Efficacy of Inhaled Insulin in Patients With Type 2 Diabetes not Controlled With Diet and Exercise

A 12-week, randomized, comparative trial

Ralph A. DeFronzo, MD[1]
Richard M. Bergenstal, MD[2]
William T. Cefalu, MD[3]
John Pullman, MD[4]
Sam Lerman, MD[5]
Bruce W. Bode, MD[6]
Lawrence S. Phillips, MD[7]
for the Exubera Phase III Study Group

OBJECTIVE — Effective type 2 diabetes management requires prompt intervention if glycemic control is not achieved by nonpharmacological means. This study investigates whether inhaled insulin (INH; Exubera) can achieve target glycemic control in patients failing on diet and exercise.

RESEARCH DESIGN AND METHODS — Patients with suboptimal control on diet and exercise (HbA_{1c} [A1C] 8–11%) were randomized to 3 months' treatment with either INH before meals ($n = 76$) or rosiglitazone 4 mg twice a day ($n = 69$), in conjunction with a diet and exercise regimen. The primary end point was percentage of patients achieving A1C <8.0%.

RESULTS — The INH and rosiglitazone groups had comparable baseline A1C values (9.5 vs. 9.4%, respectively). Significantly more patients achieved A1C <8.0% (83 vs. 58%, adjusted odds ratio 7.14 [95% CI 2.48–20.58], $P = 0.0003$), A1C <7.0% (44 vs. 18%, 4.43 [1.94–10.12]), and A1C ≤6.5% (28 vs. 7.5% 5.34 [1.83–15.57]) with INH. A1C decrease was greater with INH (−2.3% vs. −1.4%, adjusted treatment group difference: −0.89% [95% CI −1.23 to −0.55]) with final mean A1C values of 7.2 and 8.0% for INH and rosiglitazone, respectively. Hypoglycemia (episodes per subject-month) was higher with INH (0.7 vs. 0.05, risk ratio 14.72 [95% CI 7.51–28.83]), with no severe hypoglycemic episodes. Pulmonary function changes were small and comparable between groups.

CONCLUSIONS — INH could be an effective therapy for people with type 2 diabetes early in the course of their disease.

Diabetes Care **28:1922–1928, 2005**

From the [1]University of Texas Health Science Center, San Antonio, Texas; the [2]International Diabetes Center, Minneapolis, Minnesota; the [3]Pennington Biomedical Research Center, Baton Rouge, Louisiana; [4]Mercury Street Medical, Butte, Montana; the [5]Center for Diabetes and Endocrine Care, University of Miami, Miami, Florida; [6]Atlanta Diabetes Associates, Atlanta, Georgia; and the [7]Division of Endocrinology, Emory University School of Medicine, Atlanta, Georgia.

Address correspondence and reprint requests to Ralph A. DeFronzo, University of Texas Health Science Center, Diabetes Division, 7703 Floyd Curl Dr., San Antonio, TX 78284. E-mail: albarado@uthscsa.edu.

Received for publication 17 December 2004 and accepted in revised form 20 April 2005.

W.T.C. has served on an advisory panel for, has received honoraria from, and has received grant/research support from Pfizer and Aventis. J.P. has received honoraria and grant/research support from Pfizer. B.W.B. has received honoraria from Pfizer, sanofi-aventis Group, Lilly, and NovoNordisk and grant/research support from Pfizer.

Abbreviations: ADA, American Diabetes Association; DL_{co}, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in 1 s; FFA, free fatty acid; FPG, fasting plasma glucose; INH, inhaled insulin; PFT, pulmonary function test; PPG, postprandial plasma glucose; SMBG, self-monitoring blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Effective type 2 diabetes management requires prompt intervention if the goals for glycemic control are not achieved by nonpharmacological means. In the early stages of type 2 diabetes, recommended treatment strategies involve the initiation of oral agent therapy, particularly metformin or a thiazolidinedione (1).

Correcting insulin deficiency that manifests itself early in the natural history of type 2 diabetes (2) represents a potential strategy for improving glycemic control. Furthermore, the early use of insulin therapy may slow the loss of endogenous insulin secretion (3). Insulin therapy is, therefore, increasingly being considered earlier in the treatment cascade (4).

Inhaled insulin (INH; Exubera) is a rapid-acting, dry-powder insulin delivery system developed by Pfizer (New York, NY) and sanofi-aventis Group (Bridgewater, NJ) in conjunction with Nektar Therapeutics (San Carlos, CA) (5). Implementing insulin therapy with a noninvasive delivery system may encourage physicians and patients to accept insulin as an earlier treatment option. This study was conducted in patients with type 2 diabetes suboptimally controlled by diet and exercise alone (HbA_{1c} [A1C] >8%) and investigated whether premeal INH can achieve an A1C <8.0% (6) in significantly more subjects than rosiglitazone.

