Addressing Unmet Needs with Prandial Insulin: A Focus on Orally Inhaled Human Insulin

John E. Anderson, MD

ROLE OF INSULIN IN TYPE 1 AND TYPE 2 DIABETES MELLITUS

Patients with type 1 diabetes mellitus (T1DM) require insulin therapy because their bodies are unable to produce insulin.[1] Although patients with type 2 diabetes mellitus (T2DM) might be able to produce insulin, they may not be able to use it efficiently and suffer defects in glucose metabolism. Insulin therapy can be used across the spectrum of T2DM and the American Diabetes Association recommends initiation of insulin therapy (with or without additional agents) in patients newly diagnosed with T2DM who have symptoms of hyperglycemia (ie, polyuria, polydipsia), glycated hemoglobin (HbA_{1c}) ≥10%, and/or blood glucose levels ≥300 mg/dL. Insulin also is recommended in patients who are not achieving glycemic goals with lifestyle changes and oral antihyperglycemic agents.[1] The 2018 American Association of Clinical Endocrinologists/American College of Endocrinology algorithm suggests insulin be used alone or with other glucose-lowering agents in patients with an initial HbA_{1c} >9.0% or as part of dual or triple therapy for patients with HbA_{1c} ≥7.5%.[2]

All patients with T1DM and approximately 40% of patients with T2DM require both basal and prandial insulin.[1-3] Insulin historically has been administered as a series of daily subcutaneous (SC) injections or by continuous (SC) insulin infusion using an insulin pump.

John E. Anderson, MD, Past President, The Frist Clinic, Nashville, Tennessee

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UNMET NEEDS WITH INJECTABLE INSULINS

Although injectable insulin has been the standard of care for >90 years, challenges remain.[4-6] These include patient concerns about their ability to self-administer injections, pain associated with injections, general uneasiness about injection, and social discomfort related to using syringes in public.[5-7] Hypoglycemia, weight gain, the need for multiple daily injections, and the need to carry the dosing equipment and glucose monitor are widely recognized as barriers to effective insulin therapy.

A great deal of complexity is associated with coordinating the timing of prandial doses with meals, monitoring blood glucose, and determining the proper dose based on the size and composition of the meal and current blood glucose concentration.[4-7] Patients might experience anxiety related to the timing of mealtime insulin injections. Subcutaneously injected insulin, even the rapid-acting insulin analogs (insulin aspart, insulin glulisine, and insulin lispro), are absorbed slowly enough into systemic circulation that the insulin concentration can remain elevated up to 6 hours after dosing. As a consequence, the time-action profiles of injectable prandial insulins do not match the absorption of prandial glucose and can put patients at risk of postprandial hypoglycemia, especially 2 to 5 hours after the meal (late postprandial hypoglycemia).[8,9]

Several approaches have been taken to simplify insulin therapy. The most straightforward is to make it easier for patients to self-administer the dose. For example, mechanical, tubeless, disposable patch pumps can be affixed to the skin to deliver insulin via cannula or small needle from a reservoir that is changed every 1 to 3 days. One product, V-Go (Valeritas, Inc.), provides rapid-acting insulin at a basal rate, with the ability to deliver discrete mealtime or correctional doses.[10,11] Another product, OneTouch Via by Calibra Medical, delivers 2 units of rapid-acting insulin with each actuation of the 2 buttons on the device but does not provide basal insulin coverage.[12,13]

Other routes of administration also have been explored. Oral administration of insulin has been studied for decades, with no success to date. The obstacles to oral delivery include: (1) degradation of insulin in the stomach; (2) limited diffu-

sion through intestinal mucosa into the bloodstream, and (3) variable absorption rates due to meal effects and other factors affecting gastrointestinal motility.[14]

