

# Inhaled Insulin Provides Improved Glycemic Control in Patients With Type 2 Diabetes Mellitus Inadequately Controlled With Oral Agents

## A Randomized Controlled Trial

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**Background:** The long-term benefits of good glycemic control are well established. The aim of this proof-of-concept study was to determine whether glycemic control can be improved in patients with type 2 diabetes mellitus with suboptimal glycemic control, despite therapeutic dosages of oral antihyperglycemic agents (OHAs), by the addition of preprandial inhaled insulin (INH).

**Methods:** Sixty-eight patients with inadequately controlled type 2 diabetes mellitus (glycosylated hemoglobin, 8.1%-11.9%), despite therapy with a sulfonylurea and/or metformin, were randomized to receive INH in addition to their prestudy OHA therapy (INH+OHA group, n=32) or to continue taking their prestudy OHA alone for 12 weeks (OHA group, n=36). Premeal INH doses were delivered in 1 to 2 inhalations of 1-mg or 3-mg doses (equivalent to 3 IU and 9 IU, respectively, of subcutaneously injected regular insulin).

**Results:** At week 12, there was a significantly greater reduction in glycosylated hemoglobin for the INH+OHA

cohort (mean reduction, -2.3%) compared with the OHA-only cohort (mean reduction, -0.1%,  $P<.001$ ). Eleven patients (34%) receiving INH+OHA achieved glycosylated hemoglobin values of less than 7%, compared with none taking OHAs only. Fasting plasma glucose improved significantly more in the INH+OHA group compared with the OHA-only group (-60.69 mg/dL [-3.37 mmol/L] greater reduction,  $P<.001$ ), and the postprandial increase in glucose was significantly lower in those patients receiving INH+OHA ( $P=.02$ ). There was 1 report of severe hypoglycemia in the INH+OHA group (home blood glucose, 54 mg/dL [3.0 mmol/L]) and a greater increase in body weight. Pulmonary function was unchanged in both groups.

**Conclusion:** The addition of preprandial INH to existing OHAs improves glycemic control without the need for injections in patients with type 2 diabetes mellitus failing to achieve satisfactory control with OHAs alone.

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**T**YPE 2 diabetes mellitus represents a heterogeneous metabolic dysfunction, with patients displaying defects in insulin secretion and peripheral insulin sensitivity. Functional defects in the pancreatic beta cell are crucial to the development of type 2 diabetes mellitus<sup>1-4</sup> and occur early in the course of the disease.<sup>5,6</sup> Oral antihyperglycemic agents (OHAs) depend on pancreatic beta cell function for their action; therefore, their maximal efficacy is limited by dose-response considerations and by declining beta cell function. A high proportion of patients with type 2 diabetes mellitus has poor glycemic control, despite therapeutic dosages of OHAs.<sup>7</sup>

Data from the UK Prospective Diabetes Study and the Diabetes Intervention Study have revealed an association between good glycemic control and a reduction in microvascular<sup>8</sup> and macro-

vascular<sup>9</sup> complications in type 2 diabetes mellitus. Therefore, it is imperative that patients with type 2 diabetes mellitus who fail to achieve satisfactory glycemic control with an OHA are treated more effectively.

Patients with type 2 diabetes mellitus who are inadequately controlled with OHA therapy are often treated with insulin, alone or in combination with an OHA.<sup>10,11</sup> Insulin has the advantage of being almost infinitely titratable and is effective in achieving treatment goals. However, physicians and patients often resist initiating insulin therapy for several reasons, including the fear that injections may be painful or difficult to administer, the number of injections required to achieve good control, and the perception that commencing insulin treatment reflects a significant worsening of the disease.<sup>12,13</sup>

Recently, a dry powder-inhaled insulin (INH) system has been developed to

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provide a new method for the treatment of diabetes mellitus. The pulmonary route exploits the large vascular bed and permeability of the alveoli to deliver insulin directly into the bloodstream. Inhaled insulin is under investigation for preprandial administration of rapid-onset insulin in type 1 and type 2 diabetes mellitus and has been shown in preliminary short-term clinical studies<sup>14-16</sup> to provide safe and effective control of meal-related glycemia.