RESEARCH DESIGN AND METHODS

— Male and female subjects with type 2 diabetes ($n = 402$), as defined by the American Diabetes Association (ADA) (7), were screened at 40 centers in the U.S. Inclusion criteria included *1*) ≥2 months since diagnosis of type 2 diabetes, *2*) age 30–80 years, *3*) stable diet and exercise regimens for ≥2 months, *4*) no pharmacological therapy for diabetes, *5*) A1C = 8–11%, *6*) fasting plasma C-peptide ≥0.2 pmol/ml, *7*) BMI ≤40 kg/m^2, *8*) willingness for self-

monitoring of blood glucose (SMBG), and *9*) written informed consent. Exclusion criteria were *1*) poorly controlled asthma, clinically significant chronic obstructive pulmonary disease, or other significant respiratory disease; *2*) smoking during the last 6 months; *3*) abnormal screening chest X-ray, pulmonary function (carbon monoxide diffusing capacity of the lung [DL_{co}] <75%, total lung capacity <80% or >120%, and forced expiratory volume in 1 s [FEV_1] <70% of predicted); *4*) major organ system disease other than diabetes as determined by history, physical examination, routine blood tests, and urinalysis; *5*) abnormal electrocardiogram; *6*) systemic glucocorticoids or other drugs that affect glucose metabolism; *7*) drug or alcohol abuse; *8*) predisposition to severe hypoglycemia (≥2 severe episodes within the past 6 months); *9*) hospitalization or emergency room visit due to poor diabetic control within the past 6 months; or *10*) pregnancy, lactation, or planned pregnancy.

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the protocol was approved by independent local institutional review boards.

This open-label, parallel-group, multicenter study consisted of a 4-week lead-in phase and a 12-week randomized treatment phase. During the lead-in, patients received 60 min of dietary instruction consistent with ADA recommendations (8) (30% fat, calories sufficient to maintain ideal body weight) and were asked to maintain the diet throughout the study. Patients also were instructed to perform 30 min of moderate-intensity exercise on at least 3 days per week, according to ADA guidelines (9). Dietary counseling was given at weeks −3 and 12, and the importance of diet and exercise was reinforced during clinic visits. During the lead-in phase, patients also were instructed in the use of the inhaler device using empty blisters. Patients were provided with a new glucose test meter (Accu-Chek Complete; Roche Diagnostics, Basel, Switzerland) and were asked to perform SMBG at least four times daily (just before breakfast, lunch, supper, and bedtime) for the duration of the study. Compliance with SMBG was summarized by percent of glucose monitoring performed (<50%, 50-<75%, or >75%), calculated as the total glucose monitoring performed divided by the number of days which required four-times–daily monitoring.

Eligible patients were randomized using a computer-generated scheme to receive either INH or rosiglitazone. Blocking by center was used to minimize the imbalance between the sizes of the treatment groups. Variable block sizes of 2 and 4 were used in random order to minimize predictability, and the allocation ratio within each block was 1:1. Allocation was performed using interactive voice response technology.

Subjects were telephoned daily for SMBG results on at least the first 5 days after randomization. Clinic visits were weekly for the first 4 weeks and every other week for the subsequent 8 weeks.

INH was administered <10 min before meals and was always preceded by SMBG. The dry insulin powder was packaged in blister packs of either 1 or 3 mg. One to two inhalations were administered per dosing session, with each inhalation using one blister.

Each patient in the INH group had an individualized recommended insulin dose for each of the dosing times. Recommended initial doses were based on each patient's weight and on factors such as meal size, time of day, and recent or anticipated exercise. The target glucose range was 80–140 mg/dl (4.4–7.8 mmol/l) before meals and 100–160 mg/dl (5.6–8.9 mmol/l) before bedtime. If the glucose concentration was outside this range, patients could decrease or increase the dose by one inhalation of the 1-mg strength INH. Similar adjustments could be considered in anticipation of a smaller- or larger-than-usual meal, and INH could be administered on an "as-needed" basis, if warranted.

Patients assigned to rosiglitazone (Avandia; GlaxoSmithKline, Middlesex, U.K.) received 4 mg twice daily (maximum dosage) and were instructed to maintain a diet and exercise regimen identical to that of the INH group. Rosiglitazone doses were not adjusted.

