

Inhaled Insulin in Patients with Asthma and Chronic Obstructive Pulmonary Disease

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ABSTRACT

The effect of inhaled insulin in subjects with diabetes and chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), is of particular interest because these diseases are quite common, and it is likely that patients with asthma or COPD who are poorly controlled on oral agents and are reluctant to start subcutaneous insulin would benefit from inhaled insulin to improve their glucose control. Since patients with asthma or COPD have varied pulmonary symptoms and abnormal pulmonary function, it is important to establish the pulmonary safety and efficacy of inhaled insulin in subjects with diabetes and asthma or COPD. Pharmacokinetic and pharmacodynamic studies in non-diabetic subjects with asthma consistently show lower absorption of inhaled insulin and lesser glucose lowering effects by ~30–40%, as compared to subjects without asthma. Thus, it would be expected that the dose of insulin required to obtain equivalent glycemic control would be higher by ~30–40% in subjects with asthma and diabetes (as compared to subjects without asthma but with diabetes). However, prior administration of a bronchodilator inhaler in individuals with asthma and diabetes reverses airway obstruction and thus may obviate the need for increased insulin requirements. In contrast to patients with asthma, in patients with COPD and diabetes, the absorption of inhaled insulin appears to be variable (higher or lower than in non-COPD subjects). Whether this variability is secondary to differences in inhalation devices or different study populations is not clear at present. Overall, data from the clinical studies indicate that inhaled insulin is effective and well tolerated in subjects with diabetes and chronic lung disease. However, preliminary, limited data from the longer-term clinical studies suggest that there is a marginally greater decline in pulmonary function tests in subjects with asthma/COPD and diabetes compared to subjects with diabetes and no chronic lung disease. Thus, there is a clear need for longer-term studies in subjects with diabetes and chronic lung disease in order to further clarify the safety and efficacy of inhaled insulin in this population.

INTRODUCTION

INTENSIVE INSULIN THERAPY has been clearly demonstrated to reduce long-term complications in patients with type 1 and type 2 diabetes.^{1,2} Many patients with type 2 diabetes who fail oral agents are unwilling to start/take

daily insulin injections and delay starting insulin therapy.³ Prominent among the reasons for reluctance to start insulin in the majority of individuals is the anticipated difficulty/pain with insulin injections.⁴ The recent availability of inhaled insulin represents a noninvasive delivery system that would possibly overcome

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this reluctance and improve patient compliance with insulin treatment.⁵

Several studies to date have demonstrated not only the pharmacokinetics (PK) and pharmacodynamics (PD) of inhaled insulin,^{6–8} but also its safety and efficacy in patients with type 1 and type 2 diabetes.^{9,10} Results from these studies indicate a clear dose–response relationship between escalating doses of inhaled insulin and PK/PD parameters.⁸ In patients with type 1 and type 2 diabetes and no chronic lung disease, inhaled insulin is not only well tolerated, but also improves glycemic control to a similar extent as subcutaneous (SQ) insulin injection.^{9,10} However, the PK/PD of inhaled insulin and its safety and efficacy in patients with diabetes and chronic lung disease, including asthma and chronic obstructive pulmonary disease (COPD), still need to be fully characterized. Asthma is a chronic inflammatory disorder of the airways characterized by episodes of wheezing, shortness of breath, chest tightness, and cough and is among the most common chronic diseases in the United States, affecting an estimated 16 million (7.5%) U.S. adults in 2004.¹¹ In addition, more than 12 million people in the United States have been diagnosed with COPD—a progressive condition that includes emphysema and chronic bronchitis, both chronic inflammatory diseases of the lungs.¹² Post hoc analysis of data from the Nurses' Health Study even suggests that COPD may be a risk factor for developing type 2 diabetes.¹³ Although the exact prevalence of diabetes in those with chronic lung disease is not known, but given the above numbers, it is likely to be considerable, and patients with diabetes and chronic lung disease would also benefit from the option of a noninvasive delivery system for insulin administration like inhaled insulin.

