

Troglitazone in Combination With Sulfonylurea Restores Glycemic Control in Patients With Type 2 Diabetes

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OBJECTIVE — To determine if the combination of troglitazone (a peroxisome proliferator-activated receptor- γ activator) and sulfonylurea will provide efficacy not attainable by either medication alone.

RESEARCH DESIGN AND METHODS — There were 552 patients inadequately controlled on maximum doses of sulfonylurea who participated in a 52-week randomized active-controlled multicenter study. Patients were randomized to micronized glyburide 12 mg q.d. (G12); troglitazone monotherapy 200, 400, or 600 mg q.d. (T200, T400, T600); or combined troglitazone and glyburide q.d. (T200/G12, T400/G12, T600/G12). Efficacy measures included HbA_{1c}, fasting serum glucose (FSG), insulin, and C-peptide. Effects on lipids and safety were also assessed.

RESULTS — Patients on T600/G12 had significantly lower mean (\pm SEM) FSG (9.3 ± 0.4 mmol/l; 167.4 ± 6.6 mg/dl) compared with control subjects (13.7 ± 0.4 mmol/l; 246.5 ± 6.8 mg/dl; $P < 0.0001$) and significantly lower mean HbA_{1c} (7.79 ± 0.2 vs. $10.58 \pm 0.18\%$, $P < 0.0001$). Significant dose-related decreases were also seen with T200/G12 and T400/G12. Among patients on T600/G12, 60% achieved HbA_{1c} $\leq 8\%$, 42% achieved HbA_{1c} $\leq 7\%$, and 40% achieved FSG ≤ 7.8 mmol/l (140 mg/dl). Fasting insulin and C-peptide decreased with all treatments. Overall, triglycerides and free fatty acids decreased, whereas HDL cholesterol increased. LDL cholesterol increased slightly, with no change in apolipoprotein B. Adverse events were similar across treatments. Hypoglycemia occurred in 3% of T600/G12 patients compared with $< 1\%$ on G12 or troglitazone monotherapy.

CONCLUSIONS — Patients with type 2 diabetes inadequately controlled on sulfonylurea can be effectively managed with a combination of troglitazone and sulfonylurea that is safe, well tolerated, and represents a new approach to achieving the glycemic targets recommended by the American Diabetes Association.

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Abbreviations: ADA, American Diabetes Association; apo B, apolipoprotein B; AUC, area under the curve; DCCT, Diabetes Control and Complications Trial; FFA, free fatty acid; FSG, fasting serum glucose; MTT, meal-tolerance test; PPAR- γ , peroxisome proliferator-activated receptor- γ .

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

Type 2 diabetes is a chronic and progressive disease that affects more than 16 million people in the U.S., half of whom do not even know they have the disease (1,2). The cost of treating diabetes and its long-term complications (retinopathy, nephropathy, neuropathy, and cardiovascular disease) reached \$92 billion in 1992 (2,3).

Type 2 diabetes is characterized by insulin resistance and a relative deficiency in insulin secretion. Defective glucose recognition marks the early manifestation in the deterioration of β -cell function leading to insulin secretory deficiency (4–6). When diet and exercise fail to maintain good glycemic control, sulfonylureas have been traditionally used as first-line therapy because they increase basal as well as glucose-stimulated insulin release. However, not all patients respond to sulfonylureas initially, and secondary failures are common, probably because of further deterioration in β -cell function and/or increases in insulin resistance (7–9).

The results of the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and other studies in type 2 diabetes have provided unequivocal evidence that glycemic control is key to reducing the risk of long-term complications, such as retinopathy, nephropathy, and neuropathy (10,11). These results have helped redefine the treatment guidelines recommended by the American Diabetes Association (ADA).

