An Open, Randomized, Parallel-Group Study to Compare the Efficacy and Safety Profile of Inhaled Human Insulin (Exubera) With Metformin as Adjunctive Therapy in Patients With Type 2 Diabetes Poorly Controlled on a Sulfonylurea

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OBJECTIVE — To compare the efficacy and safety profile of adding inhaled human insulin (INH; Exubera) or metformin to sulfonylurea monotherapy in patients with poorly controlled type 2 diabetes.

RESEARCH DESIGN AND METHODS — We performed an open-label, parallel, 24-week, multicenter trial. At week −1, patients uncontrolled on sulfonylurea monotherapy were divided into two HbA_{1c} (A1C) arms: ≥8 to ≤9.5% (moderately high) and >9.5 to ≤12% (very high). Patients were randomized to adjunctive premeal INH ($n = 225$) or metformin ($n = 202$). The primary efficacy end point was change in A1C from baseline.

RESULTS — In the A1C >9.5% arm, INH demonstrated a significantly greater reduction in A1C than metformin. Mean adjusted changes from baseline were −2.17 and −1.79%, respectively; between-treatment difference was −0.38% (95% CI −0.63 to −0.14, $P = 0.002$). In the A1C ≤9.5% arm, mean adjusted A1C changes were −1.94 and −1.87%, respectively (−0.07% [−0.33 to 0.19], $P = 0.610$), consistent with the noninferiority criterion. Hypoglycemia (events/subject-month) was greater in the INH (0.33) than in the metformin (0.15) group (risk ratio 2.16 [95% CI 1.67–2.78]), but there were no associated discontinuations. Other adverse events, except increased cough in the INH group, were similar. At week 24, changes in pulmonary function parameters were small and comparable between groups. Insulin antibody binding increased more with INH but did not have any associated clinical manifestations.

CONCLUSIONS — In patients with type 2 diabetes poorly controlled on a sulfonylurea (A1C >9.5%), the addition of premeal INH significantly improves glycemic control compared with adjunctive metformin and is well tolerated.

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Abbreviations: ADA, American Diabetes Association; DL_{co}, carbon monoxide transfer factor; FEV_1, forced expiratory volume in 1 s; INH, inhaled human insulin.

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

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In patients with type 2 diabetes for whom diet and exercise do not provide adequate glucose control, pharmacologic intervention is required. This usually begins with oral antidiabetic agents, most commonly metformin and the second-generation sulfonylureas, which collectively reduce insulin resistance in peripheral and hepatic tissues and increase insulin secretion and therefore are often used in combination (1). Although there is as yet no evidence that such combination therapy reduces diabetes-associated morbidity or mortality, a number of clinical trials have shown these agents to have significant additive effects on indexes of metabolic control (2–6).

A gradual rise in HbA_{1c} (A1C) is inevitable, however, because of the progressive nature of the β-cell defect in type 2 diabetes, and the majority of patients will ultimately require insulin. However, most seek to avoid or postpone insulin therapy when possible, believing it represents a decline in their condition (7,8). In addition, they may not be prepared to self-inject daily (9,10). Improvements in insulin delivery may overcome some of the barriers to insulin therapy and encourage its use earlier in the disease process. Inhaled human insulin (INH; Exubera [insulin human {rDNA origin inhalation powder}]) is a dry-powder formulation and inhaler system developed by Pfizer in collaboration with Nektar Therapeutics that has recently been approved in both the U.S. and European Union for the treatment of type 1 and type 2 diabetes in adults (11). INH therapy has proven effective in patients failing to obtain adequate glycemic control with diet and exercise (12), has demonstrated improved glycemic control compared with oral antidiabetic agents (13,14), and has been shown to be comparable to subcutaneously injected insulin (15). The objective of this study was to investigate the

efficacy and safety profile of INH as adjunctive therapy with metformin in patients with type 2 diabetes poorly controlled with sulfonylurea monotherapy.

RESEARCH DESIGN AND METHODS

— This was an open-label, multicenter, parallel-group, comparator study conducted and led by academic investigators and managed by Pfizer Global Research and Development (the sponsor). The study protocol was approved by the independent local institutional review boards of all participating centers, and all patients provided written informed consent. The study was conducted in compliance with the ethical principles originating from the Declaration of Helsinki.