The primary efficacy end point was the percentage of patients achieving an A1C <8.0% at 12 weeks or at the time of discontinuation. A1C was measured at weeks −4, −1, 0, 6, and 12. The mean of week −1 and week 0 A1C values was taken as the baseline value. Secondary efficacy end points included changes in the following parameters: A1C, fasting plasma glucose (FPG), 2-h postprandial plasma glucose (PPG) following a standardized 16-oz meal comprising 480 kcal (66 g carbohydrate, 29 g protein, 11 g fat [Boost; Mead Johnson Nutritionals, Evansville, IN]) and most recent pre-breakfast dose of INH (weeks 0 and 12), body weight (week −4 and every 4 weeks, thereafter), and fasting serum lipids (weeks 0 and 12). Additional secondary end points were the percentage of patients achieving an A1C <7%, as well as hypoglycemic event rates and severity. Hypoglycemia was defined as typical symptoms without glucose measurement but prompt resolution with food intake, typical symptoms with glucose concentrations <59 mg/dl (<3.3 mmol/l), or any glucose measurement <50 mg/dl (<2.8 mmol/l), with or without symptoms. Hypoglycemia was defined as severe if the subject had a neurological symptom, was unable to treat him/herself, and had either a blood glucose measurement <49 mg/dl (2.8 mmol/l) or the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose. The percentage of patients achieving an A1C ≤6.5% was added as a post hoc analysis.

Safety was assessed by adverse event reporting and clinical and laboratory tests. All observed or reported adverse events were recorded regardless of the suspected causal relationship to the study medications. These included exacerbations of the preexisting illness and the emergence of new manifestations or complications.

Laboratory tests (hematology and biochemistry, fasting lipid profile, and insulin antibodies) were performed at screening and at week 12 by a central laboratory (Quintiles Laboratories, Smyrna, GA). A1C was determined using the Bio-Rad VARIANT II analyzer (Bio-Rad Laboratories, Hercules, CA) in a central laboratory compliant with the National Glycohemoglobin Standardization Program. Liver function tests were performed at screening and at weeks 6 and 12. Physical examinations were undertaken at screening and at weeks 0, 4, 8, and 12. An electrocardiogram was done at screening and at week 12. Comprehensive pulmonary function tests (PFTs), using methods certified by the American Thoracic Society (10), were performed at weeks −3 and 12.

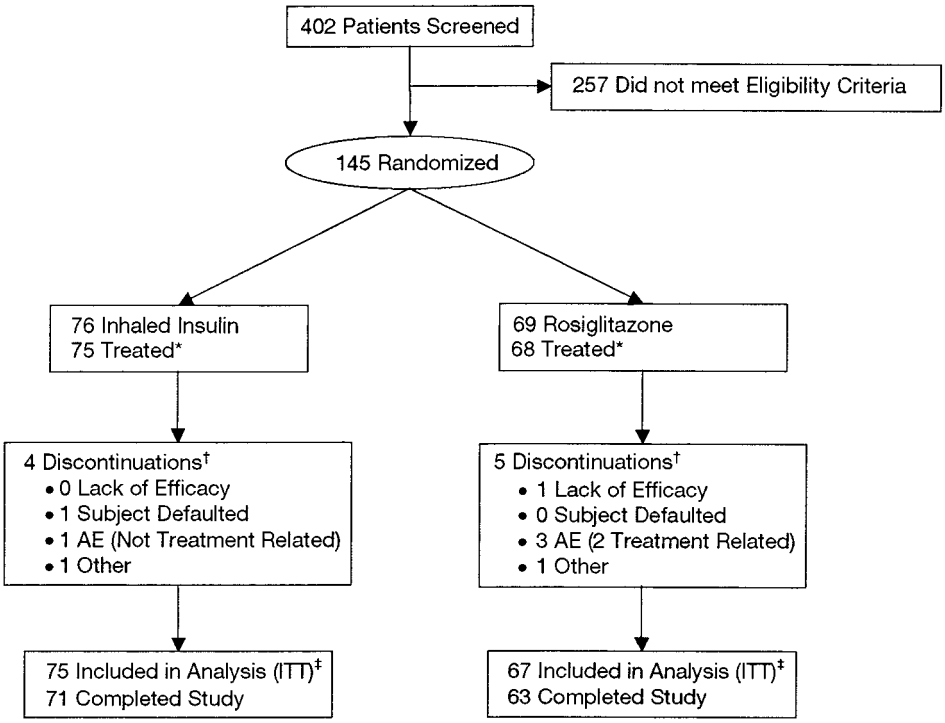

Figure 1—*Subject disposition. *One patient in each group withdrew consent after randomization but before treatment. †Discontinuation from the study by itself did not exclude a subject from analysis. ‡Subjects were excluded from the ITT set for lack of baseline or postbaseline A1C values.*

Statistical analysis

A sample size of 106 subjects per group was calculated to provide 80% power to detect at least a 20% difference in response rates (proportion of patients achieving A1C <8.0%) using a two-sided test at the 5% significance level. A response rate of 35% was assumed for the rosiglitazone group. To account for a possible 5% drop-out rate, 112 patients per treatment group were to be enrolled. However, due to slow enrollment, the study was halted at 145 patients.