Troglitazone is a thiazolidinedione that binds and activates the nuclear receptor peroxisome proliferator-activated receptor- γ (PPAR- γ), a mechanism believed to mediate enhanced insulin sensitivity in animal models of diabetes and insulin resistance as well as in humans (12). Unlike sulfonylurea, troglitazone does not stimulate insulin release, nor does it mimic its actions (13). Troglitazone has been shown to improve hyperglycemia, hyperinsulinemia, and insulin-mediated glucose disposal, as well as the dyslipidemia associated with type 2 diabetes (14–19). However, depending on the relative contributions of insulin resistance and insulin secretion, reversing insulin resistance alone may still

leave the patient in a state of relative insulin deficit if sulfonylurea treatment is withdrawn. Hence, we hypothesized that the combination of two medications, one that targets insulin resistance and another that targets insulin secretion, could potentially provide superior efficacy to that achieved by either medication alone. This study was conducted to evaluate the safety and efficacy of combination troglitazone and sulfonylurea therapy for the management of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study subjects and protocol

A total of 552 patients with type 2 diabetes (20 not optimally controlled on maximal doses of a sulfonylurea (fasting glucose >7.8 mmol/l or 140 mg/dl) participated in this study. The study was conducted at 30 centers in the U.S. (see APPENDIX) and followed a common protocol, which was approved by investigational review boards and ethics committees. Informed consent was obtained from all patients.

Inclusion criteria included HbA_{1c} outside the normal range ($>5.9\%$), fasting serum glucose (FSG) >7.8 and <16.7 mmol/l (>140 and <300 mg/dl), and fasting C-peptide ≥ 0.5 nmol/l (1.5 ng/ml). Exclusionary criteria included chronic use of insulin, history of ketoacidosis, symptomatic diabetic neuropathy, retinopathy, liver disease, renal disease, anemia, cardiovascular abnormalities such as Class III or IV congestive heart failure, significant hypertension, cancer, or a major vascular medical event within the previous 3 months.

Patients who met all inclusion and exclusion criteria discontinued their pre-study diabetic medications and enrolled in a 4-week, unblinded, baseline phase. In this phase, patients were treated with 12 mg micronized glyburide, which is the maximum recommended dose. At the end of baseline, patients who still exhibited a FSG >7.8 mmol/l (140 mg/dl) were enrolled in a 52-week, double-blind, active-controlled treatment phase. In total, 545 of the 552 patients initially enrolled were randomized to one of seven treatment arms: an active control arm that consisted of 12 mg micronized glyburide (G12) alone; troglitazone alone at 200, 400, or 600 mg once daily (T200, T400, or T600); or a combination of each troglitazone dose with G12 for 52 weeks

(T200/G12, T400/G12, T600/G12). A sulfonylurea dose-reduction algorithm that maintained the study blind was implemented for patients achieving an FSG <4.4 mmol/l (80 mg/dl). All patients were instructed on a weight-maintenance diet consistent with the nutritional recommendations of the ADA (21).

Clinical, metabolic, and safety assessments

Medical history, complete physical examinations, and electrocardiograms were assessed before and after treatment. Safety parameters—including vital signs, diabetes-related symptoms, hypoglycemic events, adverse events, and routine laboratory tests (including blood chemistry, hematology, urinalysis, and lipid profile)—were monitored every 4 weeks.

Efficacy parameters

Markers of glycemic control, including HbA_{1c} and FSG levels, were the primary efficacy parameters. Changes in insulin and C-peptide levels and markers of lipid metabolism (total cholesterol, triglycerides, and lipoproteins) were also assessed. A meal-tolerance test (MTT) substudy was administered to all patients in nine centers (80 patients). In this substudy, patients consumed one-third of their total daily caloric requirements in the form of a liquid meal (Sustacal) in the fasting state, and blood specimens for glucose, insulin, and C-peptide were obtained at -10 , 30, 60, 90, and 120 min.