Inclusion criteria were *1*) age 35–80 years; *2*) type 2 diabetes diagnosed at least 6 months before screening; *3*) poorly controlled outpatients (A1C 8–12%) failing maximal doses of a sulfonylurea alone (glibenclamide ≥10 mg/day [standard formulation], glibenclamide ≥7 mg/day [micronized formulation], gliclazide ≥160 mg/day, glipizide ≥10 mg/day, or glimepiride ≥3 mg/day or equivalent) for a minimum of 2 months before screening; *4*) pulmonary function tests within the following ranges: carbon monoxide transfer factor (DL_{CO}) ≥75%, total lung capacity 80–120% inclusive, and forced expiratory volume in 1 s (FEV_1) ≥70% of predicted value; and *5*) written informed consent.

Exclusion criteria included moderate or severe asthma or chronic obstructive pulmonary disease; clinically significant abnormalities on chest X-ray; smoking within 6 months before randomization; concomitant therapy with hypoglycemic agents or agents that may affect glycemic control, e.g., oral steroids; fasting C-peptide ≤0.2 nmol/l; major organ system disease; abnormalities on laboratory screening; known drug or alcohol dependence; and pregnancy, lactation, or planned pregnancy.

After screening, patients continued therapy with the sulfonylurea brand and dose on which they entered the study during the 4-week run-in period; this treatment was continued throughout the study. Before randomization, patients were divided into arms based on week −1 A1C values: A1C ≥8 to ≤9.5% ("moderately high") and A1C >9.5 to ≤12% ("very high"). The cutoff of 9.5% was based on the median baseline A1C in an earlier study of similar design (13).

Randomization was concealed and used an interactive telephone system. The investigator dialed a central database and answered a series of prompts (protocol number, patient identification). The interactive system randomized the patient to INH or metformin (1 g twice daily throughout the study). Subjects were advised to follow an American Diabetes Association (ADA) diet, consisting of 30% fat and calories sufficient to maintain ideal body weight (16), for the duration of the study, and they received exercise instructions in line with ADA recommendations (17). The importance of the diet and exercise regimen was reinforced at clinic visits (weeks −4, −1, 0, 6, 10, 14, 18, and 24).

INH was administered within 10 min before meals. Before beginning the study, patients were trained in the inhalation procedure. INH was available in 1- and 3-mg dose blister packs (1 mg equivalent to ~2.5–3.0 units of subcutaneously injected insulin) (18).

Patients were instructed in self-monitoring of blood glucose (MediSense Precision QID Blood Glucose Sensor). All patients performed home glucose monitoring a minimum of three (preferably four) times daily. As with conventional insulin therapy, dosing of INH involved an empirical, ongoing process of individualized dose titration based upon each subject's glucose response. Initial recommended doses for INH were based on factors including the patient's weight and degree of glycemic control. Administration was preceded by a blood glucose test, and the dose was adjusted weekly at the discretion of the investigator, based on self-monitored blood glucose results, to achieve a mean fasting glycemic target of 4.4–7.8 mmol/l (80–140 mg/dl). The subject was to use the recommended dose when the self-measured premeal glucose value was in the range of 4.4–10.0 mmol/l (80–180 mg/dl). In the event of lower (<4.4 mmol/l) or higher (>10 mmol/l) glucose values at the time of dosing, the subject could adjust the dose down or up by one inhalation of the 1-mg strength of INH. Patients could also adjust doses in anticipation of a smaller- or larger-than-usual meal or on an "as-needed" basis. Subjects randomized to adjunctive metformin underwent a period of dose titration, during which the dose was increased from 500 mg once daily to 1 g twice daily.

The primary objective was to demonstrate that adjunctive INH, compared with adjunctive metformin, achieves better glycemic control at 24 weeks in patients with baseline A1C >9.5% and is noninferior to metformin in patients in the combined A1C arms. Noninferiority in the moderately high A1C arm (≤9.5%) was assessed secondarily. The primary efficacy end point was change in A1C from baseline to week 24. A1C was measured prescreening and at weeks −6, −4, −1, 0, 6, 10, 14, 18, and 24. Secondary efficacy end points included percentage of patients achieving A1C ≤7 and ≤8% at week 24 (A1C criterion of 8% chosen as it was the ADA action level at the time of the study [3]), incidence and severity of hypoglycemic events, change in fasting plasma glucose and 2-h postprandial glucose, change in fasting lipid profile, body weight, and discontinuation rate. Efficacy analyses were based on patients randomized.

