Insulin 70/30 Mix Plus Metformin Versus Triple Oral Therapy in the Treatment of Type 2 Diabetes After Failure of Two Oral Drugs

Efficacy, safety, and cost analysis

OBJECTIVE — Subjects (n = 188) with type 2 diabetes and inadequate response to two oral medications (A1C >8.0%) were randomly assigned to treatment with either a third oral medication or an insulin 70/30 mix b.i.d. plus metformin for a comparison of efficacy, safety, and cost.

RESEARCH DESIGN AND METHODS — The protocol called for aggressive dose titration to achieve target values of fasting blood glucose (80–120 mg/dl), postprandial glucose (<160 mg/dl), and A1C (<7%). These efficacy parameters were evaluated at weeks 2, 6, 12, and 24 of therapy. If dose adjustments failed to achieve targeted glycemic control, subjects were switched to an alternate therapy.

RESULTS — At the end of study (week 24 of therapy), A1C and fasting plasma glucose (FPG) values showed comparable decreases in the two treatment groups. Only 31% (oral therapy) and 32% (insulin plus metformin) of subjects achieved target values of A1C (<7%). A total of 10 of the 98 subjects randomized to triple oral therapy (10.2%) who failed to improve sufficiently were switched to insulin therapy. An additional four subjects dropped out of the oral treatment group due to adverse events felt to be potentially drug related. Only two of the subjects randomized to insulin plus metformin had to be switched to basal-bolus regimens (regular insulin and NPH insulin). Cost analysis determined that insulin plus metformin (mean cost $3.20/day) provided efficacy equal to that of a triple oral drug regimen ($10.40/day).

CONCLUSIONS — Insulin 70/30 mix plus metformin was as effective as triple oral therapy in lowering A1C and FPG values. The triple oral regimen was not as cost effective, and a high percentage of subjects (total of 16.3%) did not complete this regimen due to lack of efficacy or side effects.

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Abbreviations: FPG, fasting plasma glucose; ITT, intent-to-treat; UKPDS, U.K. Prospective Diabetes Study.

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

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cost considerations of adding a second or third class of oral antidiabetic drug to a therapeutic regimen. Where insulin therapy is instituted, the addition of metformin to insulin therapy has been shown to result in significant decreases in fasting plasma glucose (FPG) and A1C values, as well as reduced insulin requirements (10).

The purpose of this study was to compare the efficacy, safety, and cost of two possible approaches for managing failure of combination therapy with two oral medications: 1) adding a third class of oral antidiabetic drug or 2) switching treatment to insulin 70/30 mix b.i.d. plus metformin.

**RESEARCH DESIGN AND METHODS**

**Design and subjects**

This was a multicenter, open-label, parallel group trial of 24 weeks. Subjects 18 years of age or older with type 2 diabetes for at least 2 years (mean ± SD, 10.4 ± 6.9 years) and BMI values of 25–50 kg/m² were included in the study. Subjects were willing to initiate insulin therapy and had previously received at least 3 months of continuous treatment with failure of two oral medications (A1C >8.0%). The protocol received institutional review board approval. All subjects provided written informed consent before study-related procedures.

Subjects were excluded for any of the following criteria: failure to use adequate contraceptive measures (women of childbearing potential), evidence of renal disease (elevated creatinine >1.4 mg/dl) or a liver disease (alanine aminotransferase >2.5 times the upper limit of normal), substance abuse, or mental incapacity or a language barrier precluding an adequate understanding or cooperation with study procedures.

Screening visit tests were confirmed by the central laboratory, and the randomization visit occurred 14 days later. Subjects were randomly assigned (1:1) to receive either a third oral medication (in a different pharmacologic category from the two previously prescribed) or insulin 70/30 mix in combination with metformin. Medications were added or discontinued as appropriate and titrated to the maximum recommended dose of each respective package insert. At randomization, subjects were provided dietary counseling (American Diabetes Association guidelines) by a diabetes nurse educator.

The following drugs were prescribed during the study: insulin secretagogues; glimepiride (Amaryl; Aventis, Bridgewater, NJ), glyipizide (generic), sustained-release glipizide (Glucotrol XL; Pfizer, New York, NY), glyburide (generic), and repaglinide (Prandin; Novo Nordisk Pharmaceuticals, Princeton, NJ); thiazolidinediones: rosiglitazone (Avandia; GlaxoSmithKline, Triangle Park, NC), pioglitazone (Actos; Takeda Pharmaceuticals, Lincolnshire, IL); and metformin (Glucophage; Bristol Myers Squibb, Princeton, NJ). Insulins used during the study were Novolin 70/30 (70% NPH, 30% regular rDNA human insulin; Novo Nordisk Pharmaceuticals), Novolin N (NPH; Novo Nordisk Pharmaceuticals), and Novo R (Regular; Novo Nordisk Pharmaceuticals) human insulin isophase suspension recombinant DNA origin. Insulin was supplied in cartridges (Penfill) and administered using NovoPen 3 (Novo Nordisk Pharmaceuticals).