A recent study<sup>17</sup> in healthy subjects examining the time-action profiles of INH compared with subcutaneously injected (SC) insulin lispro and regular insulin showed that INH has a rapid onset of action (indicated by time to early half maximal effect) and was significantly faster (mean  $\pm$  SE, 32  $\pm$  8 minutes) than regular insulin (mean  $\pm$  SE, 48  $\pm$  15 minutes;  $P = .001$ ) and faster than insulin lispro (mean  $\pm$  SE, 40  $\pm$  15 minutes;  $P = .07$ ). The duration of action (time to late half maximal effect) of INH (mean  $\pm$  SE, 382  $\pm$  95 minutes) was between that of insulin lispro (mean  $\pm$  SE, 309  $\pm$  45 minutes;  $P < .05$ ) and regular insulin (mean  $\pm$  SE, 413  $\pm$  108 minutes; not significant). A further study<sup>18</sup> in patients with type 2 diabetes mellitus has shown that INH is rapidly and reproducibly absorbed, making it a suitable agent for the control of meal-related glucose excursions. In addition, it has recently been suggested that INH is associated with improved patient satisfaction in those with type 1<sup>19</sup> and type 2<sup>20</sup> diabetes mellitus.

Previous studies have demonstrated that an INH treatment regimen provided glycemic control comparable to that of a conventional SC insulin regimen in patients with type 1<sup>15</sup> or type 2<sup>21</sup> diabetes mellitus. The aims of this 3-month proof-of-concept study were to determine whether glycemic control could be improved in patients with type 2 diabetes mellitus failing to achieve satisfactory glycemic control with OHA therapy by the addition of preprandial INH, and to determine the tolerability and safety of INH therapy in this population.

## METHODS

### STUDY DESIGN

The study was a randomized, open-label, multicenter, parallel-group study comprising a 4-week run-in phase and a 12-week treatment period. Patients were recruited at 9 academic health centers and clinical research centers in the United States. The protocol was approved by each center's institutional review board, and all patients gave written informed consent.

### PATIENTS

Patients recruited into the study had a primary diagnosis of type 2 diabetes mellitus with a glycosylated hemoglobin (HbA<sub>1c</sub>) between 8.1% and 11.9%, inclusive, despite treatment with a therapeutic dosage of a sulfonylurea (glyburide, glipizide, or glimepiride) and/or metformin. Glycosylated hemoglobin was determined during a screening examination (week -4) before study entry.

For inclusion in the study, male or female adults aged 35 to 65 years had to have a fasting plasma C-peptide of at least 0.6 ng/mL ( $\geq 0.2$  pmol/mL), body weight between 100% and 175% of ideal, and normal chest radiographic findings and pulmonary function. Patients with major organ system disease, a

history of epilepsy or asthma or other respiratory diseases, 2 or more hypoglycemic episodes within the past year, or who were smokers (any smoking within the past 6 months) were excluded from the study.

## TREATMENT

During the 4 weeks before randomization, all patients continued their usual OHA therapy and visited the clinic for instruction on appropriate diet, home glucose monitoring, pulmonary function tests, and assessment of glycemic control.

Patients continued their OHA regimens (dosage unchanged) and were randomized using a computer-generated randomization scheme to receive an additional INH regimen (INH+OHA) or to receive no additional therapy (OHAs only) and were followed up for 12 weeks. For the first 4 weeks after randomization, weekly clinic visits were required. The additional INH regimen consisted of preprandial INH administered immediately before meals using a dry powder aerosol delivery system (Nektar Therapeutics, San Carlos, Calif; Pfizer Inc, New York, NY; and Aventis, Bridgewater, NJ).