Analytical methods

All biochemical measurements were made by Corning-Nichols Laboratories (San Juan Capistrano, CA) on blood collected in the fasting state. HbA_{1c} was measured using automated ion-exchange high-performance liquid chromatography (Bio-Rad Variant); serum glucose by enzymatic (hexokinase) method (Hitachi 747-200); insulin by a two-site immunoenzymometric assay (sensitivity 2.5 μ U/ml, no cross-reactivity with C-peptide); and C-peptide with a double antibody radioimmunoassay (sensitivity 0.25 ng/ml). Nonesterified free fatty acids (FFAs) (long- and medium-chain FFA) were determined enzymatically (NEFA C-test, WACO Chemicals). After ultracentrifugation, serum total triglycerides were measured using the lipase/esterase, glycerol-kinase, and pyruvate-kinase method. After ultracentrifugation, HDL cholesterol was measured by the dextran sulfate-mag-

nesium chloride precipitation and enzymatic (cholesterol oxidase) method (Hitachi 704). Serum LDL was measured after ultracentrifugation by cholesterol oxidase method (Hitachi 914). Apolipoprotein B (apo B) was determined by immunonephelometry using specific antisera to human apo B (Boehringer Mannheim Diagnostics).

Statistical analysis

Statistical analyses were performed on an intent-to-treat population (all patients with baseline values and at least one measurement during the double-blind phase) with the last observation carried forward. All patients randomized to the double-blind phase were included in the safety analysis. Analysis of covariance was applied to the change from baseline for the efficacy parameters. Step-down tests of linear trend and Bonferroni-Holm adjustments were used for pair-wise comparisons. Dunnett's test was performed to establish 95% CIs for between-treatment comparisons. All tests were two-sided and conducted at a level of significance of 0.05.

RESULTS

Treatment group demographics

The baseline characteristics of the patients randomized to the seven treatment arms are shown in Table 1. Each group was composed of between 76 and 82 patients, predominantly men. In general, the patients were obese and had had known type 2 diabetes for an average of 8.4 years. Mean HbA_{1c} values and FSG levels indicated poor glycemic control in this patient population (Table 1).

FSG and HbA_{1c}

Statistically significant and dose-related decreases in both FSG and HbA_{1c} were observed in the combination groups compared with the control group (G12). FSG mean values for the troglitazone monotherapy and G12 groups increased by 0.6–2.4 mmol/l (11.1–42.4 mg/dl), whereas the levels for the combination groups decreased by 1.7–3.1 mmol/l (31.0–56.4 mg/dl) (Table 2). The differences between the final FSG values of the control arm and the combination arms were -3.0 for the T200/G12, -3.4 for the T400/G12, and -4.4 mmol/l for the T600/G12 groups (-53.7 , -60.8 , and -79.1 mg/dl) ($P \leq 0.0001$, Table 2). The dose-related response of FSG was corroborated by the signifi-

Table 1—Profile of study patients at baseline by treatment group

	Troglitazone monotherapy (mg)			Troglitazone/glynase combination (mg/mg)			Micronized glyburide (mg)
	200	400	600	200/12	400/12	600/12	12
n	78	81	78	78	76	82	79
Age (years)	58.5 ± 10.4	58.9 ± 10.6	56.4 ± 10.2	56.9 ± 10.4	57.1 ± 10.2	56.3 ± 11.6	58.7 ± 10.8
≥65 years	26 (33)	20 (25)	17 (22)	19 (24)	20 (26)	18 (22)	23 (29)
Sex (M/F)	40/38	43/38	48/30	54/24	50/26	49/33	49/30
BMI (kg/m ²)	32.7 ± 6.7	34.0 ± 7.9	32.3 ± 7.1	31.3 ± 5.0	31.2 ± 5.7	31.5 ± 6.9	31.9 ± 6.1
Duration of diabetes (years)	8.6 ± 5.7	8.8 ± 7.8	7.7 ± 5.5	8.7 ± 6.1	8.7 ± 5.9	7.7 ± 6.1	9.0 ± 8.4

Data are means ± SD, n, or n (%).

cantly greater difference in the mean change for the T600/G12 group than the T200/G12 group ($P = 0.009$).