Safety analyses were based on actual treatment received. Evaluations included full pulmonary function tests, physical examination, 12-lead electrocardiogram, chest X-ray, clinical laboratory safety tests, and insulin antibodies. Observed and volunteered adverse events were recorded.

Patients were instructed to check blood glucose if they experienced symptoms of hypoglycemia. Hypoglycemia was defined as one of the following: characteristic symptoms of hypoglycemia with no blood glucose check but prompt resolution with food intake, subcutaneous glucagon, or intravenous glucose; characteristic symptoms of hypoglycemia with blood glucose ≤3.3 mmol/l (59 mg/dl); or any blood glucose measurement ≤2.7 mmol/l (49 mg/dl). Severe hypoglycemia was based on the Diabetes Control and Complications Trial criteria (19).

Statistical methods

Statistical analyses were performed by the sponsors in accordance with a predetermined statistical analysis plan. A sample size of 90 patients in each baseline A1C arm (180 patients per treatment group) was planned to provide 80–94% power to detect a 0.7% difference in change from baseline A1C between the groups and 81–95% power to ensure that the change from baseline A1C with adjunctive INH is "at least as good as" that with adjunctive metformin. To account for a possible 20% drop-out rate, a total of 450 patients (225 per treatment group) were to be recruited for the study.

The primary analysis population was the intent-to-treat set, defined a priori in

the protocol as all randomized patients with a baseline A1C and at least one post-baseline A1C value. The primary model was an ANCOVA with baseline A1C as a continuous covariate and indicator variables for country and a four-level term for A1C arm by treatment group: A1C ≤9.5 (INH), ≤9.5 (metformin), >9.5 (INH), and >9.5% (metformin). A1C arm-specific (A1C ≤9.5 vs. >9.5%) and combined A1C arm comparisons between the INH and metformin groups were made. Due to the multiplicity of testing, a significance level of 0.025 was used to test the hypothesis of superiority. The supplemental claim for noninferiority (combined A1C arm) was met if the upper bound of the two-sided 95% CI of the difference in change from baseline A1C did not exceed 0.5%. If the week 24 observation was not available, the last observation was carried forward.

Treatment effects on the secondary end points were estimated based on an ANCOVA model containing the baseline value of the secondary end point and the center as covariates. A1C arm-specific and combined analyses were performed. The percentage of patients reaching predefined glycemic control goals (A1C <8% and <7%) at week 24 was analyzed using the method of logistic regression (20). The hypoglycemic event rate ratio was estimated using the survival analysis counting process approach for recurrent events, where the analysis model included only a term for treatment (21).