Inhaled insulin, another route of administration, has been investigated for >80 years.[15] In 2006, the US Food and Drug Administration (FDA) approved Exubera (Nektar Therapeutics/Pfizer) as the first inhaled insulin for patients with T1DM or T2DM.[16] Exubera was withdrawn from the market several months after its release because of limited commercial success. The lack of success was attributed to: (1) a large, bulky, complicated inhaler; (2) the cumbersome administration process; (3) Exubera doses were labeled in milligrams rather than units, making the conversion difficult; and (4) requirement for full pulmonary function tests because of small pulmonary function changes associated with the drug. After patients overcame these hurdles, the pharmacokinetics (PK)/pharmacodynamic (PD) of Exubera was so similar to SC administration of rapid-acting insulin analogs that Exubera was considered a "convenience" product. Finally, a small potential lung cancer signal was seen in former heavy smokers.[17,18]

ORALLY INHALED INSULIN

Notwithstanding the limitations observed with Exubera, pulmonary delivery of insulin remains a viable route for administration. In contrast to SC insulin that is absorbed from a localized region around the injection site, pulmonary delivery exploits the large area of the alveoli for absorption into the systemic circulation.[19] In addition, oral inhalation avoids physiologic barriers such as peptidases in the GI tract and first-pass metabolism.[16]

Afrezza (MannKind) is a rapid-acting, orally inhaled insulin approved by the FDA in 2014 to improve glycemic control in adults with T1DM or T2DM.[20] It is composed of Technosphere® insulin inhalation powder, a dry powder formulation of recombinant human insulin adsorbed onto carrier Technosphere microparticles (median diameter 2.0 to 2.5 μm) that are within the optimal size range for delivery deep into the lung.[8,20] Inhaled Afrezza is delivered using cartridges that are loaded into a thumb-sized delivery device. The current Afrezza inhaler is smaller and more efficient than the MedTone delivery system used in clinical development through 2010.[8,16]

PHARMACOKINETICS/PHARMACODYNAMICS

Inhaled Afrezza is characterized by a rapid onset and short duration of action.[8,21] Upon inhalation, Afrezza particles dissolve in the neutral pH of the lung and insulin is rapidly absorbed into the circulation.[8,16] Afrezza exhibits a linear, dose-related response. Time to maximum plasma drug concentration (10 to 15 minutes) and peak glucose-lowering effect (approximately 45 minutes) for Afrezza are shorter than with regular human insulin or insulin lispro.[8,21,22] This has been demonstrated repeatedly in crossover, hyperinsulinemic, euglycemic glucose clamp studies. The most recent was a study in 30 patients with T1DM in which the onset of metabolic activity for Afrezza occurred earlier than for insulin lispro (15 to 19 minutes vs 45 to 52 minutes), and the duration of action for Afrezza was approximately 2 to 3 hours shorter than equivalent doses of insulin lispro (1.8 to 6.4 hours vs 5.0 to 9.8 hours).[23] Afrezza's glucose disposal effect occurs earlier than that of SC insulin. For example, the rate of glucose disposal over the first 60 minutes after administration is 34% greater for Afrezza than SC regular human insulin ($P < .05$) and 4% less for Afrezza than SC insulin lispro (P = NS).[24]

Because Afrezza is administered by oral inhalation, the potential effects of an acute upper respiratory tract infection (URTI) on the PK/PD profile were investigated.[25] No significant impact was observed among patients with T1DM or T2DM who developed an URTI while being treated with Afrezza. Similarly, the PK profile is not significantly different in persons with mild-to-moderate chronic obstructive pulmonary disease (COPD) compared with healthy controls.[26]

EFFICACY OF AFREZZA INHALED INSULIN

Clinical studies from 2010 and earlier used the MedTone inhalation device, while more recent phase 3 trials (Affinity 1 and Affinity 2) used the currently available Afrezza inhaler in patients with T1DM or T2DM, respectively.[16,27-29] Efficacy results from the Affinity 1 and 2 trials are summarized in **TABLE 1**.[27,28] The results from Affinity 1 and 2 generally were consistent with those of a meta-analysis of 12 earlier clinical trials vs SC insulin or SC rapid-acting analog in T1DM and T2DM. The meta-analysis showed a mean HbA_{1c} reduction from baseline of 0.55% with Afrezza (95% confidence interval [CI], 0.34%-0.78%). The mean reduction in HbA_{1c} was slightly larger in patients receiving SC insulin (net treatment difference was 0.13% in T1DM and 0.19% in T2DM), but the difference was not statistically significant.[30]