The primary efficacy end point was analyzed using intention-to-treat data. The intent-to-treat population was defined as all randomized subjects with a baseline value and at least one postbaseline measurement. A logistic regression model with baseline A1C as a continuous covariate and grouping variables for center and treatment was fitted to the week 12 natural log of the odds of achieving versus not achieving the treatment goal. If the week 12 A1C value was not available, the last available postbaseline value was carried forward. The odds ratio (OR), along with its two-tailed 95% CI and associated *P* value, was calculated.

Treatment effects on the secondary parameters were evaluated using an ANCOVA model with baseline values as continuous covariates and grouping variables for center and treatment. All hypoglycemic events occurring between randomization and the last active treatment plus 1 day were included in the hypoglycemic event rate analyses. The risk of hypoglycemia was estimated by the crude hypoglycemic event rate for each group (the number of episodes reported per subject-month of treatment for total episodes and per 100 subject-months for severe episodes). The risk ratio was estimated using the survival analysis counting process approach for recurrent events, which only included a term for treatment.

Treatment group differences (INH − rosiglitazone) in PFT parameter changes from baseline were estimated at week 12 using an ANCOVA model. The model included terms for treatment and center and covariates known to have a physiologic relationship with pulmonary function, including baseline PFT, age (years), baseline height (meters), and sex.

RESULTS

— Of the 143 patients enrolled in the study, 75 received INH and 68 received rosiglitazone. One subject from each group was randomized but never received any study medication. Seventy-one subjects in the INH group and 63 in the rosiglitazone group completed the study (Fig. 1). The baseline characteristics of subjects were comparable in both treatment groups and are shown in Table 1.

The proportion of subjects reaching the study goal of A1C <8% was significantly higher in the INH group versus the rosiglitazone group (82.7 vs. 58.2%, adjusted OR 7.14 [95% CI 2.48–20.58], $P = 0.0003$) (Fig. 2). Similarly, the proportion of subjects achieving the ADA-recommended goal of A1C <7% (11) (44.0 vs. 17.9%, 4.43 [1.94–10.12]) or the American Association of Clinical Endocrinologists' recommended A1C level of ≤6.5% (12) (28.0 vs. 7.5%, 5.34 [1.83–15.57]) was higher in the INH group (Fig. 2). The absolute reduction in A1C at week 12 was greater in the INH group (−2.3 vs. −1.4%, adjusted treatment group difference −0.89% [−1.23 to −0.55]) with mean final A1C values of 7.2 and 8.0% for INH and rosiglitazone, respectively (Fig. 3).

A greater number of hypoglycemic episodes were reported in the INH group compared with the rosiglitazone group (0.7 vs. 0.05 episodes per subject-month, risk ratio 14.72 [95% CI 7.51–28.83]). Over the entire study period, a total of 153 hypoglycemic episodes (36 patients) were reported in the INH group compared with 9 (5 patients) in the rosiglitazone group. The highest frequency of hypoglycemic events experienced with

Table 1—*Baseline characteristics of subjects randomized and treated*

	INH	Rosiglitazone
n	75	68
Age (years)	53.0 ± 10.7 (28–76)	54.4 ± 11.0 (29–80)
Sex (M/F)	48/27	31/37
Ethnicity (white/other) (%)	77/23	71/29
C-peptide (pmol/ml) at screening	1.09 ± 0.42 (0.36–2.05)	1.11 ± 0.41 (0.40–2.15)
BMI (kg/m^2)	31.9 ± 4.7 (20–44)	32.7 ± 6.6 (22–48)
Duration of diabetes (years)	4.3 (0.08–22.0)	3.1 (0.01–18.00)
A1C (%)	9.5 ± 1.1	9.4 ± 0.9
FPG (mg/dl)	208 ± 56	199 ± 50
2-h PPG (mg/dl)	293 ± 82	281 ± 71
Total cholesterol (mg/dl)	195.3 ± 38.3	199.9 ± 49.9
HDL cholesterol (mg/dl)	36.1 ± 8.7	40.1 ± 10.6
LDL cholesterol (mg/dl)	116.3 ± 31.8	119.4 ± 29.5
Triglycerides (mg/dl)	224.1 ± 193.8	194.3 ± 147.8

Data are means ± SD or means ± SD (range), unless otherwise indicated.

INH occurred during meal times, between 12:00 and 1:00 P.M. (13%), 6:00 and 8:00 P.M. (25.3%), or 9:00 and 10:00 P.M. (13.3%); the remaining 49% of cases spread across all other times. No severe hypoglycemic episodes were reported in the study.