HbA_{1c} changes mirrored those of FSG, with the expected 4-week lag in HbA_{1c} response (Fig. 1). The greatest improvement in HbA_{1c} was noted 4–8 weeks after the start of treatment with combination

therapy, and FSG had responded significantly by week 4. This degree of glycemic control was maintained throughout the study, particularly in the T600/G12 group.

The mean reductions from baseline for HbA_{1c} for combination groups were -0.70 to -1.75% (Figs. 1 and 2, Table 2). In contrast, HbA_{1c} increased 0.85 – 1.92% in the

monotherapy and G12 groups, respectively. The differences between the G12 control group (0.90%) and the T200/G12, T400/G12, and T600/G12 groups were -1.60 , -1.81 , and -2.65% , respectively ($P \leq 0.0001$, Table 2). In addition, the decrease from baseline in HbA_{1c} for the T600/G12 group was significantly greater

Table 2—Mean changes from baseline values in glycemic parameters after 52 weeks of treatment (intent-to-treat population with last observation carried forward)

	Troglitazone monotherapy (mg)			Troglitazone/glynase combination (mg/mg)			Micronized glyburide (mg)
	200	400	600	200/12	400/12	600/12	12
n	78	78	76	78	76	80	79
HbA _{1c} (%)							
Baseline	9.5 ± 0.16	9.4 ± 0.16	9.7 ± 0.19	9.5 ± 0.15	9.7 ± 0.15	9.4 ± 0.17	9.6 ± 0.14
Change from baseline	1.92 ± 0.20	0.85 ± 0.20	0.93 ± 0.20	-0.70 ± 0.20	-0.91 ± 0.20	-1.75 ± 0.20	0.90 ± 0.20
Mean difference from control	1.02*	-0.05	0.03	-1.60†	-1.81†	-2.65†	—
FSG (mmol/l)							
Baseline	12.5 ± 0.3	11.7 ± 0.3	12.7 ± 0.3	12.4 ± 0.3	12.7 ± 0.3	12.1 ± 0.3	12.2 ± 0.3
Change from baseline	2.3 ± 0.4	1.1 ± 0.4	0.6 ± 0.4	-1.7 ± 0.4	-2.1 ± 0.4	-3.1 ± 0.4	1.3 ± 0.4
Mean difference from control	1.1	-0.1	-0.6	-3.0†	-3.4†	-4.4†	—
Total insulin (pmol/l)							
Baseline	231.8 ± 25.1	236.8 ± 15.1	218.8 ± 14.4	202.3 ± 10.8	178.7 ± 8.6	189.4 ± 11.5	195.9 ± 11.5
Change from baseline	-60.3 ± 10.1	-42.3 ± 10.1	-82.7 ± 10.1	-27.6 ± 10.1	-42.2 ± 10.1	-43.6 ± 10.1	-10.4 ± 10.1
C-peptide (nmol/l)							
Baseline	1.0 ± 0.04	1.0 ± 0.05	1.0 ± 0.05	0.9 ± 0.04	0.9 ± 0.04	1.0 ± 0.04	0.9 ± 0.03
Change from baseline	-0.32 ± 0.02‡	-0.26 ± 0.02	-0.33 ± 0.03‡	-0.25 ± 0.02	-0.25 ± 0.03	-0.25 ± 0.02	-0.22 ± 0.02
MTT							
n	8	8	11	13	13	15	12
MTT glucose AUC (mg · h ⁻¹ · dl ⁻¹)							
Baseline	574 ± 37	568 ± 36	558 ± 29	629 ± 43	598 ± 20	583 ± 26	582 ± 22
Change from baseline	5 ± 34	37 ± 60	-137 ± 37‡	-155 ± 51‡	-114 ± 29‡	-94 ± 36‡	35 ± 25
MTT insulin AUC (μIU · h ⁻¹ · ml ⁻¹)							
Baseline	155 ± 39	141 ± 24	171 ± 22	149 ± 18	123 ± 14	134 ± 19	124 ± 13
Change from baseline	-47 ± 10	-54 ± 20	-66 ± 13	-40 ± 11	-25 ± 10	-27 ± 15	-22 ± 8
MTT C-peptide AUC (ng · h ⁻¹ · ml ⁻¹)							
Baseline	8.3 ± 1.4	9.7 ± 1.2	10.4 ± 1.1	10.0 ± 1.2	9.8 ± 1.4	10.1 ± 0.7	8.8 ± 0.8
Change from baseline	-2.2 ± 0.7	-4.2 ± 0.9	-3.1 ± 0.9	-3.7 ± 0.8	-3.8 ± 0.9	-2.9 ± 0.6	-2.3 ± 0.7