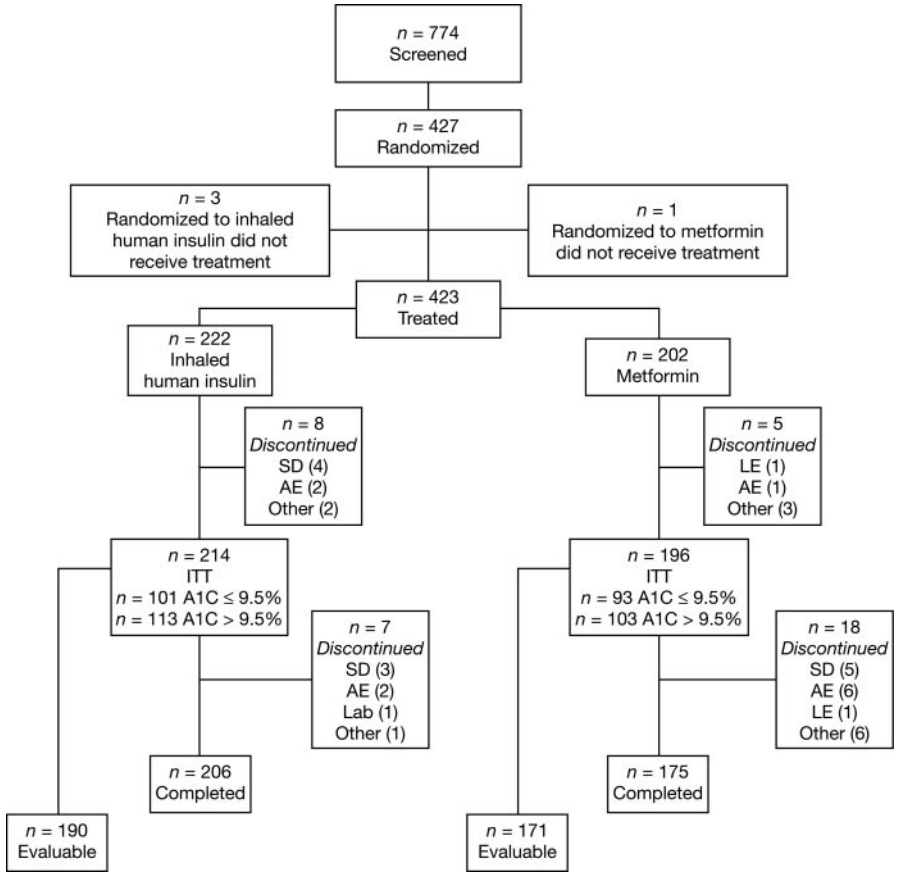

Figure 1— *Patient disposition for patients with type 2 diabetes failing sulfonylurea therapy randomized to adjunctive INH or metformin. For one subject in the INH and three subjects in the metformin intent-to-treat (ITT) groups, some of the data were not available at data cut off although they had completed the study. AE, adverse event; LE, lack of efficacy; SD, subject defaulted. Other: does not meet entrance criteria, protocol violation, or other.*

RESULTS

Demography and baseline characteristics

Of 774 patients screened, 427 were randomized to treatment and 410 qualified for the intent-to-treat analysis: 214 patients to INH and 196 patients to metformin (Fig. 1). Demographic and clinical characteristics were similar between the INH and metformin groups at study entry for all A1C arms; results for the combined A1C arms are shown in Table 1.

Efficacy

The study met the primary objectives of demonstrating improved glycemic control to metformin for patients in the very high A1C arm (A1C >9.5%) and noninferior glycemic control for patients in the moderately high A1C arm (A1C ≤9.5%). For the A1C >9.5% arm, the mean adjusted change from baseline was −2.17% (INH) and −1.79% (metformin); between-treatment difference was −0.38% ([95% CI −0.63 to −0.14], $P = 0.002$) (Table 1 and Fig. 2). INH also demonstrated a significantly greater decrease from baseline in adjusted mean A1C at 24 weeks than metformin in the combined A1C arms (−2.06 vs. −1.83%, respectively); between-treatment difference was −0.22% ([−0.40 to −0.05], $P = 0.014$) (Table 1).

At baseline, few patients had A1C <8% and none had A1C <7% in either group. By the end of study, 137 patients (64%) in the INH and 114 patients (58%) in the metformin combined A1C arms had A1C <8%, and 54 INH patients (25%) and 45 metformin patients (23%) achieved A1C <7% (Table 1).

There were no differences between A1C arms by treatment group for either fasting plasma glucose or 2-h postprandial glucose; therefore, results are presented for the combined A1C arms. The decrease in fasting plasma glucose from baseline to week 24 was similar in both groups, and the difference between treatment groups was small (Table 1). At week 24, there were similar, substantial decreases from baseline in 2-h postprandial glucose (Table 1).

Analysis of week 24 data from the combined A1C arms showed that adjunctive INH treatment was associated with a mean weight gain of 3 kg compared with a mean weight drop of 0.1 kg with metformin. The difference between adjusted mean changes was 3.14 (95% CI 2.56–3.71). The weight changes tended to stabilize toward the end of the treatment period.

Fasting lipid values did not differ within A1C arms by treatment; therefore, results are presented for the combined A1C arms. The metformin group had a trend for greater reductions in total and LDL cholesterol than the INH group (Table 1). No differences in treatment effect were observed for triglycerides and HDL cholesterol (Table 1).