Changes from baseline in FPG, measured on the morning before the standardized meal, were comparable between groups (−64 vs. −56 mg/dl [−3.56 vs. −3.11 mmol/l], respectively; adjusted treatment group difference: −4 mg/dl [−0.22 mmol/l] [95% CI −18 to 9]). Absolute mean changes from baseline in 2-h PPG (following the standardized meal) also were comparable between groups (−92 vs. −92 mg/dl [−5.11 vs. −5.11 mmol/l], respectively; 4 mg/dl [0.22 mmol/l]; [−18 to 26]). The pre-Sustacal INH dose was not adjusted for the carbohydrate content of the meal, but instead subjects took the same INH dose as they were taking after 24 weeks. Twenty-four–hour SMBG favored INH in terms of average daily blood glucose (−76 vs. −69 mg/dl [−4.22 vs. −3.83 mmol/l]; −14 mg/dl [−0.78 mmol/l]; [−25 to −3]). Most subjects in both treatment groups performed SMBG at least 75% of the time (87 and 97% for INH and rosiglitazone groups, respectively).

Average daily INH doses remained stable during the study (14.9 mg at week 6 vs. 15.3 mg at week 12). The improvements in glycemic control were accompanied by changes in body weight. The mean unadjusted change from baseline in body weight was 1.9 kg for the INH group and 0.8 kg for the rosiglitazone group (adjusted treatment group difference 0.95 kg [95% CI −0.18 to 2.09]). There was a large decrease in median serum triglyceride levels compared with baseline in the INH group (−35 mg/dl) but not in the rosiglitazone group (±0 mg/dl). Those treated with rosiglitazone had increases in total and LDL cholesterol levels (median changes +10.5 and +15.0 mg/dl) compared with the INH group (−2.0 and +4.5 mg/dl). Both groups experienced small increases in HDL cholesterol (median changes +4 mg/dl with INH vs. +3 mg/dl with rosiglitazone).

A greater proportion of patients in the INH group experienced treatment-related adverse events compared with the rosiglitazone group (51 and 22 patients, respectively). Most, however, were of mild to moderate severity, with the most common being hypoglycemia. Two treatment-unrelated severe adverse events were reported in the rosiglitazone group (one gastric ulcer and one cholecystitis) and none in the INH group. There were two discontinuations due to treatment-related adverse events in the rosiglitazone group (one headache, peripheral edema, myalgia, and chest pain; one elevated liver function tests) and one in the INH group

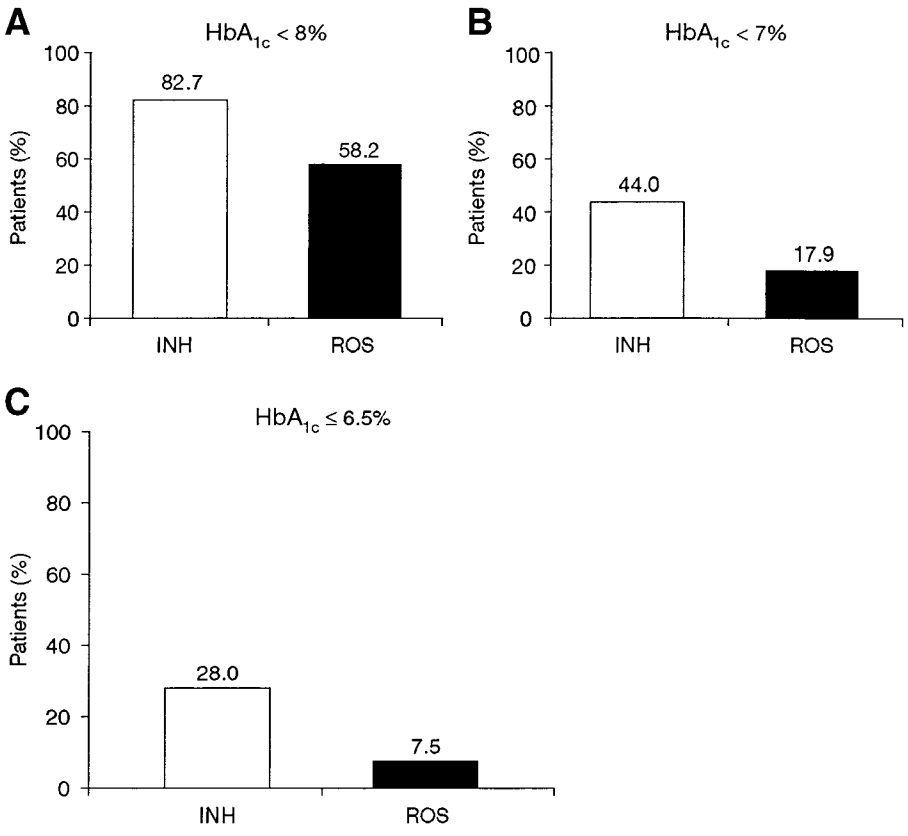

Figure 2—*Percentage of patients achieving target glycemic levels in the inhaled INH and rosiglitazone (ROS) groups. Adjusted OR INH-rosiglitazone 7.14 [95% CI 2.48–20.58], P = 0.0003 (A), 4.43 [1.94–10.12] (B), and 5.34 [1.83–15.57] (C).*