However, the use of inhaled insulin in patients with diabetes and chronic lung disease will have to be considered in the context of a small, but significant, decline in forced expiratory volume in 1 s (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO), which occurs shortly (within 3 months) of starting inhaled insulin in people with normal pulmonary function.^{14,15} It is, however, comforting to note that in the studies to date, after this initial small decline in FEV1 and DLCO, the further rate of decline in DLCO and FEV1 is the same as that in com-

parator groups treated with SQ insulin or oral antidiabetic agents.^{14–16} Also, in one of the studies so far, when inhaled insulin was discontinued for 6 weeks, there was a reversal of the initial, early small decline in FEV1 and DLCO.^{15,16} Currently, inhaled insulin (Exubera®, Pfizer Inc., New York, NY) (using the device from Nektar, San Carlos, CA) is not approved for subjects with diabetes and asthma, COPD, or other chronic lung disease.¹⁶ Subjects with diabetes who start inhaled insulin are required to have pulmonary function tests (PFTs) measured at baseline, after 6 months, and periodically thereafter.¹⁶

Optimal delivery of insulin into the deep lung is affected by several factors, including particle size and other factors related to the insulin delivery device. Optimal pulmonary insulin delivery is also greatly affected by several respiratory factors, including inspiratory effort, tidal volume, peak flow, etc.^{17–19} In studies with one of the insulin inhalation devices—the AERx® insulin diabetes management system (iDMS) device (Novo Nordisk, Princeton, NY; Aradigm Corp., Haywood, CA)—it was noted that the PK and PD parameters of inhaled insulin were affected by certain respiratory maneuvers and that significantly less insulin absorption was observed when aerosol delivery occurred during a shallow inspiration.¹⁹ Subjects with asthma and COPD have altered pulmonary function, and the distribution and absorption of inhaled insulin could be affected by the degree of airflow obstruction and other pathophysiological changes in these patients. There is also the concern that pulmonary delivery of insulin could potentially evoke a hyper-reactivity reaction of the airways in these subjects and trigger an acute attack of asthma.

In this article, we will discuss the PK, PD, safety, and clinical efficacy of inhaled insulin in subjects with asthma and COPD.

INHALED INSULIN AND ASTHMA

PK/PD of inhaled insulin in subjects with asthma

The first published study investigating the PK/PD of inhaled insulin in patients with asthma was done in subjects with chronic asthma who did not have diabetes²⁰ (Table 1). This study was an open-label, two-part, paral-

TABLE 1. ABSORPTION AND GLUCOSE LOWERING EFFECT OF INHALED INSULIN

<i>Study reference, device</i>	<i>Dose of inhaled insulin</i>	<i>Number of participants</i>	<i>Mean age (years)</i>	<i>Inhaled insulin absorption</i>	<i>Glucose lowering effect of inhaled insulin</i>
Henry et al., ²⁰ Novo-Nordisk insulin/AERx device	Single dose of 1.57 mg (equivalent of 45 units SQ) on 2 different dosing days	28 without asthma, FEV1 98%, FEV1/FVC 97% 17 with asthma, FEV1 77%, FEV1/FVC 83%	31		
Pfizer data submitted to the FDA (2006), ¹⁵ Pfizer Exubera insulin/Nektar device	Not known	Not known	Not known	Decreased by 26% compared to healthy patients without asthma Decreased by 20–30% in those with asthma compared to those without asthma	Decreased by 30% compared to healthy patients without asthma Not known
Rave et al., ²¹ Lilly HIIP insulin/Alkermes device	Single dose of 5.2 mg (equivalent of 12 units SQ) HIIP on 2 different dosing days	15 healthy controls 15 subjects with chronic bronchitis 15 subjects with emphysema	38 53 58	Decreased by 44% compared to healthy controls Decreased by 22% compared to healthy controls	Decreased by 40% compared to healthy controls Decreased by 33% compared to healthy controls
Pfizer data submitted to the FDA (2006), ¹⁵ Pfizer Exubera insulin/Nektar device	Not known	12 health controls 12 subjects with chronic bronchitis and emphysema	Not known	Increased by 50% compared to non-COPD controls	Not known