Afrezza has demonstrated effective control of postprandial hyperglycemia in clinical trials.[27-29] In the Affinity 2 trial of insulin-naïve patients with T2DM, Afrezza produced clinically meaningful reductions in postprandial glucose (PPG) levels at weeks 12 and 24 compared with baseline as demonstrated by less variability in the 7-point glucose profile (based on self-monitored blood glucose values taken immediately before every meal, 90 minutes after the meal, and at bedtime) compared with placebo.[28] These findings were consistent with those of an earlier trial in patients with T2DM that was poorly controlled with basal insulin with or without oral antihyperglycemic agents.[29] In that study, patients receiving Afrezza plus insulin glargine had significantly lower 1 hour

TABLE 1 Efficacy of Afrezza

	Affinity 1[27]		Affinity 2[28]	
Methods				
Design	Randomized, open-label, 24 week		Randomized, double-blind, placebo-controlled, 24-week	
Type of diabetes	Type 1		Type 2	
Intervention	Afrezza (n = 174) vs prandial aspart (n = 170)		Afrezza (n = 177) vs placebo (n = 177)	
Adjunctive therapy	Basal insulin (NPH or detemir, or glargine)		Oral antihyperglycemic agents	
Mean HbA_{1c} levels at baseline (TI/comparator)	Afrezza 7.94%	Aspart 7.92%	Afrezza 8.35%	Placebo 8.35%
Results				
	Afrezza	Aspart	Afrezza	Placebo
Reduction in HbA_{1c} vs baseline	–0.21%	–0.40%	–0.82%	–0.42%
Treatment difference Afrezza-comparator	0.19% vs aspart (95% CI, 0.02 to 0.36) met criteria for noninferiority		–0.40% vs placebo (95% CI, –0.57 to –0.23)	
Proportions of patients reaching $HbA_{1c} \leq 7\%$	18%	31%	38%	19%
Changes in 7-point glucose profiles	Lower fasting glucose	Lower glucose concentrations at other time points	Clinically meaningful reductions in postmeal glucose values	—

Abbreviations: CI, confidence interval; HbA_{1c}, glycated hemoglobin; NPH, neutral protamine Hagedorn; TI: technosphere insulin.

PPG levels than those receiving biaspart insulin (171 mg/dL vs 209 mg/dL; $P = .0001$), while 2-hour PPG levels were similar between groups (213 mg/dL in both groups). Consistent with its short duration of action, glucose excursions—ie, fluctuations in blood glucose either above or below the normal range—at 2 hours were higher among patients receiving Afrezza than those receiving biaspart.

The PK/PD profile of Afrezza provides excellent glucose control in the early postprandial period, but its duration of action might be too short to cover meals that are absorbed over longer times.[29,31] The short duration of action, however, also suggests a second dose could be administered with minimal risk of hypoglycemia. This hypothesis was tested in several pilot studies.[31,32] In a single-arm, 45-day study of patients with T1DM (N = 15), a second dose (administered if the 2-hour PPG level was ≥180 mg/dL) was used 38% of the time and reduced mean HbA_{1c} from 7.86% to 7.47% with no increase in the time spent with blood glucose <60 mg/dL.[32] In a T2DM study of SC rapid-acting insulin in patients with inadequate glycemic control with optimized basal insulin and oral agents, 21% of patients (n = 19) receiving Afrezza took a second dose (administered if the 90- to 120-minute PPG level was >140 mg/dL).[31] The reduction in HbA_{1c} levels over 16 weeks was similar in the 2 groups, while the Afrezza group did not experience higher incidences of hypoglycemia and adverse events than those on SC therapy.