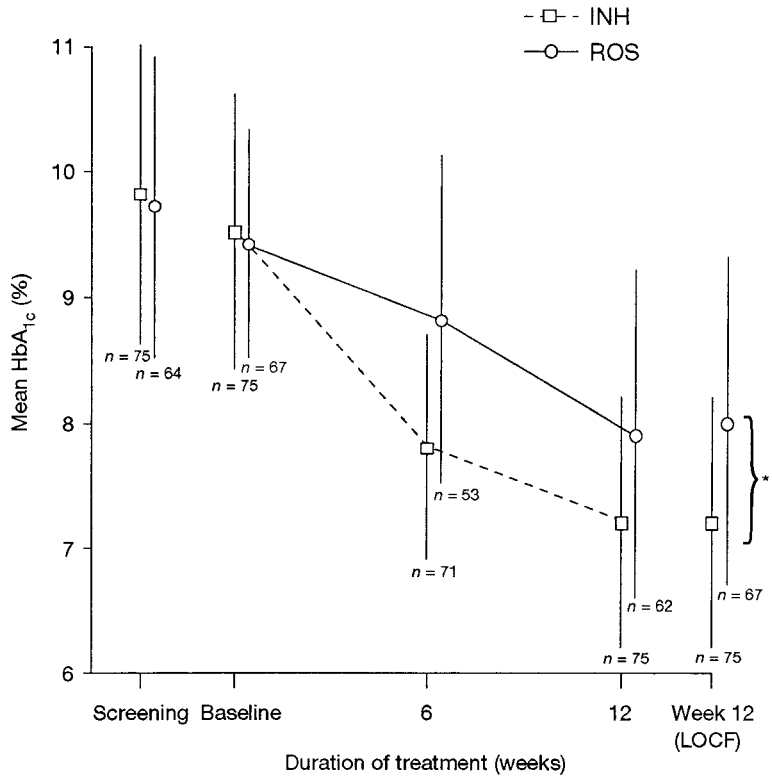

Figure 3—*Decline from baseline in A1C throughout the study in the INH and rosiglitazone (ROS) groups. *INH-rosiglitazone adjusted treatment group difference at week 12 (LOCF [last observation carried forward]) −0.89 [95% CI −1.23 to −0.55].*

(bronchitis). Changes in PFT results were comparable between treatment groups (small, nonprogressive, and not statistically significant versus baseline), and lung function was generally stable over the study period. Mean changes from baseline at week 12 for FEV_1 (−0.016 vs. −0.001 l), forced vital capacity (0.002 vs. 0.009 l), total lung capacity (0.033 vs. 0.064 l), and DL_{co} were (−0.973 vs. −0.829 ml · min^{-1} · $mmHg^{-1}$) for the INH and rosiglitazone groups, respectively. The adjusted INH-rosiglitazone difference was −0.016 (95% CI −0.079 to 0.046), −0.006 (−0.088 to 0.076), −0.030 (−0.213 to 0.152), and −0.144 (−1.081 to 0.792) for FEV_1, forced vital capacity, total lung capacity, and DL_{co}, respectively. Cough was reported more frequently in the INH group (8.0 vs. 1.5%) but was generally mild and decreased in incidence and prevalence over the study period. There were no notable changes in other safety parameters.

At week 12, median insulin antibody binding in both groups and mean antibody binding in the rosiglitazone group were below the limit of quantitation (<3% binding). Mean ± SD antibody binding in the INH group was 6.2 ± 8.5%. Increases in insulin antibody binding had no clinical correlates; specifically, they were not associated with a rise in A1C or adverse events.

CONCLUSIONS — In the present study, correcting the defect in early phase insulin secretion using premeal INH administration was effective in achieving defined targets of glycemic control in a group of type 2 diabetic patients that was suboptimally controlled on diet and exercise (83% for A1C <8%, 44% for A1C <7%, and 28% for A1C ≤6.5%). To our knowledge, this represents the only demonstration that ADA goals for glycemic control can be achieved in many type 2 diabetic patients using only a rapid-acting insulin.

The study shows that INH monotherapy improves glycemic control more quickly than rosiglitazone, which may take ≥18 weeks to achieve peak glucose lowering activity (13). However, it cannot be ruled out that a longer study duration may have resulted in greater glucose lowering in the rosiglitazone arm. Furthermore, other preprandial insulins might be expected to have similar glucose-lowering properties as INH, although injected preprandial insulin is not commonly used as initial therapy in patients with type 2 diabetes who are suboptimally controlled on diet and exercise therapy.

It generally is felt that short-acting insulin controls PPG levels, whereas long-acting insulin, especially when administered at bedtime, reduces FPG concentrations (14). However, in the present study, rapid-acting INH reduced the FPG concentration by 64 mg/dl. During the standardized meal, reductions in PPG concentrations were similar in INH- and rosiglitazone-treated patients. These results might appear at odds with the 64%-greater A1C reduction in the INH group than the rosiglitazone group. Inability to observe a greater decrease in PPG during the standardized meal test in the INH group may be explained by failure to individually adjust the insulin dose based on the amount of carbohydrates and calories in the meal. INH achieved improvements in average daily blood glucose and 2-h PPG based on an inpatient meal test, but these changes were similar to those observed with rosiglitazone.