**Dosing information**

Subjects were contacted via telephone after 1 week of treatment, and clinic visits were scheduled after 2, 6, 12, and 24 weeks of treatment with a follow-up visit 2 weeks after the end of the study. Subjects maintained blood glucose diaries and brought these to each clinic visit for review. Blood glucose diaries, A1C (screening, weeks 2, 6, 12, and 24), and hypoglycemic events were monitored at each visit to aid in adjusting therapy dosage. Treatment goals were as follows: fasting blood glucose of 80–120 mg/dl, postprandial glucose <160 mg/dl, and A1C <7%. These goals were aggressively pursued to the maximum recommended doses (or tolerability) of oral therapies or in subjects randomized to insulin therapy with dose adjustments made as necessary.

Insulin therapy was initiated with insulin 70/30 mix b.i.d. (starting dose, 0.75 units/kg). Two-thirds of the dose was given before breakfast and the remainder before dinner. Dose adjustments of 10% of the current dose were suggested every other day, until the glycemic (FPG and postprandial glucose) targets were achieved. Larger dose changes were made at investigator discretion. Patients failing three oral drugs (two consecutive self-monitored unexplained morning FBGs >300 mg/dl, despite aggressive dose increments according to drug labels), rather than being withdrawn from the study, were transferred to insulin/metformin therapy, or if on insulin plus metformin the patients were switched to a multiple-injection regimen (starting at 8.0 units of regular insulin before each meal and NPH insulin at bedtime), which was adjusted as necessary. If patients refused the transfer, they were withdrawn from the study. Adequate dietary counseling was provided to facilitate management of meal-related insulin.

For triple oral therapy, three classes of agents were defined: 1) secretagogues, 2) metformin, and 3) thiazolidinediones. Subjects continued the drugs of two classes previously in use, and the investigator added a drug of the third class, which was a drug choice at the investigator’s own discretion. Doses were titrated to the maximum recommended doses and based on tolerability. Failure to reach treatment goals (same criteria as used for insulin plus metformin group) called for a switching of treatment to the insulin plus metformin regimen.

Safety parameters included general physical examination, medical history, electrocardiogram, and urinalysis at screening and week 24. Vital signs were determined at each clinic visit, and clinical chemistry was assessed at screening and at weeks 12 and 24. Dosing guidance was performed at each visit, based on subject blood glucose diaries (including a twice weekly 4-point blood glucose profile). If glycemic goals were not met, the need to transfer to insulin plus metformin (from triple oral therapies) or transfer to multiple daily injections (insulin plus metformin group) was assessed at weeks 6 and 12.

**Cost analysis**

A cost analysis was conducted using current Drug Topics 2001 Red Book values (October 2001), where cost for individual subjects was based upon the average daily drug administered during the 24-week trial. The average retail value cost was used. Generic drugs were used where applicable. Costs of liver function tests (performed every 8 weeks), recommended for certain oral agents, were estimated at $15.00 per test over the 24 weeks to the triple oral hypoglycemic agent group ($15.00 total or $0.09/day added to cost of oral regimens). The cost of instruction
Triple oral therapy vs. insulin plus metformin

Table 1—Demographics, baseline values, and completion status

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<th>Triple oral therapy</th>
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<td>90</td>
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<td>54 ± 10.8</td>
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<tr>
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<td>74 (76)</td>
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<td>Weight (kg)</td>
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<td>Duration diabetes (years)</td>
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Data are means ± SD and n (%). †Five subjects did not initiate treatment (one subject moved out of state due to family illness, one subject had dramatically improved blood glucose before starting study therapy [final A1C 7.0%], and 3 subjects withdrew consent). Includes discontinuation due to withdrawal of consent, time constraints, unable to follow-up, patient moved to another city, or weight gain.

Laboratory analysis

Laboratory analyses for all 21 clinical study sites were performed by a central laboratory (Medical Research International, Highland Heights, KY). A1C was determined by high-performance liquid chromatography and FPG by a hexokinase method. LDL was imputed from total cholesterol, triglycerides, and HDL using the methods of Friedewald et al. (11). In subjects with triglyceride levels greater than 400 mg/dl, LDL concentrations were not imputed.