SAFETY OF TECHNOSPHERE INHALED INSULIN

As with other insulin products, the most common adverse event associated with Afrezza is hypoglycemia. The incidences of hypoglycemia and severe hypoglycemia occurring in the Affinity 1 and 2 trials are summarized in **TABLE 2**. A meta-analysis of 5 studies in patients with T1DM or T2DM found similar results; severe hypoglycemia was reported less frequently with Afrezza (12% of patients) than with SC insulin (19% of patients; odds ratio [OR] 0.61; 95% CI, 0.35-0.92).[30] Furthermore, the timing of hypoglycemic events with Afrezza reflects its rapid onset and short duration of action. As evidenced by results of the Affinity 1 study, hypoglycemic event rates within 2 hours after meals were similar among the treatment groups, but were 2 to 3 times less frequent 2 to 5 hours after meals in patients randomized to Afrezza.[27]

Cough is the most common nonhypoglycemic adverse effect (**TABLE 2**), reported by 29% of patients receiving Afrezza in a meta-analysis of 7 studies.[27-30] Cough induced by Afrezza is generally mild, transient, occurring within 10 minutes of inhalation, typically occurs within the first month of treatment, and decreases over time with continued use.[30] Patients with persistent or recurring cough require close monitoring of lung function and, if necessary, treatment discontinuation.[20] Although cough is the most common adverse event leading to discontinuation (2.8% of patients discontinued

TABLE 2 **Safety of Afrezza**

	Affinity 1[27]		Affinity 2[28]	
	Afrezza	Aspart	Afrezza	Placebo
Proportions of patients reporting adverse effects	58%	43%	61%	51.1%
Withdrawal due to adverse effects	9.2%	0%	4%	5.1%
Proportions of patients reporting hypoglycemia[a]	96%	99.4%	67.8%	30.7% (*P*< .0001)
Proportions of patients reporting severe hypoglycemia[b]	18.4%	29.2% (*P*= .0156)	5.7%	1.7%
Proportions of patients reporting cough	31.6%	2.3% (*P*< .05)	23.7%	19.9%
Withdrawal due to cough	5.7%	0%	1.1%	3.4%
Change in mean weight	–0.4 kg	+0.9 kg (*P*= .01)	+0.5 kg	–1.1 kg (*P*< .0001)
Change in mean FEV_1 (L)	–0.07 L	–0.04 L	–0.13 L	–0.04 L

Abbreviations: FEV_1, forced expiratory volume in 1 second.

[a]Self-monitored blood glucose <70 mg/dL and/or presence of symptoms of hypoglycemia.

[b]Event requiring third-party assistance.

due to cough), it is reversible and resolves within 1 to 2 days after drug discontinuation.[28,30]

Patients on Afrezza lost more weight or gained less weight than those on SC prandial insulin (**TABLE 2**).[27,28] A meta-analysis of 3 studies reported significantly less weight gain compared with SC prandial insulin (net difference –1.1 kg).[30]

Given the concerns about earlier inhaled insulin products, the potential impact of Afrezza on lung function has been investigated closely. One such investigation was a 2-year, phase 3 clinical study comparing patients on Afrezza with patients receiving usual care and a cohort of healthy volunteers as a reference group to characterize normal changes in pulmonary function.[33] Small declines from baseline in forced expiratory volume in 1 second (FEV_1) were observed in all 3 groups, with the smallest change occurring in those without diabetes. The mean change in FEV_1 at 24 months was –0.09 L in healthy volunteers, –0.11 L in patients receiving usual care, and –0.15 L in patients receiving Afrezza. The net difference between the Afrezza and usual care groups was 0.037 L (95% CI 0.014-0.06 L). For reference, baseline FEV_1 was approximately 3.1 L in patients with diabetes. The decline was significantly greater for Afrezza at 3 months; thereafter through 24 months, the rate of change in FEV_1 and forced vital capacity (FVC) was not significantly different between groups. The small, non-progressive decline in lung function was considered by investigators to not be clinically meaningful.[33] In Affinity 1 and Affinity 2, slight declines in FEV_1 also were observed in the Technosphere insulin (TI) groups relative to comparators, were not associated with cough status, and were judged as unlikely to be clinically meaningful.[27,28] In Affinity 2, for example, the FEV_1 declined 4.5% for TI vs 1.4% for placebo at 24 weeks (end of treatment difference –0.09 L; 95% CI, –0.12 to –0.05).

