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

SHERWYN SCHWARTZ, MD[1]
RICHARD SIEVERS, DO[2]
POUL STRANGE, MD, PHD[3]
WILLIAM H. LYNESS, PHD[4]
PRISCILLA HOLLANDER, MD[5]
FOR THE *INS-2061 STUDY TEAM

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.

Diabetes Care 26:2238–2243, 2003

From the [1]Diabetes and Glandular Disease Clinic, San Antonio, Texas; [2]Wells Institute for Health Awareness, Kettering, Ohio; [3]Princeton Junction, New Jersey; [4]Novo Nordisk Pharmaceuticals, Inc., Princeton, New Jersey; and [5]Baylor University Medical Center, Dallas, Texas.

Address correspondence and reprint requests to Sherwyn Schwartz, MD, Diabetes and Glandular Disease Clinic, 5197 Medical Dr., San Antonio, TX 78229. E-mail: sschwartz@dgdclinic.com.

Received for publication 24 September 2002 and accepted in revised form 6 May 2003.

*INS-2061 Study Team: Rahim Bassiri, Bruce Bode, Alan Burshell, Daniel Einhorn, Norman Fishman, Janet McGill, Priscilla Hollander, Adi Mehta, Melissa Meredith, James H. Mersey, Stasia Miaskiewicz, Daniel Nadeau, Kwame Osei, Julio Rosenstock, Mohammed Saad, Sherwyn Schwartz, John Shelmet, Richard Sievers, Denise Tonner, and Angelina Trujillo.

S.S. is employed by and is on the board of directors of the Diabetes and Glandular Disease Clinic, P.A., which is a physicians' clinical practice related to the treatment of diabetes and its complications, and holds stock in Diabetes and Glandular Disease Clinic, P.A. and Diabetes and Glandular Disease Research Associates, P.A.; P.H. received funds from Novo Nordisk Pharmaceutical to conduct studies on insulin therapy versus triple oral therapy as part of a multicenter study.

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.

The U.K. Prospective Diabetes Study (UKPDS) demonstrated that intensive glycemic control reduced the overall risk of diabetic eye disease, kidney damage, stroke, and overall mortality (1). Although diet and exercise can improve glycemic control early in the course of the disease, oral medications often become the mainstay of type 2 diabetes treatment (2). Exercise may be contraindicated in some subjects with type 2 diabetes (3). Whereas diet and exercise have been demonstrated to delay the onset of type 2 diabetes (4), the success rate of diet and exercise regimens in the long term is poor (5). Matthews et al. (6) examined individuals who had failed diet therapy and had initiated oral monotherapy. In subjects treated with glibenclamide, 48% required additional therapy after 6 years. A 40% failure rate of tolbutamide monotherapy occurred over the same time span. Also using UKPDS data, Turner et al. (7) found that when the subjects were treated with diet, insulin, or sulfonylureas, only 8%, 42%, or 24%, respectively, were able to maintain A1C levels below 7% after 9 years. After 3 years of monotherapy, nearly 50% of subjects were unable to maintain their target levels of A1C.

Because many subjects have a fear of needles that may affect compliance with insulin therapy (8), oral therapy (often using combinations) has been the most frequently prescribed treatment approach for type 2 diabetes. Such regimens are rational because diabetes is a disease affecting multiple systems. Furthermore, whereas monotherapy has been shown on average to lower A1C by 1–2%, glycemic effects appear to be additive when oral drugs are used in combination therapy (9).

A patient treated with three oral drugs is subjected to an additive risk of adverse events, and dose adjustments may become complex. In addition, there are the

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/m^2 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), glipizide (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