Statistical methods

Power calculations were based on an estimate that a 0.6% decrease in A1C would be clinically meaningful. Based on previous studies, the SD for A1C was estimated at 1.3%. Thus, enrolling 75 subjects in each group would provide 80% power to detect a 0.6% difference in A1C between treatment groups.

To determine whether treatment groups were comparable at baseline, demographic parameters were analyzed using either ANCOVA or the Cochran-Mantel-Haenszel test.

Efficacy analysis (change in A1C values) at visits 2, 6, 12, and 24 and between-treatment comparisons of weight, FPG, total cholesterol, LDL, HDL, and triglycerides were made using ANCOVA for the intent-to-treat (ITT) population that included all subjects randomized who received at least one dose of study medication. For subjects who were transferred to insulin plus metformin or to multiple daily injections, analyses were performed separately.

RESULTS — Demographics, baseline values, and patient disposition are provided in Table 1. Both treatment groups were comparable at screening. No statistical differences were noted for any demographic parameters.

Ninety subjects were randomized to the insulin plus metformin treatment group. Eighty-five subjects received insulin plus metformin, and 5 subjects did not initiate treatment for various reasons (1 subject moved out of state due to family illness, 1 had dramatically improved blood glucose before starting study therapy [final A1C 7.0%], and 3 subjects withdrew consent). Ninety-eight subjects received triple oral therapy (exactly 50% of triple oral therapy subjects received rosiglitazone, and 50% received pioglitazone). Six subjects discontinued insulin, and 10 discontinued oral therapy. Adverse events led to one discontinuation in the insulin group (pyelonephritis) and three in the oral therapy group. Each group had one discontinuation due to noncompliance. Other discontinuation reasons (lost to follow-up, withdrawal of consent, time constraints, and moving to another city) accounted for four insulin plus metformin dropouts and six oral therapy dropouts.

As per protocol design, at each visit the investigator had the option of changing therapy (dose adjustments or changing regimen) if targets were not met. During the study, 22.4% of subjects (2 of 85 treated) failed to achieve targets in insulin plus metformin regimens and were switched to basal-bolus therapy using regular and NPH insulin. However, in the triple oral therapy arm of the study, 10 (10.2%) subjects (10 of 98) failed at maximum recommended doses and were switched to the insulin plus metformin regimen. These treatment switches occurred during weeks 6 and 12. At the week 24 visit, three additional subjects were removed from triple oral therapy due to failure to improve. Including these subjects and dropouts due to adverse events, treatment failures were 16.3% (16 of 98) and 3.5% (3 of 85) for the triple oral drug group and 70/30 insulin therapies, respectively.

Values for A1C, FPG, and lipid profiles are presented for all subjects ran-
domized who received at least one dose of study medication (ITT). The A1C values changed markedly (Fig. 1A). Baseline A1C was 9.62 ± 1.25% for subjects in the triple oral therapy and 9.65 ± 1.62% in the insulin group. A1C values at weeks 2 and 6 demonstrated the efficacy of both treatments. However, insulin plus metformin treatment achieved improvements in A1C values at weeks 2 and 6 (9.03 ± 1.35% and 8.11 ± 1.20%) that were significantly greater than response to triple oral therapy (P = 0.001 and <0.001, respectively). Although statistically significant, the more rapid response in the insulin plus metformin regimen is of doubtful clinical significance. At weeks 12 and 24, no statistically significant difference in A1C between the two groups was observed (final values at week 24 were 7.59 ± 1.4% for triple oral therapy and 7.59 ± 1.25% for insulin plus metformin [P = 0.772]). A last observation carried forward analysis for all subjects completing the assigned therapy gave final A1C of 7.66 ± 1.39% for triple oral therapy and 7.70 ± 1.25% for insulin plus metformin (P = 0.963) (final A1C reductions were 1.77 and 1.96%, respectively).

The distribution of A1C values at study end was comparable in both treatment groups (Fig. 1B). The percentage of subjects achieving A1C values <8% was 61% in both groups (P = 0.897). Thirty-one percent and 32% of subjects were able to reach targeted A1C values of <7% in the triple oral therapy and insulin plus metformin groups, respectively (P = 0.898) (Fig. 1C).

The two treatment groups had similar FPG values at screening and week 24 (Fig. 2A). At week 24, mean changes from baseline FPG values were −55 and −65 mg/dl for the triple oral therapy and insulin plus metformin, respectively (P = 0.288).