Before randomization, patients were trained to use the inhalation device for the administration of premeal insulin. Insulin was delivered 3 times daily before meals, with the insulin dose given in 1 to 2 inhalations. The dry insulin powder was packaged in distinctly labeled blister packs of 1-mg and 3-mg doses, the equivalent of approximately 3 IU and 9 IU, respectively, of SC insulin. The target meal glucose response was a 2-hour postprandial increment of less than 60 mg/dL ( $< 3.3$  mmol/L), and the recommended insulin dosage was reviewed at each visit to the clinic. Initial premeal dosages were given based on body weight. The recommended preprandial starting dosages were 2 mg for patients with a body weight of less than 60 kg, 3 mg for patients 60 to less than 80 kg, and 4 mg for those between 80 and 99 kg. Administration of insulin was always preceded by a blood glucose measurement, and the insulin dosage was adjusted weekly, based on glucose monitoring results, to achieve a target self-monitored premeal glucose in the range of 100 to 160 mg/dL (5.6-8.9 mmol/L). In the event that the self-monitored blood glucose measurements were lower ( $< 100$  mg/dL [ $< 5.6$  mmol/L]) or higher ( $> 160$  mg/dL [ $> 8.9$  mmol/L]) than the target range, patients adjusted the dosage of insulin accordingly. All subjects were provided with a glucose test meter (One Touch Profile; Lifescan Inc, Milpitas, Calif). Study participants using a new treatment regimen with INH were required to perform home glucose monitoring a minimum of 4 times daily, just before breakfast, lunch, supper, and bedtime. Subjects who continued taking OHAs alone were required to monitor their blood glucose a minimum of twice daily, before breakfast and supper.

## ASSESSMENTS

The primary study end point was the change in HbA<sub>1c</sub> level from baseline to week 12. Glycosylated hemoglobin was measured before randomization and at weeks 4, 8, and 12. Secondary efficacy end points included change in fasting glucose and 2-hour postprandial plasma glucose increment, change in fasting lipid profile, incidence and severity of hypoglycemic events, body weight, and measures of pulmonary function.

*Hypoglycemia* occurring during the study was defined by the occurrence of 1 of the following: (1) typical clinical picture without blood glucose measurement, (2) typical clinical picture with blood glucose measurement confirming blood glucose less than 60 mg/dL ( $< 3.3$  mmol/L), or (3) any glucose measurement less than 50 mg/dL ( $< 2.8$  mmol/L). Patients recorded hypoglycemic episodes on weekly glucose monitoring worksheets. An episode was defined a priori as

being severe if it required the assistance of another person or involved seizures or coma. All other episodes were graded as mild to moderate.

Fasting and postprandial glucose levels in response to a standard meal were measured before and after the 12 weeks of treatment. A standardized morning meal study was conducted after patients had fasted for 8 to 10 hours overnight. Treatment was administered 10 minutes before the meal. Plasma glucose was measured at -15, 0, 30, 60, 90, 120, and 180 minutes. Insulin levels were measured at -15, 0, 30, 60, 90, and 120 minutes.

Spirometry, including forced expiratory volume in 1 second, and forced vital capacity and diffusion capacity to carbon monoxide were performed at -3, 6 (spirometry only), and 12 weeks.

## STATISTICAL ANALYSIS

Change in HbA<sub>1c</sub> from baseline to week 12 was assessed using analysis of covariance with baseline HbA<sub>1c</sub>, treatment, and center as covariates. Baseline was defined as the mean of measurements at weeks -1 and 0. The study size was estimated to provide 80% power to ensure that the upper limit of the 2-sided 95% confidence interval (CI) for the difference in change from baseline HbA<sub>1c</sub> of 1.0% between treatment groups would not exceed 1.0%. Unless otherwise stated, results are expressed as mean change ± SE.

