efficacy data suggest that inhaled insulin is as effective as subcutaneously administered insulin in matching the physiological needs of patients with type 1 diabetes.

Type 2 diabetes

While insulin therapy is mandatory in patients with type 1 diabetes, treatment of type 2 diabetes requires a different approach, depending on the stage of progression of the disease. Type 2 diabetes treatment algorithms typically start with a diet and exercise regimen, followed by single and then combination therapy with oral antidiabetic agents (OA) and finally SC insulin. To date, Exubera is the only inhaled insulin formulation that has been extensively studied at each of these stages.

Similar to what was observed for type 1 diabetic patients, substituting SC mealtime insulin with inhaled insulin allowed maintenance of glycemic control as indicated by comparable levels of HbA_{1c}. Three studies with different types of inhaled insulins (Exubera, AERx [iDMS] and KOS) have demonstrated comparable declines from baseline HbA_{1c} with inhaled insulins when compared with various SC insulin regimens (including mixed regular insulin, NPH, and fast-acting human insulin) in patients with type 2 diabetes^{17–20} (Table 1). Exubera resulted in improved overall glycemic control when added to, or substituted for, dual OA therapy^{21–23} (Table 1; Figure 2). For example, both in patients failing sulfonylurea therapy²¹, and in patients failing metformin therapy²² (HbA_{1c} 8–12%), Exubera demonstrated greater reductions from

Table 1. Summary of studies performed with inhaled insulins in patients with type 2 diabetes

Reference	Study duration	n	Inhaled insulin regimens	Inhaled insulin – mean change in HbA _{1c} from baseline, %	Comparator regimens	Comparator – mean change in HbA _{1c} from baseline, %	Treatment comparison
Rosenstock <i>et al.</i> ¹⁷	12 weeks	119	Premeal Technosphere pulmonary insulin	–0.76	Inhaled Technosphere placebo	–0.32	$p = 0.0019$
Hollander <i>et al.</i> ¹⁸	24 weeks	298	Premeal Exubera plus bedtime Ultralente	–0.07	At least two daily injections of SC insulin	–0.6	Adjusted treatment group difference: –0.07%, (95% CI –0.32 to 0.17)
Hermansen <i>et al.</i> ¹⁹	12 weeks	107	Premeal AERx (iDMS) plus evening NPH insulin	–0.69	Mealtime fast-acting SC insulin plus evening NPH insulin	–0.77	$p = 0.60$
Barnett <i>et al.</i> ²¹	24 weeks	427	Premeal Exubera	–2.06	Metformin added to sulphonylurea	–1.83	Adjusted treatment group difference: –0.2% (95% CI –0.40 to –0.05); $p = 0.014$
Barnett <i>et al.</i> ²²	24 weeks	476	Premeal Exubera	–2.03	Sulphonylurea added to metformin	–1.88	Adjusted treatment group difference: –0.2% (95% CI –0.34 to 0.01); $p = 0.058$
Rosenstock <i>et al.</i> ²³	12 weeks	306	Premeal Exubera, or premeal Exubera plus dual OAs	–1.9	Dual OAs	–0.2	NA
DeFronzo <i>et al.</i> ²⁴	12 weeks	145	Premeal Exubera	–2.3	Rosiglitazone twice daily	–1.4	Adjusted treatment group difference: –0.89% (95% CI –1.23 to –0.55)
Hausman <i>et al.</i> ²⁵	28 days	24	Premeal Kos	–1.23	Bedtime insulin glargine	–1.05	NA

CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; NA = not available; OAs = oral antidiabetic agents; SC = subcutaneous

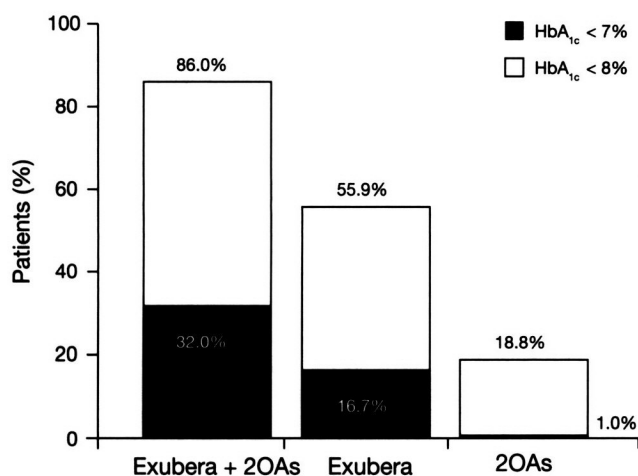


Figure 2. Percentage of patients achieving target HbA_{1c} < 7% and < 8% with Exubera, oral antidiabetic agents (OAs), and Exubera in combination with OAs (Exubera + OAs). With permission from Rosenstock et al.²³. HbA_{1c} = glycosylated hemoglobin