Table 1—*Demographic, baseline characteristics, and week 24 outcome data for patients with type 2 diabetes poorly controlled on sulfonylurea monotherapy randomized to adjunctive INH versus adjunctive metformin*

Parameter	Sulfonylurea + INH		Sulfonylurea + metformin		Difference between adjusted mean change (95% CI)
	Baseline	Week 24	Baseline	Week 24	
n (male/female)	222 (122/100)		201 (102/99)		
Age (years)	60.8 (37–79)		60.0 (35–79)		
Weight (kg)	80.3 (50–129)		81.1 (52–136)		
BMI (kg/m^2)	28.5 (20–48)		29.1 (20–57)		
BMI <30	93 (41)				
BMI 30–35	83 (36)				
BMI ≥35	53 (23)				
Diabetes duration (years)	9.6 (0.7–37.3)		8.8 (0.5–33.0)		
C-peptide (pmol/ml)	1.12 (0.20–4.80)		1.11 (0.30–6.60)		
Average total daily dose of study drug (mg)*					
A1C >9.5%	10.7	13.6	1 g twice daily		
A1C ≤9.5%	8.9	10.5	1 g twice daily		
Combined	9.9	12.1	1 g twice daily		
A1C arms (%)					
A1C >9.5%	10.51 ± 0.71	7.85 ± 0.96	10.62 ± 0.87	8.26 ± 1.23	−0.38 (−0.63 to −0.14); $P = 0.002$
A1C ≤9.5%	8.80 ± 0.52	7.36 ± 0.84	8.75 ± 0.53	7.39 ± 0.84	−0.07 (−0.33 to 0.19); $P = 0.610$
Combined	9.70 ± 1.06	7.62 ± 0.94	9.73 ± 1.19	7.85 ± 1.14	−0.22 (−0.40 to −0.05); $P = 0.014$
Patients achieving A1C <8%					
A1C >9.5%		55 (48.7)		46 (44.7)	1.11 (0.64–1.93)
A1C ≤9.5%		82 (81.2)		68 (73.1)	1.78 (0.86–3.69)
Combined		137 (64.0)		114 (58.2)	1.29 (0.84–1.99)
Patients achieving A1C <7%					
A1C >9.5%		23 (20.4)		15 (14.6)	1.45 (0.69–3.01)
A1C ≤9.5%		31 (30.7)		30 (32.3)	0.96 (0.51–1.79)
Combined		54 (25.2)		45 (23.0)	1.15 (0.72–1.84)
Treatment-related hypoglycemic events					
A1C >9.5%		61 (52.1)		23 (21.3)	
A1C ≤9.5%		51 (48.6)		30 (32.3)	
Combined		112 (50.5)		53 (26.4)	
Mean insulin antibodies (μU/ml)	1.04 ± 0.38	17.40 ± 35.40	1.00 ± 0.00	1.00 ± 0.00	
Median percentage binding	1.00	8.4	1.00	1.00	
Fasting plasma glucose (mmol/l)	220.0 ± 55.0	172.0 ± 45.0	219 ± 55	169 ± 46	2.39 (−5.81 to 10.59)
2-h postprandial glucose (mmol/l)†	238.4 ± 47.3	162.9 ± 33.6	230.7 ± 47.7	171.7 ± 34.6	−11.40 (−18.60 to −4.19)
Total cholesterol (mmol/l)	5.36 ± 1.11	5.31 ± 1.01	5.35 ± 1.05	5.13 ± 1.00	0.17 (0.03–0.31)
LDL cholesterol (mmol/l)	3.31 ± 0.92	3.28 ± 0.83	3.26 ± 0.90	3.09 ± 0.84	0.15 (0.02–0.27)
Triglycerides (mmol/l)	2.04 ± 1.45	1.81 ± 1.03	2.07 ± 1.10	1.86 ± 0.99	−0.04 (−0.20 to 0.12)
HDL cholesterol (mmol/l)	1.16 ± 0.33	1.21 ± 0.35	1.17 ± 0.34	1.21 ± 0.34	0.00 (−0.04 to 0.04)
FEV_1 (l)	2.80 ± 0.74	2.71 ± 0.70	2.84 ± 0.74	2.80 ± 2.74	−0.07 (−0.12 to −0.03)
DL_{CO} (ml · min^{-1} · mmHg^{-1})	24.83 ± 5.77	24.56 ± 6.08	24.75 ± 6.18	24.80 ± 6.19	−0.32 (−1.10 to 0.46)
Forced vital capacity (l)	3.45 ± 0.93	3.36 ± 0.89	3.49 ± 0.88	3.46 ± 0.89	−0.06 (−0.11 to −0.01)
Total lung capacity (l)	5.65 ± 1.30	5.65 ± 1.43	5.52 ± 1.19	5.57 ± 1.27	−0.04 (−0.19 to 0.11)

Data are *n* (%), means ± SD, and means (range). *Average total daily inhaled human insulin and metformin dose at week 4. †Two-hour postprandial glucose was calculated from home glucose measurements.