Secondary end points, lipid tests, and body weight were assessed similarly. Data were analyzed on an intent-to-treat basis, carrying the last observation forward. The proportion of patients with acceptable glycemic control (defined as evaluable HbA<sub>1c</sub> <8% and <7%) by the end of the study was analyzed using Fisher exact method for small sample sizes. For each treatment group, the odds of achieving vs not achieving glycemic control (HbA<sub>1c</sub> <8%) were calculated as the percentage of subjects with end-of-study HbA<sub>1c</sub> less than 8% divided by the percentage of subjects without end-of-study HbA<sub>1c</sub> less than 8%. The CI for the odds ratio is calculated based on the log odds ratio.

## RESULTS

One hundred patients were screened for the study, and 69 were randomized to treatment, of whom 68 provided evaluable data (INH+OHA group, n=32; and OHA group, n=36). In the efficacy analysis, 1 patient was excluded from the INH+OHA group because of a lack of HbA<sub>1c</sub> post-baseline values. There were no statistically significant between-group differences in baseline characteristics (**Table 1**). The mean daily doses of OHAs before entry into the study were maximal or near maximal and are provided in **Table 2**. The mean daily doses of INH were as follows: week 4, 12.5 ± 0.9 mg; week 8, 13.0 ± 1.0 mg; and week 12, 12.7 ± 1.0 mg, with doses of 1 mg and 3 mg of INH being approximately equivalent to 3 IU and 9 IU of SC insulin, respectively.

### MEAN CHANGE IN HbA<sub>1c</sub>

After 12 weeks of treatment, patients receiving OHAs alone showed little change in HbA<sub>1c</sub> level: mean, 9.9% ± 0.2% at baseline to 9.8% ± 0.2% at week 12 (**Figure 1**). However, those receiving INH+OHA showed a marked improvement in HbA<sub>1c</sub>, from 9.8% ± 0.2% at baseline to 7.5% ± 0.2% at week 12. The difference between the ad-

**Table 1. Baseline Characteristics of Subjects\***

Characteristic	Inhaled Insulin Plus Oral Agents (n = 33)	Oral Agents (n = 36)
Male/female	19/14	26/10
Age, y	52.7 ± 1.37 (34-65)	49.9 ± 1.37 (33-64)
Duration of diabetes, y	9.5 (2.0-18.0)	6.9 (1.0-19.0)
Ethnicity		
White	23	21
Hispanic	8	12
Other	2	3
Weight, kg	92.3 ± 2.68 (60-122)	91.6 ± 2.02 (65-119)
Body mass index, kg/m <sup>2</sup>		
Men	30.8 ± 0.7 (24-40)	29.9 ± 0.6 (22-40)
Women	32.1 ± 0.9 (23-41)	33.3 ± 0.9 (27-41)
HbA <sub>1c</sub> , %	9.8 ± 0.2 (8.0-12)	9.9 ± 0.2 (8.0-11.9)

\*Data are mean ± SD (range) or number of subjects. P > .05 for all comparisons.

justed mean changes for the 2 treatments (-2.2 in favor of INH) was statistically significant (95% CI, -2.7 to -1.7; P < .001).

Twenty-one patients (66%) receiving INH+OHA achieved HbA<sub>1c</sub> less than 8% by week 12, compared with 3 patients (8%) receiving OHAs alone. The odds ratio (INH+OHA group/OHA group) of achieving vs not achieving HbA<sub>1c</sub> less than 8% was 21.0 (95% CI, 5.2-84.2; P < .001). Eleven patients (34%) receiving INH+OHA also achieved HbA<sub>1c</sub> less than 7%, compared with no patients receiving OHAs alone.

### INCIDENCE OF HYPOGLYCEMIA

In the INH+OHA group, 22 patients (69%) experienced a total of 57 hypoglycemic events, a crude event rate of 0.64 events per subject-month. Fifty-six of these were mild to moderate. Only 1 event (home blood glucose, 54 mg/dL [3.0 mmol/L]) in the INH+OHA group was classified as severe, solely because third-party assistance was received.