baseline compared with adding metformin²¹ or adding a sulfonylurea²². In addition, when Exubera was used as first-line therapy in patients failing a diet/exercise regimen²⁴, it resulted in a 1.3% reduction in HbA_{1c} and 44% of patients reaching target HbA_{1c} < 7.0% after 12 weeks. However, it is recognized that the comparator used in this study, rosiglitazone, may take up to 24 weeks to exert its full effect. Interestingly, improvement of glycemic control, as obtained with KOS inhaled insulin during a 28-day study²⁵, was associated with a lowering of serum triglycerides.

In summary, the Exubera clinical trial program has provided detailed information about the role of inhaled insulins at various different stages of type 2 diabetes treatment algorithm. From these data, treatment with inhaled insulin provides an opportunity for initiating insulin treatment without further delay in patients with type 2 diabetes patients with secondary failure to OAs.

Safety

The safety profile of SC insulin has been well established. Exubera is the only inhaled insulin formulation that has reported detailed safety data to date on general adverse events, respiratory adverse events, pulmonary safety, and insulin antibodies from several Phase 2 and 3 studies^{11,12,18,20-24}. Data published from other inhaled insulins in development are currently limited or mostly presented in abstract form only^{15,17,19,25}.

Overall, inhaled insulins seem to be well tolerated. The frequency and nature of adverse events is similar between treatment groups, and most adverse events are characterized as mild to moderate^{11,12,18,20-24}. Exubera

is not indicated for children, adolescents or pregnant women²⁶.

As is the case with SC insulin, hypoglycemia is the most commonly reported adverse event with all inhaled insulins (Exubera, AERx [iDMS], Technosphere pulmonary insulin, AIR [HIIP], KOS)^{11,12,14,15,17-19,21-23}. Studies have consistently reported that in patients with type 1 or type 2 diabetes, the overall nature, frequency and severity of hypoglycemic events with inhaled insulins are similar to that of SC insulin^{11,12,14,15,18,19-24}. In patients with type 2 diabetes not adequately controlled by OAs, Exubera was associated with an increased risk of hypoglycemia when compared with comparator add-on OA therapy²¹⁻²⁴. To the authors' knowledge, AIR (HIIP) insulin is the only formulation that has reported an increased risk of nocturnal hypoglycemia¹⁵, and hypoglycemic rates have not yet been reported with Technosphere pulmonary insulin system. There was also a small imbalance in chest pain between Exubera and comparator groups (4.7% vs. 3.2%, respectively), although more than 90% of events were classified as mild or moderate²⁶.

When considering respiratory adverse events, studies with Exubera have reported a greater incidence of cough than comparator therapies. However, cough occurred within minutes of dosing, was mild, decreased with continued use, and rarely resulted in treatment discontinuation (1.2% of patients)²⁶. Studies with Exubera have also reported dyspnea, although most events are mild to moderate, and only 0.4% of patients discontinued therapy due to dyspnea (compared to 0.1% for patients receiving comparator therapies)²⁶. One study with the KOS formulation reported no difference in pulmonary adverse events between patients receiving inhaled insulin and those receiving insulin glargine²⁵.

Pulmonary function is an important aspect of the safety profile for any compound delivered via the lungs. Exubera is the only inhaled insulin formulation for which pulmonary function has been studied extensively and in detail; data from studies of up to 2 years' duration in patients with type 1 or type 2 diabetes, some of which used highly standardized pulmonary function methodology have been collected²⁷. Pulmonary function data from other inhaled insulins, with unclear rigor regarding pulmonary function methodology, thus far consist of two published studies (AERx [iDMS] and AIR [HIIP])^{15,19} and several abstracts (KOS and Technosphere pulmonary insulin)^{17,25}.