Data are means ± SEM, unless otherwise indicated. * $P \leq 0.001$, † $P \leq 0.0001$, ‡ $P \leq 0.05$ compared with control subjects. Mean changes and differences from control group for HbA_{1c}, FSG, total insulin, and C-peptide are adjusted for the effects of baseline and center in the analysis of covariance. To convert values for FSG to micromoles per liter, multiply by 0.0551. To convert values for total insulin to picomoles per liter, multiply by 7.175. To convert values for C-peptide to nanomoles per liter, multiply by 0.331.

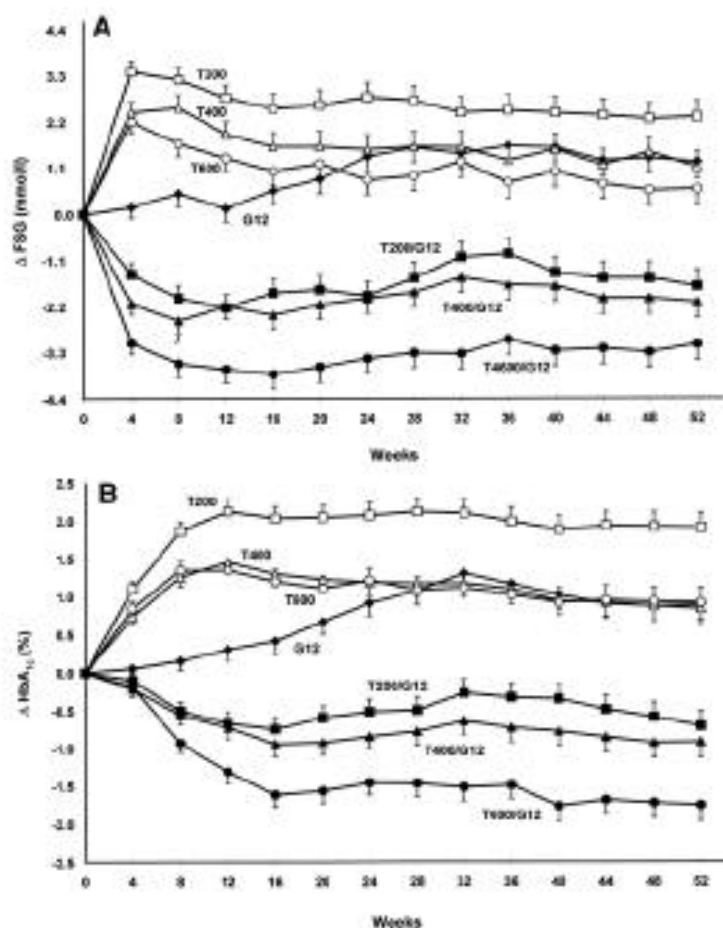


Figure 1—A: Mean change from baseline of FSG over 52 weeks of treatment. B: Mean change from baseline of HbA_{1c} over 52 weeks of treatment.

($P < 0.05$) than that of the T200/G12 and T400/G12 groups.