Six patients (17%) in the OHA-only group experienced a total of 6 events, a crude event rate of 0.06 events per subject-month. This represents a risk ratio (INH+OHA group/OHA group) for any hypoglycemic event of 10.7 (95% CI, 4.6-24.8; P < .001).

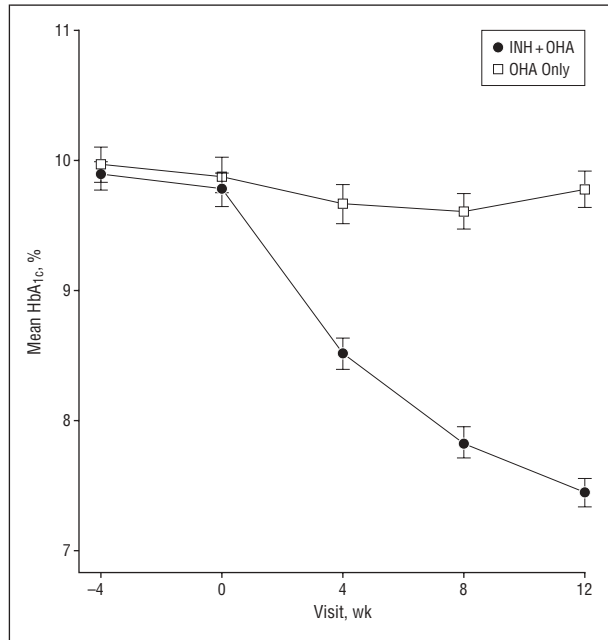
### FASTING AND POSTPRANDIAL PLASMA GLUCOSE

Fasting plasma glucose levels decreased substantially from 227.48 ± 8.69 mg/dL (12.62 ± 0.51 mmol/L) at baseline to 172.36 ± 8.50 mg/dL (9.57 ± 0.49 mmol/L) at week 12 in those receiving INH+OHA, compared with a reduction from 254.06 ± 11.54 mg/dL (14.10 ± 0.64 mmol/L) to 244.86 ± 9.16 mg/dL (13.59 ± 0.51 mmol/L) in the OHA-only group. The adjusted change from baseline in those receiving INH+OHA was -61.60 ± 1.25 mg/dL (-3.42 ± 0.01 mmol/L) at week 12, compared with -0.92 ± 0.27 mg/dL (-0.05 ± 0.01 mmol/L) in the OHA-only group; the difference between the adjusted mean changes from baseline (-60.69 mg/dL [-3.37 mmol/L])

**Table 2. Mean Daily Dose of Oral Agents at Baseline**

Agent	Inhaled Insulin Plus Oral Agents (n = 33)		Oral Agents (n = 36)	
	No. (%)	Mean Daily Dose, mg	No. (%)*	Mean Daily Dose, mg
Glyburide	7 (21.2)	16	11 (30.6)	14
Glipizide	5 (15.2)	16	6 (16.7)	10
Glimepiride	0	...	1 (2.8)	4
Metformin	2 (6.1)	1750	1 (2.8)	2000
Glyburide + metformin	8 (24.2)	15 + 1756	7 (19.4)	20 + 1729
Glipizide + metformin	8 (24.2)	15 + 1463	6 (16.7)	14 + 1850
Glimepiride + metformin	3 (9.1)	7 + 2517	4 (11.1)	8 + 2138

\*Percentages do not total 100 because of rounding.