Acute bronchospasm and wheezing were observed after inhalation of Afrezza in 29% (5 of 17) of patients with asthma who did not take their usual bronchodilator; no bronchospasm was observed in 13 individuals without asthma.[20] This was accompanied by a substantial mean reduction in FEV_1 of 400 mL at 15 minutes after a single dose of Afrezza. Similarly, in a small group of patients with COPD (n = 8), a mean decline in FEV_1 of 200 mL was observed 18 minutes after Afrezza inhalation.[20] Therefore, Afrezza is contraindicated in patients with chronic lung disease such as asthma or COPD.

Two cases of lung cancer, 1 in controlled trials and 1 in uncontrolled trials (2 cases in 2,750 patient-years of exposure), were observed in participants exposed to Afrezza.[20] In both cases, a history of heavy tobacco use was identified. Two additional cases of lung cancer in non-smokers exposed to Afrezza were reported several years after clinical trials were completed. Minimal information was available regarding interim medical issues and these data are insufficient to determine whether Afrezza has an effect on lung or respiratory tract tumors.[20]

Afrezza is not contraindicated in patients with cancer. Rather, a risk-benefit analysis should be performed for each patient.

PATIENT SELECTION

Several of the key features and benefits of Afrezza suggest it could address some unmet needs encountered with SC

TABLE 3 Patient education checklist

✓	Adherence/self-management	Instruct on self-management procedures and verify at each visit (eg, dosing with meal, glucose monitoring, handling special situations [eg, intercurrent illness]); review key aspects of Technosphere insulin handling and storage and verify administration technique at each visit
✓	Hypoglycemia risk and monitoring	Reinforce signs/symptoms of hypoglycemia; provide written action plan
✓	Cough	Occurs in 24% to 33% of patients within 10 minutes of inhalation; mild, typically subsides after first month
✓	Change in lung function (FEV_1)	Evaluate with spirometry; a small change is generally not considered clinically relevant
✓	Lung cancer	Conduct risk-benefit analysis
✓	Diabetic ketoacidosis	Monitor blood glucose and maintain dosing during illness, infection, and other risk situations
✓	Drug interactions	Certain drugs may increase the risk of hypoglycemia; increase or decrease the blood-glucose-lowering affect; or affect the signs and symptoms of hypoglycemia. Dosing adjustments and increased glucose monitoring may be warranted
✓	Dosing	Increase dose or add second mealtime dose if glucose not well controlled and hypoglycemia not an issue
✓	Storage/handling	Refrigerate cartridges; dispose of inhaler after 15 days; video demonstration of dose administration technique: https://www.afrezza.com/hcp/afrezza-steps
✓	Affordability	Verify insurance coverage

Abbreviations: FEV_1, forced expiratory volume in 1 second.

prandial insulin. The rapid onset of TI provides easier and more flexible mealtime dosing because it is administered at the beginning of a meal rather than 15 to 30 minutes prior as required with rapid-acting SC insulin analogs. This might be of particular benefit to patients with unpredictable or erratic meal schedules. The shorter duration of action reduces the incidence of late postprandial hypoglycemia, which could be especially important in patients with hypoglycemia unawareness. Afrezza also circumvents the need to use a syringe in public and patients' dislike of injections. Additionally, Afrezza eliminates the need for any injection beyond basal insulin. This might be particularly beneficial for the 37% to 64% of patients who experience lipohypertrophy from injecting insulin and its associated increase in variability of effect.[34-36] Finally, Afrezza is associated with slightly less weight gain, which may help allay this common concern among patients.