Safety profile

All safety data are presented for the combined A1C arms, unless there were notable differences between the A1C ≤9.5 and >9.5% arms, in which case they are discussed separately. All-causality adverse events were experienced by 183 (82.4%) patients in the INH group and 155 (77.1%) patients in the metformin group. Adverse events that were possibly or probably related to the treatment regimens were experienced by 143 (64.4%) and 109 (54.2%) patients, respectively. Most adverse events were of mild or moderate severity. Five patients discontinued due to treatment-related adverse events, one (0.5%) in the INH group (excessive sweating) and four (2.0%) in the metformin group (back pain, diarrhea, gastric pain, and epigastric pain). There were 7 serious adverse events in the INH group and 15 in the metformin group; none were considered treatment related. One death (myocardial infarction) was reported during the study in the INH group; it was not considered treatment related.

The most common adverse event was

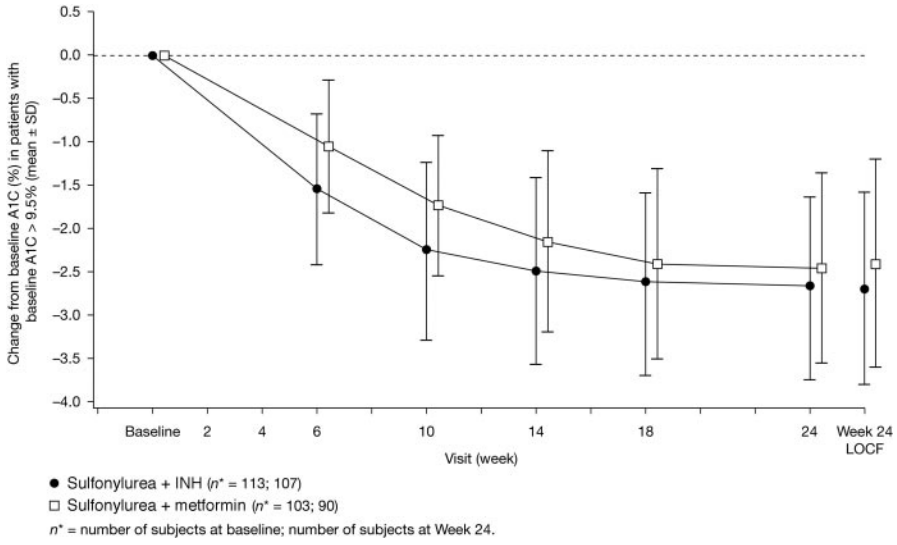

Figure 2— *Change from baseline in A1C (%) for patients with type 2 diabetes and very high baseline A1C (>9.5 to ≤12%) failing sulfonylurea therapy randomized to adjunctive INH or metformin. Mean adjusted change from baseline was −2.17% (INH) and −1.79% (metformin); between-treatment difference was −0.38% (95% CI −0.63 to −0.14);* P = *0.002.*

hypoglycemia. In the combined A1C arms, 114 INH patients had a hypoglycemic event, of which 112 were treatment-related (73 mild, 36 moderate, and 3 severe). In the metformin group, 54 patients had a hypoglycemic event, of which 53 were treatment related (41 mild and 12 moderate). The rates of overall hypoglycemia (events/subject-month) for INH compared with metformin were 0.31 vs. 0.17, respectively. This translated into a risk ratio of 1.86 (95% CI 1.56–2.22) for INH versus metformin. There were no discontinuations due to hypoglycemia in either group.

Increased cough was experienced by 9.0% (20/222) of patients in the INH group compared with 1.5% (3/201) in the metformin group. Coughs in the INH group were mild or moderate (one case); all events were mild in the metformin group. In the INH group, 12 cases of increased cough were considered treatment related compared with one in the metformin group. No patients discontinued due to cough. There were two cases of respiratory tract infection in each group that the investigator considered treatment related.