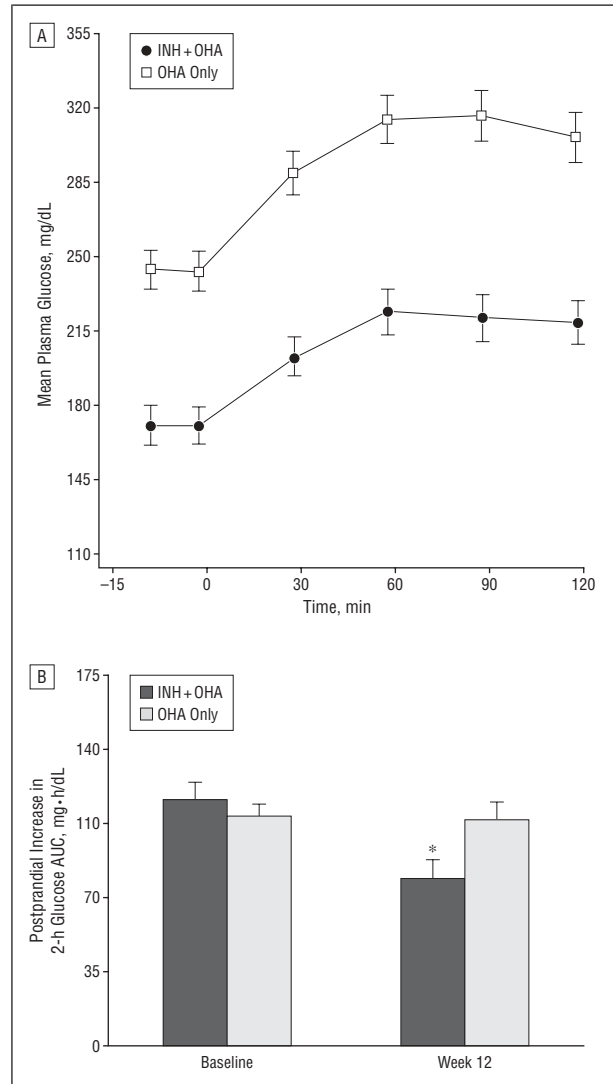


**Figure 1.** Mean glycosylated hemoglobin (HbA<sub>1c</sub>) levels during 12 weeks in patients receiving inhaled insulin plus oral antihyperglycemic agents (INH+OHA) or OHAs only. Error bars are SE.

in favor of INH) was statistically significant (95% CI, -80.64 to -40.73;  $P < .001$ ).

The adjusted change from baseline in 2-hour postprandial glucose increment (from premeal baseline) in patients receiving INH+OHA was  $-25.59 \pm 1.11$  mg/dL ( $-1.42 \pm 0.06$  mmol/L) at week 12, compared with  $-9.18 \pm 1.0$  mg/dL ( $-0.5 \pm 0.1$  mmol/L) in the OHA-only group; the difference between the changes in 2-hour glucose increment ( $-16.22$  mg/dL ( $-0.90$  mmol/L) in favor of INH) approached statistical significance (95% CI, -33.56 to 0.76;  $P = .06$ ).

**Figure 2** shows the effect of treatment on 2-hour postprandial glucose (Figure 2A) and on the increase in 2-hour postprandial glucose area under the curve above preprandial levels (Figure 2B). The postprandial glucose area under the curve was significantly less after 12 weeks' treatment in the INH+OHA group (482.61 mg·h/dL [26.79 mmol·h/L]) than in those receiving OHAs only (656.36 mg·h/dL [36.43 mmol·h/L]). The difference between the 2-hour postprandial area under the curve was  $-173.75$  mg·h/dL ( $-9.64$  mmol·h/L) in favor of INH



**Figure 2.** A, Mean postprandial glucose levels at week 12 for patients receiving inhaled insulin plus oral hypoglycemic agents (INH+OHA) or OHAs only. B, Mean postprandial increase from preprandial levels in 2-hour glucose area under the curve (AUC) for patients receiving INH+OHA or OHAs only. Asterisk indicates  $P = .02$  vs increase from preprandial levels with OHAs at 12 weeks. To convert glucose to millimoles per liter, multiply by 0.0555. Error bars are SE.

