



Inhaled Insulin—Its Incorporation into the Diabetes Treatment Regimen

a report by

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Insulin remains the mainstay of therapy for type 1 diabetes, and the incorporation of insulin therapy into late-stage type 2 diabetes has resulted in improvements in quality of life and glucose control. Since its discovery in the early half of the 20th century, insulin has evolved dramatically. The modern insulin armamentarium now includes humanized formulations that cover a wide range of properties, from long-acting to rapid action. However, the administration of insulin is still dependent on the injection route. While different routes of administration have been studied for decades, it was not until recently that technological advances made it possible to move insulin therapy into a new era—that of non-invasive insulin administration. Several strategies are in development, including inhaled, transdermal, and oral insulin formulations.

The most studied alternative—and the most clinically advanced—is the delivery of insulin via inhalation into the pulmonary system. The pulmonary route offers a number of advantages, the most prominent of which is that the highly vascularized alveolar surface is highly permeable to peptides, in contrast to the relatively impermeable upper airways. Furthermore, inhaled insulin provides both clinicians and patients with greater options in terms of glycemic control. There are currently several forms of inhaled insulin, of which only one, Exubera, has been approved for use by regulatory bodies in the US and Europe. Since it is the only approved inhaled insulin to date, more data have been collected for Exubera compared with the other investigational products. The goals of diabetes treatment and the therapeutic potential of inhaled insulin are discussed in this review, with a focus on the efficacy and safety of inhaled insulin and its application in the clinic.

Insulin Therapy

There is increasing evidence that, in diabetes, maintaining glucose control—as measured by glycemic levels (HbA_{1c})—as close to normal physiological ranges as possible plays a major role in preventing and minimizing the development of microvascular and macrovascular complications. Indeed, landmark studies such as the UK Prospective Diabetes Study (UKPDS), the Diabetes Control and Complications Trial (DCCT), and its follow-up trial, the Epidemiology of Diabetes Interventions and Complications (EDIC) Study, have provided compelling evidence that microvascular and macrovascular diabetes complications are reduced with improved glycemic control.¹⁻⁴ Recent guidelines from the American Diabetes Association (ADA) suggested that the goal for HbA_{1c} should be <7%, while the International Diabetes Federation has an even lower goal of <6.5%.^{5,6} However, these goals must be placed into a clinical context of potential complications and significant side effects, such as hypoglycemia.

A recent analysis of two US National Health and Nutrition Examination Survey (NHANES) periods indicated that we are still far from meeting goals for glucose control in the majority of patients. Moreover, glycemic control may have actually worsened over the past 20 years, particularly in the type 2 diabetes population. For the NHANES data period 1988–1994, 45% of adult patients with type 2 diabetes had an HbA_{1c} <7%. In comparison, in the later NHANES data period of 1999–2000, only 36% of patients achieved an HbA_{1c} of less than 7%.⁷

This decline may be partly explained by the fact that although many type 2 diabetes patients will eventually require intensive insulin therapy to achieve adequate blood glucose control as the disease progresses, a large number of patients remain on suboptimal therapy for two to three years before insulin is added to their treatment regimen.^{8,9} Moreover, within this patient population the need for multiple daily insulin injections may be burdensome, with typical patient concerns such as fear of and difficulty with administration and concerns about side effects contributing to treatment acceptance.^{10,11} Furthermore, physicians may also delay prescribing insulin therapy.^{10,12} These factors can increase the risk of suboptimal glycemic control, which can affect the long-term health outcomes of diabetic patients. Thus, there is a need to decrease the above risks. Recent joint guidelines from the ADA and the European Association for the Study of Diabetes (EASD) advocate a more aggressive treatment approach for type 2 diabetes. These include early use of oral medication and earlier use of insulin therapy.¹³ In light of the new algorithm and the need to decrease the risks described above, non-invasive insulin may be a helpful therapeutic option.