In published reports of 12- or 24-week studies with Exubera, AERx (iDMS), Technosphere pulmonary insulin, and AIR (HIIP), the changes in lung function are small and are usually comparable between groups^{11,12,14,15,17-19,23,28}. Where treatment group differences were observed, these occurred early (Exubera¹³),

were not clinically relevant (Exubera and AIR [HIIP])^{11,12,14,15,20}, and were reversible upon treatment discontinuation (Exubera, AERx [iDMS], and AIR [HIIP])^{13,15,19}. The only reported longer-term study has been performed with Exubera. This study showed that after the small, early differences between groups, the rate of change in lung function remained similar to comparator for up to 2 years of continuous dosing^{14,20}.

The available safety data (predominantly from Exubera studies) show alterations in pulmonary function are minor, occur early, are non-progressive for up to 2 years, and reversible upon discontinuation. However, because of the expected long duration of use of inhaled insulins, comprehensive even longer-term pulmonary studies are required for unequivocal conclusions.

Nonetheless, assessment of pulmonary function is recommended after 6 months of Exubera therapy, and annually thereafter, even in the absence of pulmonary symptoms²⁶. Patients who have a decline of $\geq 20\%$ of forced expiratory volume in 1 second (FEV₁) from baseline are encouraged to repeat pulmonary function tests; if the $\geq 20\%$ decline from baseline is repeated, Exubera should be discontinued. Exubera is not recommended for use in patients with baseline FEV₁ or carbon monoxide diffusing capacity (DL_{co}) $< 70\%$ of predicted value.

A large meta-analysis of several Exubera Phase 2/3 studies²⁹ and one study with AERx (iDMS)¹⁹ have demonstrated that antibody levels are higher with inhaled insulins than with comparator therapies. So far, no clinical consequences of insulin antibodies have been identified; insulin antibodies do not impact on insulin pharmacodynamics, glucose control, or lung function^{19,29}. Interestingly, small increases in immunoglobulin IgE were observed in four patients receiving AERx (iDMS)¹⁹, whereas studies with Exubera have only reported (IgG) antibodies²⁹. There was no induction of insulin antibodies with Technosphere pulmonary insulin¹⁷ and there are no data available on antibodies for the AIR (HIIP) formulation.

Patient preference, satisfaction, and quality-of-life measures

Novel insulin formulations must not only be efficacious and safe, but also facilitate treatment compliance. This is especially important in diabetes where treatment regimens are often complex and involve patient's self-management. Patient satisfaction with their therapeutic regimen can encourage treatment compliance, which in turn may improve treatment outcomes⁸.

One study was specifically designed to investigate patient satisfaction in subjects with type 1 ($n = 70$), or type 2 ($n = 51$) diabetes receiving Exubera or SC insulin. Patients were randomized to Exubera or SC insulin therapy (two to three injections per day based on patient's usual split/mixed regimen) in 12-week parent studies. After 12 weeks, patients were given a choice to continue on their existing therapy or switch therapies for a further 1-year extension. A pooled analysis of patients with type 1 or type 2 diabetes showed that 85% of patients treated with Exubera chose to stay on Exubera for the 1-year extension. In contrast, 75% of patients initially randomized to SC insulin chose to switch to Exubera therapy during the 1-year extension³⁰. Furthermore, at the 1-year visit in the extension studies, significantly greater improvements were observed in overall satisfaction (37.9% for the Exubera group vs. 3.1% for the SC group; $p < 0.01$) and ease of use (43.2% with Exubera vs. -0.9% with SC insulin; $p < 0.01$). These results are consistent with the findings observed from baseline to 12 weeks of the parent studies.

These data are supported by findings from two individual 6-month Exubera studies and one study with AIR (HIIP)^{11,18,31}. Favorable effects were associated with Exubera in satisfaction subscales (e.g. advocacy, burden, convenience, flexibility, general satisfaction, hassle, interference, preference). Furthermore, Exubera treatment was associated with more favorable improvements in overall quality of life and health perceptions ($p < 0.05$ in both studies). A study with AIR (HIIP) inhaled insulin also demonstrated greater insulin delivery system satisfaction ($p < 0.001$) versus SC insulin³¹.