(95% CI, -226.86 to -120.62;  $P < .001$ ). The incremental increase in postmeal glucose load over preprandial levels was also significantly reduced in patients receiving

**Table 3. Pulmonary Function Test Results**

Function	Inhaled Insulin Plus Oral Agents		Oral Agents	
	Mean ± SE Baseline Value	Change From Baseline at Week 12 (%)	Mean ± SE Baseline Value	Change From Baseline at Week 12 (%)
Forced expiratory volume in 1 s, L	3.05 ± 0.14	-0.09 (-2.7)	3.20 ± 0.13	-0.03 (-0.6)
Forced vital capacity, L	3.78 ± 0.18	-0.07 (-1.7)	3.93 ± 0.16	-0.02 (-0.2)
Total lung capacity, L	5.60 ± 0.24	0.02 (0.8)*	5.89 ± 0.24	0.05 (1.4)
Carbon monoxide diffusion capacity, mL/min per mm Hg	25.98 ± 1.27	-1.10 (-3.8)†	26.96 ± 1.06	-1.26 (-4.7)

\*n = 31.

†n = 32.

INH+OHA (Figure 2B). After 12 weeks, the 2-hour incremental postprandial glucose area under the curve was  $81.8 \pm 10.1$  mg·h/dL ( $4.54 \pm 0.56$  mmol·h/L) in the INH+OHA group, compared with  $108.60 \pm 8.45$  mg·h/dL ( $6.03 \pm 0.47$  mmol·h/L) in the OHA-only group, a difference of  $-26.80$  mg·h/dL ( $-1.49$  mmol·h/L) in favor of INH (95% CI,  $-50.07$  to  $-5.41$ ;  $P = .02$ ).

### LIPID PROFILE

After 12 weeks of treatment, patients receiving INH+OHA showed a marked reduction in fasting serum triglyceride; the mean change from baseline was  $-76.16 \pm 4.67$  mg/dL ( $-0.86 \pm 0.05$  mmol/L), compared with  $15.25 \pm 4.33$  mg/dL ( $0.17 \pm 0.05$  mmol/L) in those patients receiving OHAs alone. The difference between the adjusted mean changes for the 2 treatments ( $-91.42$  [ $-1.03$  mmol/L] in favor of INH) was statistically significant (95% CI,  $-166.4$  to  $-16.4$ ). The mean change from baseline in fasting serum cholesterol was  $-6.33 \pm 0.74$  mg/dL ( $-0.16 \pm 0.02$  mmol/L) in the INH+OHA group, compared with  $-4.19 \pm 0.69$  mg/dL ( $-0.11 \pm 0.02$  mmol/L) in patients receiving OHAs alone. The difference between the adjusted mean changes for the 2 treatments was  $-2.13$  mg/dL in favor of INH (95% CI,  $-13.96$  to  $9.69$ ) and was not statistically significant. Adjusted mean changes in high-density lipoprotein cholesterol and low-density lipoprotein cholesterol also failed to reach statistical significance (high-density lipoprotein cholesterol,  $3.08$  mg/dL [ $0.08$  mmol/L]; 95% CI,  $-0.28$  to  $6.44$ ; and low-density lipoprotein cholesterol,  $4.13$  mg/dL [ $0.11$  mmol/L]; 95% CI,  $-6.09$  to  $14.36$ ).

### BODY WEIGHT

The mean body weight for patients in the INH+OHA group increased from  $92.3 \pm 2.7$  kg at baseline to  $95.0 \pm 2.7$  kg at week 12; for the OHA-only group, body weight increased from  $91.6 \pm 2.0$  kg at baseline to  $92.1 \pm 2.0$  kg at week 12. The difference between the adjusted mean changes from baseline was  $2.5$  kg (95% CI,  $1.3$ - $3.7$ ;  $P < .001$ ).

### PULMONARY FUNCTION TESTS

All subjects underwent pulmonary function tests. The mean changes in forced expiratory volume in 1 second, forced vital capacity, total lung capacity, and diffusion

capacity to carbon monoxide were small and comparable between the 2 treatment groups (Table 3). Diffusion capacity to carbon monoxide was incorporated into the pulmonary function testing used in this trial, as it is known to be a sensitive indicator of different inflammatory processes that can potentially affect the lung.<sup>22</sup> A greater decline in forced expiratory volume in 1 second and forced vital capacity was observed in the INH+OHA group, but this was not statistically significant, and ongoing long-term studies aim to evaluate the effect of INH on pulmonary function.