lel-group study in which subjects with chronic asthma were compared to healthy subjects without asthma. The subjects with asthma were taking only short-acting inhaled β -adrenergic agonists or anticholinergic inhalers for treatment of their asthma. They had an FEV1 between 50% and 80% while β -agonist treatment was withheld for 6 h. Inhaled insulin was delivered by the AERx iDMS (developed by Aradigm Corp. with Novo Nordisk) as a pulmonary drug delivery system for liquid formulations of insulin. In the first part of the study, PK/PD parameters were evaluated after the subjects were given a fixed dose of 1.57 mg of liquid insulin (the equivalent of 45 units of insulin SQ) delivered by the AERx iDMS on two separate dosing days. In the second part, a single large dose of 4.7 mg (equivalent of 135 IU SQ) of insulin was inhaled by the subjects to assess the acute effect a large dose of inhaled insulin on pulmonary function.

The PK data after the administration of the equivalent of 45 units of insulin revealed that the values for the insulin area under the curve (AUC) from 0 to 360 min after inhaled insulin were significantly lower by 36% in the asthmatic subjects as compared to the healthy subjects without asthma ($P = 0.013$). Since the asthma patients in this study had a mean FEV1 of 77% (compared to 98% in the group without asthma), it is possible that reduced alveolar delivery of inhaled insulin could have contributed to this decrease in insulin absorption. However, the maximum concentration ($C_{\max}$) and time to maximum concentration ($T_{\max}$ for insulin were not different between the subjects with and without asthma. Consistent with the PK data showing lower absorption of insulin, the PD data [glucose area over the curve (AOC) from 0 to 360 min] also revealed that there was a lesser lowering of the serum glucose by 43% in subjects with asthma when compared to healthy subjects ($P = 0.007$). Data from this study also revealed that subjects with asthma had greater intrasubject variations in insulin AUC_{0-360} and $C_{\max}$ values than healthy subjects (coefficient of variation 47% vs. 27% and 48% vs. 25%, respectively). However, the intrasubject variability for glucose AOC_{0-360} was similar between healthy subjects and those with asthma. It should also be noted that in this

study, the PK and PD profile of inhaled insulin in those with asthma was similar (albeit at a lower level than that in those without asthma). Further, the greater variability in insulin absorption was not associated with a larger variability in glucose lowering effect. This would suggest that for a given dose of inhaled insulin, a consistent reduction in plasma glucose can be expected when inhaled insulin is administered to subjects with asthma.

Results similar to the above study were obtained for Exubera inhaled insulin.¹⁵ Data submitted by the company (Pfizer Inc.) to the Food and Drug Administration (FDA) at the time of the approval hearings indicated that the AUC and $C_{\max}$ for inhaled insulin were consistently lower by 20–30% in subjects with asthma when compared to healthy subjects.

It should be noted that the above PK/PD data are only from subjects with asthma who did not have diabetes. At the current time, there are no published data on PK/PD parameters in subjects with asthma who also have diabetes. However, there is no reason to believe that the PK/PD findings will be different in subjects with diabetes and asthma when compared to subjects without diabetes but with asthma.