There were no notable changes in blood pressure, heart rate, physical examination findings, or electrocardiograms during the study in either group.

Small declines in FEV_1 occurred in both INH and metformin groups over the 24 weeks, but declines were slightly greater in the INH group (Table 1). DL_{CO} declined slightly in the INH group and increased in the metformin group (Table 1). For both end points, the change from baseline was small and comparable between groups.

Antibody responses were higher in the INH compared with the metformin group (Table 1). Routine monitoring of patients did not reveal any clinical manifestations of increased insulin antibody percent binding.

CONCLUSIONS — The patients in this study were representative of patients typically seen in clinical practice and had a range of BMI values. Adjunctive INH met the primary objectives of demonstrating improved glycemic control to metformin for patients in the very high A1C arm (A1C >9.5%) and noninferior glycemic control for patients in the combined A1C arm. Noninferiority was also shown in the moderately high A1C arm (≤9.5%). These results were not unexpected. For patients with less advanced disease, oral agents will often provide appropriate control in combination (2–6). With prolonged exposure to elevated glucose, a state known as glucose toxicity occurs, resulting in irreversible β-cell damage, reduced insulin sensitization, and decreased insulin secretion (22,23). Oral agents such as sulfonylurea and metformin are then unlikely to provide as much incremental benefit. Although insulin levels were not measured in this study, by directly providing exogenous insulin, INH may have provided higher insulin levels than can be achieved with oral agents alone in patients in the very high A1C arm.

A secondary outcome measure was the percentage of patients achieving acceptable (A1C <8%) or good (A1C <7%) glycemic control. Mean baseline A1C levels in the current study were high, and the fasting plasma glucose titration target was 4.4–7.8 mmol/l (80–140 mg/dl) and therefore not as ambitious as in some studies (24). Nevertheless, a greater proportion of patients in the INH group achieved a mean A1C of <8% at 24 weeks.

Both insulin and sulfonylureas can be associated with weight gain and, as expected, patients taking both sulfonylurea and INH gained some weight. Therefore the addition of metformin may be the preferred next-stage option in patients currently receiving sulfonylurea therapy. However, ~15% of patients cannot tolerate metformin, and for these individuals a sulfonylurea/INH combination may be an option, as weight gain is unlikely to exceed that experienced with other sulfonylurea/oral antidiabetic agent combinations, such as sulfonylurea/thiazolidinedione therapy (25).

There were small treatment group differences in changes in pulmonary function after 24 weeks of INH therapy, but these were comparable between groups. This study could not predict whether INH effects within the lung occur following a longer-term exposure beyond 24 weeks. However, recent long-term data show no increase in treatment group differences in FEV_1 beyond those found at 6 months of therapy, when INH is administered continuously for up to 2 years (26,27).

INH was associated with an increase in insulin antibody binding, but there were no apparent clinical manifestations arising from this. The results are in line with analyses of combined data from a number of 3- to 6-month and extension studies with INH in patients with type 1 and type 2 diabetes, showing that there were no correlations between antibody binding and glycemic control (measured using A1C), insulin dose requirements, hypoglycemic events, or pulmonary function (measured by changes in FEV_1 and DL_{CO}). Antibody responses were IgG in type. Peak antibody levels in patients with type 1 and type 2 diabetes were generally observed after 6–12 months of insulin therapy (28).

A limitation of this study was the open-label design, which was necessary because it is not possible to manufacture a

suitable placebo INH system and it is not appropriate to use blinding where such titration decisions are needed. Patients entering the trial had poor glycemic control and were failing to respond to sulfonylurea therapy, suggesting that they already had significant β-cell dysfunction. Although the baseline A1C levels were high in this study, they are consistent with mean values of 8.5–9% reported for patients with type 2 diabetes on insulin therapy in nontrial settings (29,30).

The results of this study demonstrate that adding INH to sulfonylurea therapy provides effective glycemic control and may be an alternative to oral agent combination therapy in patients with type 2 diabetes. The results corroborate findings from a similar study in which adjunctive INH was compared with the addition of a sulfonylurea (glibenclamide [glyburide]) in patients poorly controlled with metformin (31). Together, these studies suggest that new ways of delivering insulin without the need for injections may help in the early adoption of insulin treatment by patients and assist in achieving and maintaining long-term optimal glycemic control.

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