When considering Afrezza for a patient, the absence of chronic lung disease must be confirmed through medical history, physical examination, and spirometry evaluation (FEV_1) before treatment.[20] Afrezza is not appropriate for patients with chronic lung disease such as COPD and asthma because of the risk of acute bronchospasm.[20] Spirometry should be repeated at 6 months and annually thereafter to monitor for small decreases in FEV_1, even in the absence of pulmonary symptoms. If lung function decreases by ≥20%, consider discontinuing TI.[20] A Risk Evaluation and Mitigation Strategy to mitigate the risk of acute bronchospasm associated with TI has been developed by the manufacturer (www.AfrezzaREMS.com).[37]

Afrezza has not been studied in all populations. There are limited data in pregnant women or lactating mothers.[20] Based on animal studies, it is likely that the insulin and carrier in Afrezza are excreted in human breast-milk, but there is insufficient information to determine the risk for adverse developmental outcomes.[20] Afrezza has not been studied in patients under the age of 18 years or in patients with renal or hepatic impairment.[20]

ADMINISTRATION AND DOSING CONSIDERATIONS

Administration

The Afrezza delivery system is composed of a small, thumb-sized inhaler and single-use cartridges containing 4 units, 8 units, or 12 units of Afrezza. Only 1 inhalation per cartridge is required. If the prescribed dose is >12 units, >1 cartridge is needed. This is accomplished by loading, administering, and removing 1 cartridge, then repeating with a second cartridge.[20] A video demonstration of the process is available at https://www.afrezza.com/hcp/afrezza-steps. Afrezza cartridges should be refrigerated until opened. Unopened foil package or blister cards not refrigerated must be used within 10 days; opened blister cards must be used within 3 days.[20] The patient does not need to clean the inhaler; it is replaced with a new one every 15 days.

Dosing

Insulin naïve patients should be started on 4 units of Afrezza at each meal. Individuals using SC mealtime insulin should be converted to TI based on a conversion chart in the product labeling. For individuals using SC premixed insulin, one half of the total daily insulin dose is given as basal insulin and the other half as TI prandial insulin, given in one-third increments at each meal. The dose is calculated using the same conversion for individuals using mealtime insulin.[20] Subsequent dosing should be adjusted based on the individual's metabolic needs, blood glucose monitoring results (via self-monitoring of blood glucose, continuous glucose monitoring, or flash glucose monitoring) and glycemic control goal.[20]

It is important to note that patients might require doses that seem high compared with SC insulin, perhaps 1.5 to 2-fold. This is a normal consequence of Afrezza's unique PK/PD profile and is not an indication of lack of effect. As with any insulin, the dose should be titrated to achieve and maintain glycemic control.

PATIENT EDUCATION

Educating patients about Afrezza includes several topics appropriate for any patient treated with insulin, as well as some specific subjects (**TABLE 3**). All these topics, particularly hypoglycemia and adherence/self-management, should be reviewed with the patient at every visit.

CONCLUSIONS

Prandial insulin analogs are improvements over earlier products, and yet there are still unmet needs for optimal treatment of patients with diabetes. These include a mismatch between onset and duration of action and PPG levels, concern for hypoglycemia, dose timing, needle phobia, and treatment complexity. Compared with SC prandial insulin, the rapid-acting inhaled insulin of Afrezza leads to better control of early PPG with less weight gain and less frequent hypoglycemia, although control of late PPG remains suboptimal in some patients. Together with the ease of use of the TI inhaler, the convenience of administering the dose at the beginning of a meal, and non-injectable administration make TI a useful option for select patients who require prandial insulin. TI is contraindicated in patients with chronic lung disease such as asthma or COPD. ●

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