Effects of inhaled bronchodilator/steroid therapy on inhaled insulin

In subjects with both diabetes and asthma, it is clinically important to assess the implications of administering inhaled insulin and inhaled bronchodilators/steroids concomitantly, since both share a common route of absorption. In a recent study Teeter et al.²² studied the effects of prior administration of albuterol (a short-acting bronchodilator) and fluticasone (an inhaled corticosteroid) on the pharmacokinetics of Exubera inhaled insulin in 67 subjects with mild-to-moderate asthma but without diabetes. The results demonstrated that prior administration of albuterol by 30 min increased the insulin $C_{\max}$ and AUC_{0-360} by ~25–35% in patients with mild asthma and by ~45–50% in patients with moderate asthma relative to the administration of inhaled insulin without albuterol. Interestingly, the increased bioavailability of inhaled insulin following prior albuterol administration resulted in mean AUC and $C_{\max}$

values that approximated those in healthy subjects without asthma. Of note is that prior administration of fluticasone had no significant effect on the PK of inhaled insulin. Although this study was performed in subjects without diabetes but with asthma, it is likely that the results will be similar in subjects with diabetes and asthma, and hence in these subjects, in order to avoid undue variability in insulin absorption, it would be prudent to recommend that the timing of inhaled insulin/bronchodilator administration be consistent.

Effects of inhaled insulin on inhaled bronchodilator/steroid therapy

In the above study,²³ in addition to studying the PK of insulin, the authors also assessed whether inhaled insulin affected the bronchodilatory response to albuterol. They measured FEV1 immediately before and 30 min after albuterol administration (with inhaled insulin delivered 10 min prior to albuterol inhalation). The results indicated that inhaled insulin had no effects on the FEV1 response to albuterol and suggested that subjects with asthma who use both inhaled insulin and bronchodilators should not anticipate a significant change in their bronchodilator dose or efficacy.

Safety of inhaled insulin in subjects with asthma

In the PK/PD studies in subjects without diabetes but with asthma, PFTs—FEV1, forced vital capacity (FVC), and FEV1/FVC—were performed on all subjects at the screening visit, at pre- and post-dose, and at a subsequent follow-up visit.²⁰ The results revealed no significant changes in FEV1, FVC, or FEV1/FVC pre- to post-dose. More importantly, in the second part of the above study,²⁰ it was observed that the delivery of a single large dose of inhaled insulin (equivalent of 135 units) had no effect on any of the measured lung function parameters, and there was no suggestion of any triggering of airway reactivity after the single administration of a large dose of inhaled insulin.

In the clinical study data submitted to the FDA at the time of the Exubera approval hearings,¹⁵ the pattern of respiratory adverse effects and the magnitude of FEV1 change in the integrated cohort of 149 subjects with diabetes

and mild to moderate asthma were similar to subjects without asthma. There were similar numbers of asthma adverse events in both the inhaled insulin group and the comparator group, and there was only one serious adverse event in a comparator patient.

Preliminary safety data are also available from a prospectively designed, ongoing 12-month study (Pfizer Study 1028) to assess the safety and efficacy of inhaled insulin in 250 subjects with prospectively defined asthma.¹⁵ At the time of submission of data to the FDA in January 2006, 139 subjects had been randomized, and 52-week PFT data were available for 27 subjects, 10 in the inhaled group and 17 in the comparator group (Table 2). In this study, although the number and total of severe asthma exacerbations were not remarkably different between groups, investigator-reported asthma adverse events were common in the comparator group, while protocol-defined nonsevere asthma exacerbation and severe asthma exacerbation were more common in the inhaled insulin group. In addition, cough and respiratory tract infection were more common in the inhaled insulin group. Three discontinuations due to respiratory adverse events were noted, all in the inhaled insulin group, two for asthma exacerbation and one for an unspecified respiratory disorder. In the 27 subjects for whom 52-week PFT data were available, there was a separation in the treatment groups: at week 52, the inhaled insulin group had an approximately 183 mL numerically greater decline from baseline FEV1 than the comparator group (a larger difference between treatment groups than what was seen in the pooled data in type 1 and type 2 diabetes from other studies, ~20–40 mL). For DLCO, after week 39 there was a separation in the treatment groups, and at week 52, the inhaled insulin group had approximately 1.75 mL/minute/mm Hg greater decline from baseline DLCO than the comparator group (again a greater difference between the treatment groups than seen in the pooled data in type 1 and type 2 diabetes, ~0.15 mL/minute/mm Hg). At present, the clinical significance of this marginally greater decline in FEV1 and DLCO in subjects with asthma and diabetes as compared to subjects without asthma but with diabetes is not clear. We need