Thus, the greater reduction in A1C with INH vs. rosiglitazone (2.3 vs. 1.4%) despite a similar reduction in FPG suggests an additional effect of INH on daily outpatient PPG levels. By reducing mean blood glucose levels, premeal INH may be sufficient to reduce glucose toxicity by reducing the activity of glucose-6-phosphatase, which is the rate-limiting step in hepatic glucose production (15). Reduction of postprandial glucose peaks also could be expected to reduce the concentrations of gluconeogenic substrates such as lactate (16–18), leading to improved suppression of hepatic glucose output. Moreover, improving postprandial glucose control by ameliorating "glucose toxicity" could lead to improved insulin secretion (19–20).

Improved glycemic control following short-acting premeal INH also could result from amelioration of lipotoxicity (21,22) that results from the reduction in plasma free fatty acid (FFA) levels secondary to lipolysis inhibition by hyperinsulinemia for 5–6 h after each meal. Chronic reduction in plasma FFA levels reduces the elevated rates of basal/postprandial hepatic glucose production, augments muscle insulin sensitivity, and

improves β-cell function (21). Although FFA concentrations were not measured in this study, substantial lowering of triglyceride levels was observed in the INH group, consistent with improved glucose control and most likely a decrease in plasma FFA. Insulin is also known to inhibit hepatic VLDL-triglyceride synthesis (23). It is well recognized that type 2 diabetes is associated with dyslipidemia, characterized by elevated triglyceride levels and decreased levels of HDL cholesterol, which contribute to an increased cardiovascular risk observed in this patient population (24). The large median decrease in triglyceride levels (−35 mg/dl) concomitant with improved glycemic control observed with INH may be associated with a reduction in risk of cardiovascular complications in patients with type 2 diabetes. During the study, there was a slight imbalance on concomitant lipid-lowering medication usage between the two groups. In the INH group, 6 subjects used a fibrate and 10 subjects used hydroxymethylglutaryl CoA inhibitors, whereas in the rosiglitazone group, 1 subject used a fibrate and 13 subjects used hydroxymethylglutaryl CoA inhibitors.

Inhaled insulin was well tolerated by type 2 diabetic patients in this study. All treatment-related adverse events with INH were of mild to moderate severity, with the most common being hypoglycemia (events-per-subject–month were 0.7 for the INH group and 0.05 for the rosiglitazone group) and mild cough (6 of 75 patients receiving INH reported cough compared with 1 of 68 patients treated with rosiglitazone). No episodes of severe hypoglycemia were reported by any patient in the INH group. There was a small increase of insulin antibody levels associated with inhaled insulin, but there were no obvious clinical or other laboratory sequelae associated with this phenomenon. Changes in PFT parameters were not different between groups over the study period. Early studies with INH demonstrated very small reductions in FEV_1 and DL_{co} versus comparator therapy. Continued INH therapy for up to 2 years shows that the differences in PFTs between the two treatment groups are not progressive (25). Additional studies are currently underway to further confirm these findings.This indicates that INH, as initial monotherapy, could be a safe and effective therapy for people with type 2 diabetes who do not achieve adequate glycemic control through diet and exercise alone.

Acknowledgments— This research was funded by Pfizer (New York, NY) and the sanofi-aventis Group (Bridgewater, NJ).

APPENDIX

The Exubera Phase III Study Group

M. Larissa Aviles-Santa, John Bagdade, Carroll Basil Williams, Joseph Bassi, Richard Bergenstal, Marshall Block, Lawrence Blonde, Bruce Bode, Seth Braunstein, Mark Burge, William Cefalu, Mayer Davidson, Ralph DeFronzo, Jerry Drucker, William Ellison, Mark Ettinger, Barbara Feuerstein, Robin Goland, Jeffrey Herbst, Roy Kaplan, David Klonoff, William Lasswell, Sam Lerman, Ellis Levin, Seth Lewis, Janet McGill, Jeffrey Miller, Sam Miller, Byron Musa, Joel Neutel, Mitchell Parker, Robert Paster, William Petit Jr, Lawrence Phillips, John Pullman, Philip Raskin, Charles Reasner, Herbert Rettinger, Stephen Richardson, Daniel Scheerer, Sherwyn Schwartz, David Smith, Evan Stein, Harvey Tilker, Melvin Tonkon, Denise Tonner, Richard Weinstein, and Ruth Weinstock.