Changes in lipid parameters are shown in Fig. 2B. Whereas baseline values for total cholesterol, LDL, HDL, and triglycerides indicated no differences between the two treatment groups, by the end of the study (week 24) significant decreases in total cholesterol and triglycerides were evident in the insulin plus metformin group (P = 0.038 and 0.033, respectively, as compared with the triple oral therapy group). Subjects in the triple oral therapy group showed a small increase in cholesterol and less of a decrease in triglyceride levels.

Mean body weight increased in both treatment groups, but there was no significant difference between the two treat-

Figure 1—A and C: A1C values. A: Decline in A1C (mean ± SEM) during the course of the study by treatment group. *Statistically significant (P < 0.05) reduction in A1C in the insulin plus metformin treatment group. B: Cumulative percentage A1C of subjects for the week 24 treatment period. ● triple oral therapy; ○ insulin plus metformin. C: Mean percentage of subjects achieving A1C values <7% and those achieving <8% at end of study (week 24).

Figure 2—A: Mean FPG values at screening and weeks 12 and 24 by treatment group. No statistically significant changes were observed between the triple oral therapy (●) and insulin plus metformin (○). B: Mean ± SEM changes for the total cholesterol, HDL, LDL, and triglycerides at week 24. *Statistically significant (P < 0.05) reduction in total cholesterol and triglyceride levels in the insulin plus metformin group as compared with the triple oral therapy group.
Triple oral therapy vs. insulin plus metformin

ment groups at week 24 (P < 0.158). Subjects in triple oral therapy gained an average of 3.5 ± 3.8 kg, and those using insulin gained 2.9 ± 4.2 kg.

**Daily cost of treatment**
The average daily cost of treatment, estimated as the mean dose for all medications taken and using Red Book cost (October 2001 costs), amounted to $10.40 ± 7.20/day for the subjects randomized to triple oral therapy. Subjects treated with insulin and metformin had therapy-associated costs of $3.20 ± 1.6/day (P < 0.001). The mean ± SD daily doses of medications for subjects in the triple oral therapy group at week 24 were as follows: metformin, 1.819.6 ± 471 mg; glimepiride, 7.55 ± 1.33 mg; glipizide, 18.33 ± 7.53 mg; glyburide, 16.28 ± 5.26 mg; pioglitazone, 33.75 ± 8.00 mg; rosiglitazone, 6.87 ± 1.82 mg; and repaglinide, 5.92 ± 3.42 mg. The insulin plus metformin group mean ± SD daily dose of metformin was 1,672.9 ± 543 mg, and the dose of insulin 70/30 mix was 62.98 ± 26.48 units/day.

**Safety**
The safety analysis was performed on the ITT population, which included all subjects randomized who received at least one dose of study medication. Liver function tests were performed every 2 months as recommended in labeling of thiazolidinediones. There were no instances of subjects being discontinued due to elevated liver enzymes during the trial. Three subjects discontinued triple oral therapy due to adverse events considered possibly related to medications (right side pain, increased creatinine, and two incidents of allergic reaction). One subject dropped out in the insulin plus metformin group (pyelonephritis). The adverse events were considered unlikely to be related to treatment.

A total of 47 of 98 patients (48%) in triple oral therapy and 57 of 85 patients (67%) in the insulin plus metformin group (P = 0.011) reported hypoglycemic events (glucose <50 mg/dl, with or without symptoms). Minor episodes (symptoms with confirmed blood glucose <50 mg/dl, no assistance required) averaged 23% in both treatment groups (45 episodes of 198 in triple oral therapy and 61 of 268 episodes in the insulin plus metformin group). Major events (assistance required) occurred only once in the insulin plus metformin group. There were 153 events (77%) associated with symptoms only (without confirmed blood glucose reading) for triple oral therapy and 206 events (77%) in the insulin-treated group. There was no correlation between the number of subjects reporting hypoglycemic episodes and week 24 A1C values for either treatment group.

**Treatment switchers**
An alternate treatment was considered for subjects who failed to reach their glycemic goals. In triple oral therapy, 10 (10.2%) subjects who failed to show adequate response were switched to regimens of insulin plus metformin. Screening A1C for this group was 10.59% ± 1.81%. Before the switch, the mean A1C value was 9.85 ± 1.70% (range −0.1 to +2.4%). Switches occurred in most cases at week 6 with two at week 12 of therapy. By the end of study, with the switch to insulin plus metformin, the mean A1C value was 8.06 ± 1.36% for these subjects.