TABLE 2. PULMONARY FUNCTIONS WITH INHALED INSULIN IN ASTHMA AND COPD

<i>Study reference, device</i>	<i>Study duration</i>	<i>Number of participants</i>	<i>FEV1 (pre-bronchodilator)</i>	<i>DLCO (mL/minute/mm Hg)</i>	<i>Difference between inhaled insulin and comparator group</i>
Pfizer Study 1028, data submitted to the FDA, ¹⁵ Pfizer Exubera insulin/Nektar device	52 weeks	10 subjects with asthma and diabetes (Type 1/Type 2) on inhaled insulin	Declined by 296 mL from baseline	Declined by 2.40 from baseline	Greater decline in FEV1 by 183 mL and DLCO by 1.75 in subjects with diabetes on inhaled insulin compared to those in the comparator group
		17 subjects with asthma and diabetes (Type 1/Type 2) on comparator agent	Declined by 113 mL from baseline	Declined by 0.65 from baseline	
Pfizer Study 1030, data submitted to the FDA, ¹⁵ Pfizer Exubera insulin/Nektar device	52 weeks	15 subjects with COPD and diabetes (Type 1/Type 2) on inhaled insulin	Declined by 127 mL from baseline	Declined by 0.34 from baseline	Lesser decline in FEV1 by 18 mL and DLCO by 0.27 in subjects with diabetes on inhaled insulin compared to those in the comparator group
		15 subjects with COPD and diabetes (Type 1/Type 2) on comparator agent	Declined by 145 mL from baseline	Declined by 0.61 from baseline	

to await the results of data from longer-term studies, which are currently in progress.

Interestingly, in the ongoing Pfizer 1028 study, subjects are being administered an asthma control questionnaire (a six-question patient-reported outcome instrument designed to assess asthma control). The questions are on a scale of 0–6, with higher scores reflecting poor control. At 52 weeks, limited data from 27 subjects (10 in the inhaled insulin group and 17 in the comparator group) demonstrated that in the inhaled insulin group, there was a slight increase (mean of 0.17) in the overall score, suggesting a slight worsening of control. In the comparator group there was a slight decrease (mean of 0.48) in the overall score, suggesting a slight improvement in asthma control.

Clinical efficacy of inhaled insulin in subjects with diabetes and asthma

There is a paucity of data on the clinical effects of inhaled insulin in subjects with diabetes and asthma. Information is, however, available from the data submitted by Pfizer, Inc. to the FDA at the time of the approval hearings for Exubera inhaled insulin.¹⁵ These data showed that in the integrated cohort of 149 patients with diabetes and mild to moderate asthma, glycemic control was maintained, and there was no excess hypoglycemia in these subjects. However, it must be mentioned that it is not clear from these data if the subjects with diabetes and asthma took the same or larger doses of inhaled insulin than subjects with diabetes but without asthma. Since the PK/PD studies above show lower absorption of insulin and consequently lower glucodynamic effects by ~30–40%, it is possible that the dose of insulin required to obtain equivalent glycemic control would be higher by ~30–40%. On the other hand, prior administration of a bronchodilator inhaler in individuals with asthma and diabetes reverses airway obstruction and thus may obviate the need for increased insulin requirements. However, it is essential that the timing/sequence of the administration of bronchodilator and inhaled insulin always be consistent.