Table 1—*Demographics, baseline values, and completion status*

	Insulin plus metformin	Triple oral therapy	*P*
Subjects randomized (*n*)	90	98	
Age (years)	54 ± 9.3	54 ± 10.8	0.118
Sex (F/M)	44 (52)/41 (48)	50 (51)/48 (49)	0.990
Race			
African American	13 (15)	11 (11)	0.858
Caucasian	61 (72)	74 (76)	
Other	11 (13)	13 (13)	
Weight (kg)	97 ± 20.6	98 ± 18.8	0.328
BMI (kg/m^2)	33 ± 6.0	34 ± 5.4	0.948
Duration diabetes (years)	10.4 ± 6.9	8.9 ± 5.7	0.548
FPG at screening (mg/dl)	220 ± 55.9	218 ± 53.4	0.352
A1C at screening (%)	9.7 ± 1.6	9.6 ± 1.3	0.774
Subjects randomized	90 (100)	98 (100)	
Subjects treated	85 (94)	98 (100)	
Subjects completed	79 (88)	88 (90)	
Discontinued before treatment	5 (6)†	0	
Discontinued during treatment	6 (7)	10 (10)	
Reasons for discontinuation			
Adverse event	1 (1)	3 (3)	
Noncompliance with protocol	1 (1)	1 (1)	
Other‡	4 (4)	6 (6)	
Switched before week 24	2 (2)	10 (10)	
Switched at week 24	0	3 (3)	

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 values before starting study therapy [final A1C 7.0%], and three subjects withdrew consent); ‡includes discontinuation due to withdrawal of consent, time constraints, unable to follow-up, patient moved to another city, or weight gain.

in use of NovoPen3 (~$50 over 24 weeks for the insulin users and $0.29/day) and costs of needles ($0.24/injection/day) were added to the insulin plus metformin regimen costs. Cost of supplies for blood glucose meters and testing (test strips and lancets) were not included in the cost analysis, because these were assumed to be equal for the two groups. The costs of dietary counseling were essentially the same for both treatment groups; hence this cost was not included. All drugs and needles were supplied through a prescription voucher system.

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 values 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 ANOCOVA 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, two (2.4%) 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-

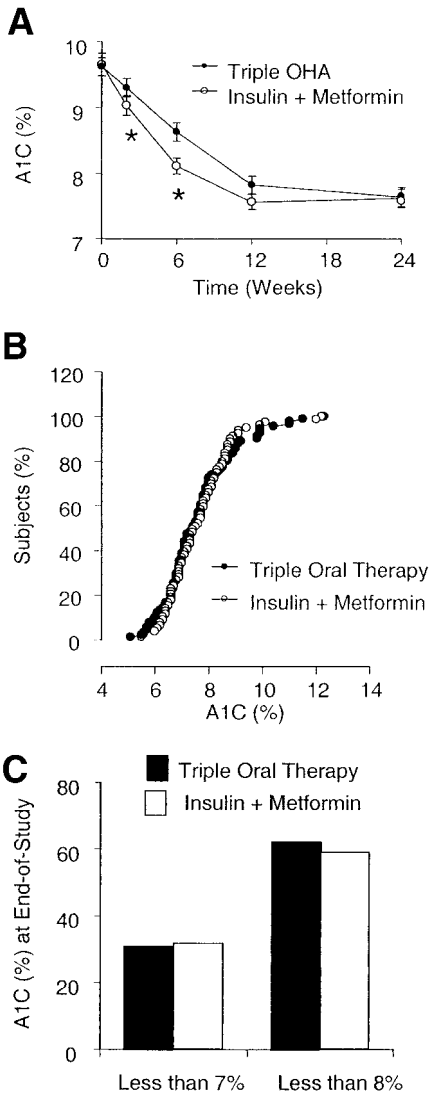

Figure 1—*A and C: A1C values. A: Decline in A1C (mean ± SEM) during the course of the study by treatment group. *Statistically significant (P < 0.05) reduction in A1C in the insulin plus metformin treatment group. B: Cumulative percentage A1C of subjects for the week 24 treatment period. ●, triple oral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

domized who received at least one dose of study medication (ITT). The A1C values changed markedly (Fig. 1*A*). 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. 1*B*). 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. 1*C*).