In the insulin group, only two subjects (2.4% of treated subjects) were switched to basal-bolus regimens using regular insulin and NPH insulin. Before the switch, these subjects had A1C values of 8.0 and 8.5%. At week 24, little improvement was noted using the basal-bolus regimen (A1C values were 8.5 and 8.6%).

If the total number of subjects failing treatment was estimated as including those who switched due to treatment failure before week 24, those who switched therapy at week 24 (no further improvement), and those who discontinued therapy due to adverse events possibly related to study medication, the total number of treatment failures was 16 (16.3%) for the triple oral therapy and three (3.5% of treated subjects) for the insulin plus metformin therapy.

**CONCLUSIONS** — Despite a protocol design of aggressive therapy, only one-third of subjects in either treatment were able to achieve an A1C value below 7%. Sixty-one percent of subjects in both groups achieved an A1C <8.0%. A few subjects in both treatment groups were able to achieve near-normal A1C levels. Limitations to achieving normal A1C may be the severity of diabetes or physiology such that certain classes of oral hypoglycemic agents are less effective, fear of hypoglycemia by either subject or physician limiting further aggressive control, and noncompliance with recommended regimens. Winocour (12) has raised concerns about the feasibility of the A1C targets of <7% being applied to all subjects. Treatment compliance may suffer if polypharmacy is involved in glycemic control and is then combined with medications for comorbid conditions of type 2 diabetes (hypertension and dyslipidemia).

There was little overall difference in treatments when A1C values, changes in FPG, and safety were compared. However, these assessments do not take into account the number of treatment failures (as assessed by the investigator). In the insulin plus metformin group, two (2.4% of treated subjects) were such failures with little additional improvement after switching to a more aggressive basal-bolus regimen. Triple oral therapy failed in 10.2% of subjects, and switching to insulin plus metformin provided additional improvement. With better options available, the triple oral therapy failure rate of 10.2% should be considered unacceptably high.

There were also more dropouts due to adverse events potentially related to medication in the triple oral therapy group. Combining the incidence of switched treatment due to lack of efficacy, discontinuation of therapy due to medication-related adverse events, and switching of therapy at the end of 24 weeks due to the need for more improvement, the triple oral therapy group had a treatment failure rate of 16.3% (16 subjects). This is in contrast with the insulin plus metformin total of 3.5%. This percentage failure may have been biased by including subjects with A1C values >8%. Undoubtedly some of these subjects might have limited insulin secretory capacity when enrolled. One subject in the triple oral therapy group achieved a reduction in A1C value from 14.1 to 6.7%, and one subject in the insulin plus metformin group had a reduction of A1C values from 11.9 to 6.2%. Cost is an important factor in treatment decisions. Liver function testing every 8 weeks adds to the cost of therapy with oral agents, but this was partly offset by needle costs involved in insulin therapy. The cost of the insulin plus metformin treatment regimen was substantially less than triple oral therapy with fewer treatment failures. Efficacy response developed slightly more rapidly for the insulin regimen, although it did
not appear to be a decisive factor with comparable efficacy in both regimens by 24 weeks. The two regimens were not distinguished by any notable safety differences.

In this clinical trial, subjects were selected as being willing to inject insulin. However, there were three subjects randomized to insulin plus metformin treatment group who withdrew consent before the start of the study. It is possible that these subjects had anxiety about injecting insulin. The reluctance to initiate insulin therapy is multifactorial. Initiation of the insulin therapy may be psychologically construed as a last-resort action, often requires referrals to another physician, and involves many psychological obstacles for the patient (fear of hypoglycemia, stigma of injection, inconvenience of more blood glucose monitoring) (13,14). Beneficial therapy might be delayed even when it is evident oral medications are no longer effective. However, a small study (n = 38) indicated that the subjects who switched to insulin therapy need not experience decreased quality of life. The study of de Grauw et al. (15) examined the effects of stratifying subjects failing oral medications into two groups: one group with enhanced compliance to diet and oral therapy and the other switched to insulin. At the end of 12 weeks, the insulin group had statistically significant improvements in A1C, FPG, and no change in quality of life or frequency of hypoglycemic episodes compared with the enhanced compliance group.

In conclusion, a regimen of insulin 70/30 mix plus metformin showed substantial cost savings relative to a triple oral therapy approach, whereas the glycemic improvement and safety findings of the two treatment approaches were largely similar. The failure of triple oral therapy to improve A1C values occurred more frequently than with insulin.

Acknowledgments—This study was supported by Novo Nordisk Pharmaceuticals, Princeton, NJ.

References