### TOLERABILITY

There were no discontinuations or dosage reductions in either group because of adverse events or laboratory test abnormalities. Twenty-seven patients in the INH+OHA group and 4 patients in the OHA-only group experienced adverse events that were possibly or probably related to the treatment regimen. Most of these were mild. Adverse events experienced by more than 10% of patients in the INH+OHA group were asthenia (5 patients [16%], all mild); tremor (10 patients [31%], 8 events were mild); and dizziness (4 patients [13%], all mild). All of these adverse events are symptoms of hypoglycemia. Cough was experienced by 1 patient (3%) in the INH+OHA treatment group, compared with no patients in the OHA-only group.

### COMMENT

The results of this proof-of-concept study show that the addition of INH to existing OHA therapy improves glycaemic control in patients with type 2 diabetes mellitus who fail to achieve optimal glycaemic control with OHA therapy alone. This finding is consistent with a previous study<sup>23</sup> that demonstrated that the addition of rapid-acting insulin lispro to an existing glyburide oral agent regimen significantly improved metabolic control in patients uncontrolled with oral agents alone, and to a significantly greater extent than the addition of isophane insulin.

The addition of premeal INH reduces the postprandial glucose burden and augments the disposal of meal-related glucose. Inhaled insulin not only resulted in the anticipated reduction in postprandial glucose but also lowered fasting glucose substantially. Its use was associated

with decreased glycosylated hemoglobin, heightening the importance of meal-related glucose control.

Inhaled insulin was well tolerated and, based on previous clinical studies,<sup>24-26</sup> incurred a risk of hypoglycemia no greater than that expected with combined OHA and SC insulin therapy. The incidence of hypoglycemic episodes was higher in the INH+OHA group, as expected, with significantly improved glycemic control. The benefits from such improved control may outweigh the risks.<sup>8</sup> In this study, pulmonary function remained unchanged. Addition of INH improved triglyceride levels, possibly due to restoration of insulin regulation of lipolysis.<sup>27</sup>

A concern with adding SC insulin to OHA therapy in patients with type 2 diabetes mellitus is potential weight gain. During the present study, a statistically significant increase in body weight occurred in patients who received INH+OHA. However, the weight gain may be related to improvement in glycemic control<sup>28</sup> and may primarily be caused by the prevention of calorie loss in urinary glucose.<sup>26</sup>

Although the UK Prospective Diabetes Study and the Diabetes Intervention Study highlighted the importance of good glycemic control in type 2 diabetes mellitus,<sup>8,9,29</sup> a large proportion of patients (particularly those who are prescribed OHAs) are not well controlled.<sup>7</sup> The addition of insulin to existing OHA therapy improves glycemic control<sup>28</sup> and is recommended when patients fail with OHAs alone.<sup>10,11</sup> However, the issues of treatment satisfaction, injection-related anxiety, and phobia are important for compliance, glycemic control, and quality of life, because approximately one quarter of patients have psychological problems with injecting insulin.<sup>13</sup> These limitations of injected insulin therapy contribute to poor glycemic control in many patients with type 2 diabetes mellitus. In this regard, it is interesting to note that a questionnaire completed at the end of the study revealed high patient satisfaction with INH: 97% of those who received it opted to continue in a 1-year extension of the therapy.

Previous studies have demonstrated that an INH treatment regimen provided glycemic control comparable to that of a conventional SC insulin regimen in patients with type 1<sup>15</sup> or type 2<sup>21</sup> diabetes mellitus. Although this proof-of-concept study did not include an SC control arm, results demonstrated that the addition of preprandial INH to existing OHAs could improve glycemic control in patients with type 2 diabetes mellitus failing to achieve satisfactory control with OHAs alone. Ongoing phase 3 studies in a larger patient population aim to establish the long-term glycemic control and safety of INH.

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