Inhaled Insulin

In theory, the ideal diabetes therapy regimen should mimic normal physiological insulin release. The treatment regimen should be tailored to the patient's degree of hyperglycemia and to the risks associated with hypoglycemia. Comorbid conditions, the ability of the patient to

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adhere to a routine, and the cost are also important considerations when choosing an appropriate regimen. Moreover, pre-prandial and post-prandial glucose (PPG) play an important role in glucose control and, as such, both need to be considered when deciding on a treatment strategy, whether oral agents and/or insulin. Fasting plasma glucose (FPG) has a greater contribution to hyperglycemia in patients with high levels of HbA_{1c}. In contrast, PPG is a more important contributor to hyperglycemia in patients who are closer to normal HbA_{1c} levels.¹⁴ Therefore, as patients approach their HbA_{1c} goal, the need to manage PPG increases.

Insulin augmentation therapy is effective in type 2 diabetes patients who are failing to maintain their HbA_{1c} goal while taking oral medications.¹⁵ Augmentation therapy with insulin may be started by adding a long-acting insulin to an oral agent regimen to provide basal insulin. As the disease progresses, especially in type 2 diabetics, the addition of pre-prandial bolus or short-acting insulin may eventually be required. Pre-prandial administration of bolus insulin provides fewer post-prandial glucose

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fluctuations, and replacement therapy using a basal-bolus insulin regimen is indicated for patients who need intensive control or have failed augmentation therapy.

It is in these settings that inhaled insulin may be most effective—as a replacement in insulin augmentation therapy or as a replacement for several bolus injections. Exubera's pharmacokinetic profile mimics the normal physiological pattern of insulin secretion in response to a meal. Furthermore, it provides a initial rise in plasma insulin levels similar to rapid-acting insulin analogs, and has a duration of action that is comparable to subcutaneous regular insulin.¹⁶

The safety and efficacy of Exubera have been evaluated in over 2,700 adults with type 1 and type 2 diabetes. The trials were regulatory studies intended to show non-inferiority to existing treatment regimens. In each trial, efficacy was assessed using HbA_{1c} as the primary outcome.

In the type 1 diabetes setting, pre-prandial administration of Exubera was shown to provide similar glycemic control to pre-prandial subcutaneous insulin regimens containing rapid-acting regular insulin as part of conventional or intensive therapy.^{17–20}

In type 2 diabetes, Exubera has been compared with oral antidiabetic agents and with a subcutaneous rapid-acting insulin regimen and as initial

antidiabetic therapy. In the initial therapy setting, pre-prandial Exubera was compared with rosiglitazone (4mg twice a day) in type 2 diabetes sub-optimally controlled on diet and exercise. Both treatment groups experienced a fall in HbA_{1c}, but the decrease in the Exubera group was significantly greater (-2.3% versus -1.4%).²¹ In a 12-week study, addition of pre-prandial Exubera to an oral regimen containing a sulfonylurea and/or metformin in patients inadequately controlled with oral agents significantly improved glycemic control compared with those on oral agents alone.²² Similarly, in subjects failing dual oral therapy, Exubera provided greater improvements in blood glucose control than did continued oral therapy, either administered alone or in addition to existing oral therapy.²³ In two open-label, randomized trials, Exubera significantly improved glycemic control in patients uncontrolled on a single oral agent (HbA_{1c} >9.5%) compared with adjunctive oral therapy.^{24,25}

Exubera has also been evaluated as part of a conventional insulin regimen in type 2 diabetes patients. An initial 12-week study in patients treated with standard subcutaneous insulin regimens or pre-prandial Exubera plus a single ultralente insulin injection at bedtime showed that both treatment regimens produced a mean HbA_{1c} reduction of approximately 0.7%.²⁶ A 24-week study of pre-prandial Exubera plus ultralente insulin versus a conventional subcutaneous insulin regimen that included regular and NPH insulin saw comparable decreases in HbA_{1c} in both groups.²⁷ A meta-analysis of inhaled insulin therapy trials in both type 1 and type 2 diabetes concluded that inhaled insulin offered a non-invasive alternative to pre-prandial subcutaneous insulin, with comparable efficacy to the injectable formulations.²⁸