References

1. Reasner CA, DeFronzo RA: Treatment of type 2 diabetes: a rational approach based on its pathophysiology. *Am Fam Physician* 63:1687–1688; 1691–1692; 1694, 2001
2. Pratley RE, Weyer C: The role of impaired early insulin in the pathogenesis of type 2 diabetes. *Diabetologia* 44:929–945, 2001
3. Alvarsson M, Sundkvist G, Lager I, Henricsson M, Berntorp K, Fernqvist-Forbes E, Steen L, Westermark G, Westermark P, Orn T, Grill V: Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients. *Diabetes Care* 26:2231–2227, 2003
4. Home P, Boulton A, Jimenez J, Landgraf R, Osterbrink B, Christiansen JS: Issues relating to the early or earlier use of insulin in type 2 diabetes. *Practical Diabetes International* 20:63–71, 2003
5. Barnett AH: Exubera inhaled insulin: a review. *Int J Clin Pract* 58:394–401, 2004
6. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 23 (Suppl. 1):S33–S49, 2002
7. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 21 (Suppl. 1):S5–S19, 1998
8. Franz MJ, Horton ED, Bantle JP, Beebe CA, Brunzell JD, Coulston AM, Henry RR, Hoogwerf BJ, Stacpoole PW: Nutrition principles for the management of diabetes and related complications (Technical Review). *Diabetes Care* 17:490–518, 1994
9. American Diabetes Association: Diabetes mellitus and exercise (Position Statement). *Diabetes Care* 21 (Suppl. 1):S40–S44, 1998
10. American Thoracic Society: *Pulmonary Function Laboratory Management and Procedure Manual*. Wanger J, Crapo RO, Irvin CG, Eds. New York, NY, American Thoracic Society, 1998
11. American Diabetes Association: Standards of medical care in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1): S15–S35, 2004
12. The American Association of Clinical Endocrinologists: The American Association of Clinical Endocrinologists medical guidelines for the management of diabetes mellitus: the AACE system of intensive diabetes self-management: 2002 update. *Endocr Pract* 8 (Suppl. 1):S40–S82, 2002
13. Phillips LS, Grunberger G, Miller E, Patwardhan R, Rappaport EB, Salzman A: Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. *Diabetes Care* 21:308–315, 2001
14. Yki-Jarvinen H, Dressler A, Ziemen M, the HOE 901/3002 Study Group: Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 23: 1130–1136, 2000
15. Barzilai N, Rossetti L: Role of glucokinase and glucose-6-phosphatase in the acute and chronic regulation of hepatic glucose fluxes by insulin. *J Biol Chem* 268:25019–25025, 1993
16. Bonadonna RC, Del Prato S, Bonora E, Saccomani MP, Gulli G, Natali A, Frascerra S, Pecori N, Ferrannini E, Bier D, Cobelli C, DeFronzo RA: Roles of glucose transport and glucose phosphorylation in muscle insulin resistance of NIDDM. *Diabetes* 45:915–925, 1996
17. Del Prato S, Bonadonna RC, Bonora E, Gulli G, Solini A, Shank M, DeFronzo RA: Characterization of cellular defects of insulin action in type 2 (non-insulin-dependent) diabetes mellitus. *J Clin Invest* 91: 484–494, 1993
18. Gastaldelli A, Baldi S, Pettiti M, Toschi E, Camastra S, Natali A, Landau BR, Ferrannini E: Influence of obesity and type 2 diabetes on gluconeogenesis and glucose

output in humans: a quantitative study. *Diabetes* 49:1367–1373, 2000
19. Leahy JL, Cooper HE, Weir GC: Impaired insulin secretion associated with near normoglycemia: study in normal rats with 96-h in vivo glucose infusions. *Diabetes* 36:459–464, 1987
20. Rossetti L, Shulman GI, Zawalich W, deFronzo RA: Effect of chronic hyperglycemia on in vivo insulin secretion in partially pancreatectomized rats. *J Clin Invest* 80:1037–1044, 1987
21. Bays H, Mandarino L, DeFronzo RA: Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. *J Clin Endocrinol Metab* 89:463–478, 2004
22. Unger RH: Lipotoxic diseases. *Annu Rev Med* 53:319–336, 2002
23. Taskinen MR, Lahdenpera S, Syvanne M: New insights into lipid metabolism in non-insulin-dependent diabetes mellitus. *Ann Med* 28:335–340, 1996
24. Krauss RM, Siri PW: Dysplipidemia in type 2 diabetes. *Med Clin North Am* 88: 897–909, 2004
25. Dreyer M, the Exubera Phase 3 Study Group: Efficacy and 2-year pulmonary safety data of inhaled insulin as adjunctive therapy with metformin or glibenclamide in type diabetes patients poorly controlled with oral monotherapy: presented at the 40th Annual Meeting of the European Association for the Study of Diabetes, September 5–9, 2004, Munich, Germany (Abstract). *Diabetologia* 47 (Suppl. 1):A44, 2004