INHALED INSULIN AND COPD

PK and PD of inhaled insulin in subjects with COPD

The PK/PD of inhaled insulin in patients with COPD was assessed in an open-label, randomized, three-period crossover trial, in which human insulin inhalation powder (HIIP) was administered by the Lilly (Indianapolis, IN)/Alkermes (Cambridge, MA) inhaled insulin system to 15 nonsmoking healthy controls subjects (mean age 38 years) and 30 nonsmoking subjects with moderate COPD (IIA or IIB per Global Initiative for Chronic Obstructive Lung Disease criteria) (Table 1).²¹ Of the subjects with COPD, 15 had chronic bronchitis (mean age 53 years), and 15 had emphysema (mean age 58 years). All subjects received two single doses of HIIP (5.2 mg) and one dose of SQ insulin lispro (12 U) on each of three study days with frequent monitoring of PFTs.

As in the patients with chronic asthma (discussed above), the PK data for patients with COPD in this study demonstrated that as compared to healthy controls, the insulin AUC_{0-360} was reduced by 22% ($P = 0.13$) in subjects with emphysema and by 44% ($P < 0.001$) in those with chronic bronchitis, suggesting less absorption of inhaled insulin. However, the T_{max} was not different between groups (median T_{max} 45–60 min), suggesting that both inhaled insulin and insulin lispro were absorbed rapidly in all three subject groups (healthy controls and those with chronic bronchitis and emphysema), independent of the route of administration. In keeping with the PK data showing less absorption of inhaled insulin, the PD data also revealed a reduction in the glucose infusion rate (GIR) during the clamp. GIR_{total} after inhaled insulin was reduced by 33% in emphysema ($P < 0.01$) and by 40% in chronic bronchitis ($P < 0.001$). Further, as in patients with chronic asthma, there was greater intra-subject variability of inhaled insulin absorption in patients with chronic bronchitis, with the coefficient of variation of the AUC_{0-360} being 52% versus 29% in the healthy controls. Surprisingly, the variability in subjects with emphysema (28% coefficient of variation) was similar to healthy controls. In this study, it is not

known if there was any variation in the glucose lowering effect of inhaled insulin (AUC GIR).

In contrast to the above study showing a reduction in overall insulin absorption and glucose lowering effect in subjects with COPD/emphysema but without diabetes after insulin inhalation administered by the Lilly/Alkermes inhaled insulin system, strikingly different results were seen in data presented to the FDA at the approval hearings for Exubera, which showed that insulin exposure following inhalation of Exubera insulin increased by approximately 50% in COPD patients.¹⁵ Few details are available from this study, except that there were 12 healthy control subjects and 12 subjects each with emphysema and bronchitis and that during the analysis of the data, six subjects had to be excluded. However, it was noted that the effect of inhaled insulin was more pronounced for insulin $C_{\max}$ and AUC and also that this was in contrast to the results obtained after Exubera administration by inhalation in subjects with asthma in whom the AUC and $C_{\max}$ for inhaled insulin were consistently lower by 20–30% when compared to healthy subjects.

The reason(s) for the differing results obtained in the above studies^{15,21} is not clear. It is possible that these differences may be due to differences in the inhalation devices used in the above two studies (Lilly/Alkermes inhaled insulin system and Pfizer/Nektar system). However, it is difficult to explain the reason for the differences in absorption using the same device (Pfizer/Nektar system) in subjects with asthma versus those with COPD, when both groups of these subjects with chronic lung disease have obstructive/restrictive airway defects. It is plausible that the COPD subjects in the Exubera study had more severe lung disease with greater alveolar permeability as in smokers who have increased insulin absorption after inhaled insulin administration. Clearly there is a need for more prospective data in this population using the various insulin delivery devices.