In the Exubera Real World Feasibility Study, treatment preferences were investigated by questionnaire upon receiving educational information about potential risks and benefits of currently available therapies and Exubera. In this hypothetical scenario, almost three times more patients would choose to initiate insulin if Exubera was available as an option (43.2%), compared with patients offered the standard choices alone (15.5%)³² (Figure 3), suggesting that Exubera may increase patient acceptance of insulin, encourage earlier initiation of insulin-based therapeutic regimens and help patients achieve glycemic control.

Limitations

Although there are various formulations of inhaled insulin, these are at different stages of clinical development. The predominant body of data originates from the extensive Phase 2 and 3 studies with Exubera, many of which have been published in peer-reviewed journals.

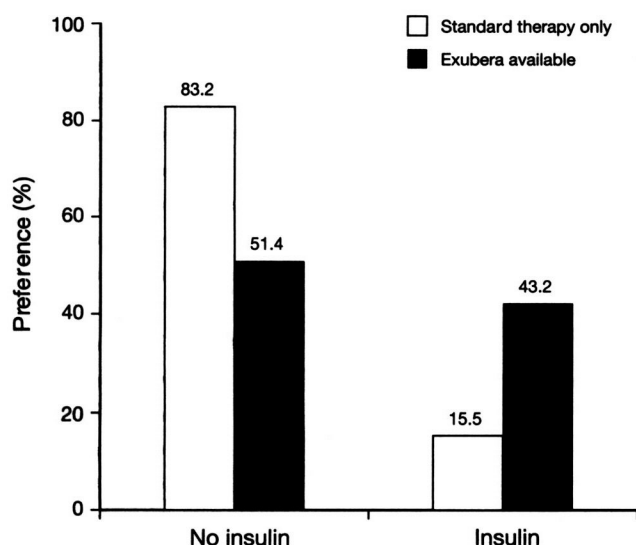


Figure 3. Proportion of patients choosing insulin-based therapeutic regimens when standard therapies only (white bars) or standard therapies plus inhaled insulin (black bars) were available as theoretical choices. With permission from Freemantle et al.³²

For the other formulations – AERx, AIR, Technosphere, and KOS – only Phase 2 studies have been published in journals (AERx and AIR), or in congress abstracts. Based on the data available, there are some findings that seem consistent between the different formulations. However, before head-to-head comparisons are performed, one major limitation is that data reviewed here are from different studies. Therefore, it is currently difficult to elucidate whether the findings are specific for one formulation, or a general class effect.

Conclusion

Ensuring strict glycemic control still remains the best strategy for the prevention of long-term complications of diabetes. This requires intensive insulin regimens in type 1 diabetes and prompt introduction of insulin therapy in type 2 diabetes. Nonetheless, appropriate use of adequate strategies of insulin therapy have been hampered by the limited compliance of patients and, too often, of physicians. Non-invasive insulin administration may now provide a means to gain some of the necessary confidence of insulin-based therapeutic regimens. In particular, the first inhaled mealtime insulin (Exubera) was recently approved in the United States and European Union for the treatment of adult patients with type 1 or type 2 diabetes. The extensive efficacy data from Exubera studies and information published so far on other inhaled insulins, suggest equivalent efficacy to SC insulin in patients with type 1 or type 2 diabetes. Furthermore, in patients with uncontrolled type 2 diabetes ($HbA_{1c} > 8\%$), Exubera alone or in combination

with OA therapy, achieved superior reductions in HbA_{1c} when compared with OA therapy. Detailed data on pulmonary function and adverse events indicate that Exubera is well tolerated, and patient-reported outcomes studies suggest that patients receiving Exubera are more satisfied with their therapy. More extensive data from other inhaled insulin formulations are expected in the future, and long-term surveillance studies will be needed to fully exploit the potential benefits of these new forms of insulin administration.

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Note on research

In preparing this article, the authors searched for references to inhaled insulin in the Medline database and in congress abstracts of the American Association of Clinical Endocrinologists (AACE), the American Diabetes Association (ADA), the American Thoracic Society (ATS), the European Association for the Study of Diabetes (EASD), and the European Respiratory Society (ERS) from 1998 to 2006.

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