Interestingly, Exubera has also demonstrated improvement in FPG and equivalence of reduction of PPG concentrations compared with subcutaneous insulins in type 1 and type 2 diabetes patients.^{19,20,26} Furthermore, weight gain, which is an important consideration in the control of diabetes and one of the concerns raised with respect to inhaled insulin, was reported to be less in with Exubera-treated patients compared with subcutaneous insulin.²⁷

Safety of Inhaled Insulin

In the Exubera clinical development program, Exubera-related adverse events were generally mild to moderate in severity, and discontinuation rates were low. Hypoglycemia, which is the most common side effect observed with insulin therapy, was similar in severity and incidence for both inhaled and subcutaneous insulins.^{19,20,27} The incidence of hypoglycemia was higher with adjunctive Exubera compared with adjunctive oral antidiabetic therapy.^{21,23–25}

Respiratory Adverse Events

A major concern in the development and use of inhaled insulin was pulmonary safety. In clinical trials, cough of mild to moderate severity has been reported in approximately 21–31% of patients receiving Exubera. The incidence and prevalence of cough generally decreased over time with therapy. Very few patients (1.2%) discontinued Exubera treatment due to cough.^{19–21,24,27}

The effect of Exubera on pulmonary function has been extensively studied in clinical trials. The spirometric measurement of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) has been used to look for the effects of inhaled insulin on airflow and airway

function. Lung volumes—and especially carbon monoxide diffusing capacity of the lung (DLCO)—have been examined to establish any effect of inhaled insulin on pulmonary parenchyma. Initial studies showed a small decrease in FEV1 in Exubera-treated patients compared with those given subcutaneous insulin or oral antidiabetes medications. In a randomized trial in type 1 diabetes patients, Exubera provoked no acute changes in FEV1 either 10 minutes or 60 minutes after a dose, both initially and even after 12 weeks of therapy. After the 12 weeks, FEV1 declined by 65ml in Exubera-treated patients versus 53ml in comparator patients compared with pre-treatment values. The mean decline in FEV1 in the Exubera group occurred early, was not progressive, and was never more than 1.3% of baseline FEV1. Furthermore, treatment group differences in FEV1 resolved within two weeks of discontinuation of inhaled insulin.²⁹

Studies have shown no significant differences in total lung capacity between patients on Exubera and those on comparator agents.^{18,23,27} However, most short-term studies have shown a small but consistent decrement in DLCO in inhaled insulin patients compared with those on oral antidiabetes medications or subcutaneous insulin.

It must be noted that exclusion criteria in many of the trials included patients with any significant or poorly controlled lung disease; FEV1 <70% (predicted); DLCO <70% (predicted); total lung capacity <70% (predicted); and a history of smoking within the prior six months. Due to the wide variations in absorption of inhaled insulin observed with smoking, cigarette smoking is a contraindication to use of inhaled insulin.

Patient Characteristics

Due to the exclusion criteria of the Exubera clinical program, inhaled insulin is contraindicated in patients who have smoked within the past six months and/or who have unstable or poorly controlled lung disease. Moreover, Exubera is not recommended for patients with asthma, chronic obstructive pulmonary disease, or interstitial lung disease. It is also recommended that patients undergo a pulmonary assessment prior to initiation of inhaled insulin therapy, including measurements of FEV1 and DLCO and chest X-ray.

Conclusion

Inhaled insulin has been studied extensively in patients with type 1 and type 2 diabetes and has been found to be as effective as subcutaneous insulin. In all studies, inhaled insulin was shown to be as effective as the injected insulin regarding change in HbA_{1c} level. The efficacy of inhaled insulin has also been studied in patients with type 2 diabetes who were on different oral agents, as well as in drug-naïve patients. Similarly, these studies demonstrated that inhaled insulin was effective in providing glycemic control. The goal of improving and maintaining glycemic control to minimize the risk of future microvascular and macrovascular complications remains elusive.

Reducing some of the barriers to insulin therapy has the potential to improve clinical outcomes and quality of life in patients with diabetes, and the availability of a non-invasive alternative offers both patients and physicians another tool in their efforts to achieve glycemic control. With other inhaled insulin delivery systems also in development, the therapeutic options will greatly increase. ■

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