Safety of inhaled insulin in subjects in subjects with COPD

In the studies published to date with Pfizer Exubera inhaled insulin,^{14,15,24,25} in subjects

with diabetes but without chronic lung disease, there is a small but significant decline in FEV1 and DLCO that occurs shortly (within 3 months) of starting inhaled Exubera inhaled insulin and does not progress for up to 2 years. In subjects with diabetes and chronic lung disease, even a small decline in lung function parameters might be considered detrimental. In this context, it is reassuring that data from a recent study using another insulin delivery system—the Technosphere® (MannKind Corp., Valencia, CA)/insulin (T/I) delivery system (an ordered lattice array of Technosphere and recombinant human insulin) showed no change in pulmonary function in 306 subjects with diabetes but without COPD after 6 months of treatment with TI as compared with treatment with SQ insulin.²⁶

Also reassuring is the fact that in the PK/PD study with the Lilly/Alkermes HIIP system,²¹ inhaled insulin was reported to be well tolerated in subjects with COPD, and no statistically significant differences were noted between the pre- and post-clamp PFTs. Of note, however, is that during the clamps both FEV1 and FVC declined modestly in both COPD groups, with no difference between the inhaled insulin and SQ insulin lispro treatments.

Of more clinical relevance are the data from the ongoing 12-month Pfizer study 1030,¹⁵ in 250 subjects with COPD (67 subjects had been randomized at the time of submission of data to the FDA in January 2006). At submission time, 52-week PFT data were available for only 30 subjects, 15 in the inhaled insulin group and 15 in the comparator group (Table 2). The interim results showed that cough and dyspnea were more common in the inhaled insulin group. There was one discontinuation due to a respiratory adverse event (COPD exacerbation) that occurred in the inhaled insulin group. The protocol-defined nonsevere and severe COPD exacerbations were more common in the inhaled insulin group. Interim PFT results suggested a 30 mL greater decline in post-bronchodilator FEV1 and an increase in post-bronchodilator DLCO at 52 weeks in the inhaled insulin group at 52 weeks. These results were considered inconsistent and difficult to interpret.

Clinical efficacy of inhaled insulin in subjects with diabetes and COPD

As with asthma and inhaled insulin, there is a paucity of data on the clinical effects of inhaled insulin in subjects with diabetes and COPD, except for information from the data submitted by Pfizer, Inc. to the FDA at the time of the approval hearings for Exubera inhaled insulin.¹⁵ These data showed that patients with mild to moderate COPD who used inhaled insulin achieved glycemic control without excessive hypoglycemia and had a pattern of respiratory adverse events and magnitude of FEV1 change similar to those seen in patients without COPD. However, it must be mentioned that it is not clear from these data if the subjects with diabetes and COPD took larger/smaller doses of inhaled insulin than subjects with diabetes but without COPD. This is especially important since in the two PK/PD studies discussed above, one study (with the Lilly/Alkermes inhaled insulin system) showed lower absorption, while the other study (with the Pfizer/Nektar system) showed higher absorption of inhaled insulin. Data from prospective, long-term studies that are in progress²⁷ may help to clarify this issue.

CONCLUSION

Overall, inhaled insulin is well tolerated and represents a safe and effective method of delivering insulin to patients with diabetes and chronic lung disease who are unsure or reluctant to start insulin treatment using the conventional SQ route. In subjects with asthma and diabetes, since there is consistently lesser absorption of inhaled insulin (as compared to subjects with diabetes but without asthma), higher doses of inhaled insulin may be needed to achieve equivalent glycemic control. However, prior administration of a bronchodilator inhaler in patients with asthma and diabetes reverses airway obstruction and may obviate the need for higher insulin requirements, provided bronchodilator and inhaled insulin use is consistent. In patients with COPD and diabetes, the absorption of inhaled insulin appears to be variable (higher or lower than in non-COPD

subjects) depending on the devices used to deliver inhaled insulin and the study population. Preliminary, limited data suggest that there is a marginally greater decline in PFTs in subjects with asthma/COPD and diabetes compared to subjects with diabetes and no chronic lung disease. Longer-term data are needed to further clarify the safety and efficacy of inhaled insulin in this population.

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