The two treatment groups had similar FPG values at screening and week 24 (Fig. 2*A*). 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. 2*B*. 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-

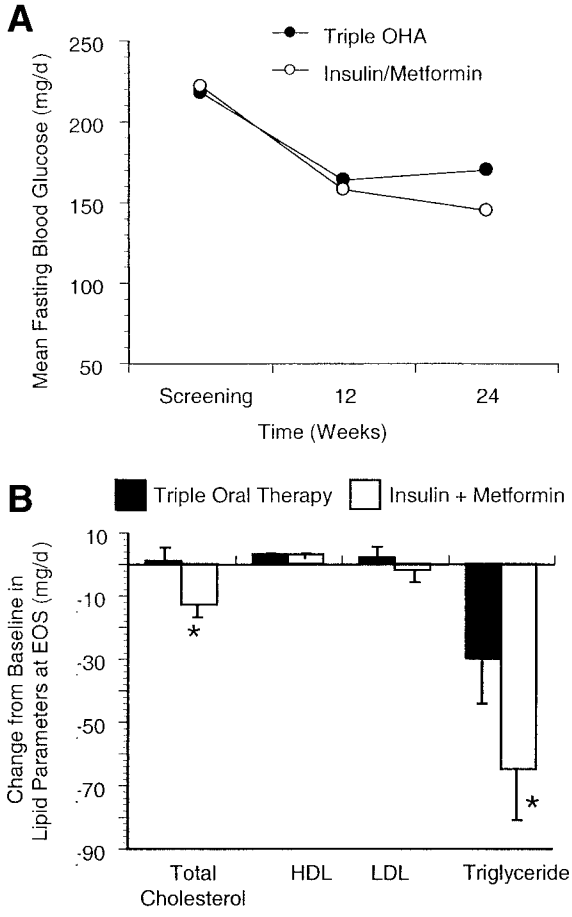

Figure 2—*A: Mean FPG values at screening and weeks 12 and 24 by treatment group. No statistically significant changes were observed between the triple oral therapy (●) and insulin plus metformin (○). B: Mean ± SEM changes for the total cholesterol, HDL, LDL, and triglycerides at week 24. *Statistically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

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 thiazolidenediones. 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 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

1. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34): UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:854–865, 1998
2. Tuomilento J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Lianne-Parikka P, Keinanen-Kiukaanniami S, Laakae M, Louheranta A, Rastas M Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
3. Horton ES: Role and management of exercise in diabetes mellitus. *Diabetes Care* 11:201–211, 1988
4. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
5. Wing RR, Venditti E, Jakicic JM, Polley BA, Lang W: Lifestyle intervention in overweight individuals with a family history of diabetes. *Diabetes Care* 21:350–359, 1998
6. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC: UKPDS 26: sulphonylurea failure in non-insulin diabetic patients over six years: UK Prospective Diabetes Study (UKPDS) Group. *Diabet Med* 15:297–303, 1998
7. Turner RC, Cull CA, Frighi V, Holman RR: Glycemic control with diet, sulfonylurea, metformin or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49): UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 281:2005–2012, 1999
8. Moellma ED, Snoek FJ, Ader HJ, Heine RJ, van der Ploeg HM: Insulin treated diabetes patients with fear of self-injecting or fear of self testing: psychological comorbidity and general well-being. *J Psychosom Res* 51:655–672, 2001
9. Inzucchi SE: Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA* 287:360–372, 2002
10. Jaber LA, Nowak SN, Slaughter RR: Insulin-metformin combination therapy in obese patients with type 2 diabetes. *J Clin Pharmacol* 25:89–94, 2002
11. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low density lipoprotein cholesterol in plasma, without the use of preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
12. Winocour PH: Effective diabetes care: a need for realistic targets. *BMJ* 324:1577–1580, 2002
13. Peacock I, Tattersall RB: The difficult choice of treatment for poorly controlled maturity onset diabetes: tablets or insulin? *BMJ* 288:1956–1959, 1984
14. Taylor R: Insulin for the non-insulin dependent. *BMJ* 296:1015, 1988
15. de Grauw WJC, Van de Lisdonk EH, van Gerwen WHEM, van den Hoogen HJM, van Weel C: Insulin therapy in poorly controlled type 2 diabetic patients: does it affect quality of life? *Br J Gen Pract* 51: 527–532, 2001