By week 52, the proportion of patients in the T200/G12, T400/G12, T600/G12 groups that had achieved an HbA_{1c} level $\leq 8\%$ were 33, 33, and 60%, respectively. Notably, 22, 21, and 41% of patients in these respective groups had met the ADA (22) target of HbA_{1c} $\leq 7\%$; and 14, 24, and 39% of patients, respectively, had achieved FSG ≤ 7.8 mmol/l (140 mg/dl) (Fig. 2). These data were calculated using the number of patients initially randomized in each treatment arm (intent to treat) as the denominator.

Insulin and C-peptide

Changes from baseline in serum insulin levels were significantly lower ($P < 0.05$) in all troglitazone monotherapy and the T400/G12 and T600/G12 combination therapy groups, compared with changes from baseline in the G12 group (Fig. 3). A concomitant decrease in both FSG and insulin was noted in the combination groups. Decreases in C-peptide reached

statistical significance only in the T200 and T600 groups ($P < 0.05$, Table 2).

Lipid parameters

Troglitazone, either alone or in combination with sulfonylurea, showed a consistent ben-

eficial trend in most lipid parameters. Circulating FFAs decreased overall (Table 3). Although no statistical significance was reached, triglyceride levels decreased in the monotherapy and combination groups but increased in the G12 group. The mean change ranged from -0.05 to -0.4 mmol/l (from -4 to -36 mg/dl) for the monotherapy groups and from -0.3 to -0.6 mmol/l (from -33 to -51 mg/dl) for the combination groups compared with an increase of 0.2 mmol/l (14 mg/dl) in the G12 group. Total cholesterol and LDL cholesterol increased modestly in all treatment groups. However, statistical significance was noted only in the monotherapy groups. No statistically significant changes were noted in apo B levels, although a downward trend in the T200/G12 and T600/G12 group was observed. Mean values for HDL cholesterol increased for all but the T400/G12 group (Table 3). The change from baseline for the T600 group (0.02 mmol/l or 4.53 mg/dl) was significantly greater ($P < 0.05$) than that for the G12 group (0.004 mmol/l or 0.15 mg/dl).

MTT

For the subset of patients that participated in the MTT, the decrease relative to pretreatment in the 0- to 2-h area under the curve (AUC) for serum glucose was significant ($P \leq 0.05$) in the T600 group and in all three combination groups. Similar trends were observed for the insulin and C-peptide AUCs for all seven groups, although none of these changes were statistically significant (Table 2).

Body weight

The mean body weight for the G12 group decreased by 0.6 kg (1.3 lb). Changes from

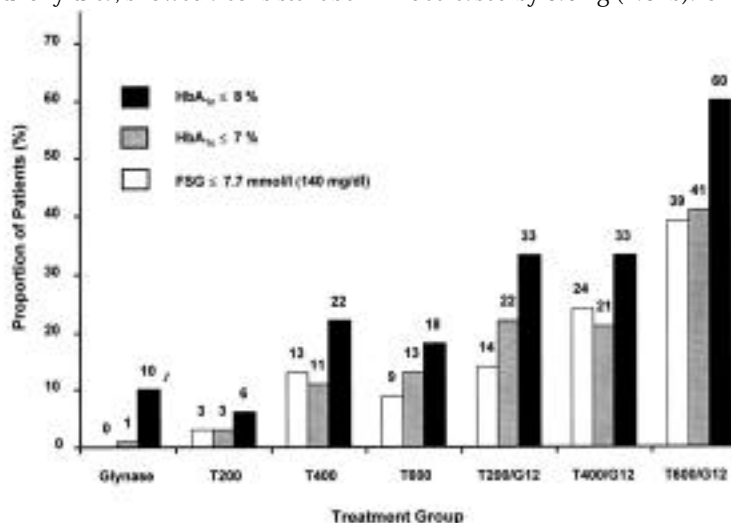


Figure 2—Proportion of patients reaching ADA recommended glycemic values.

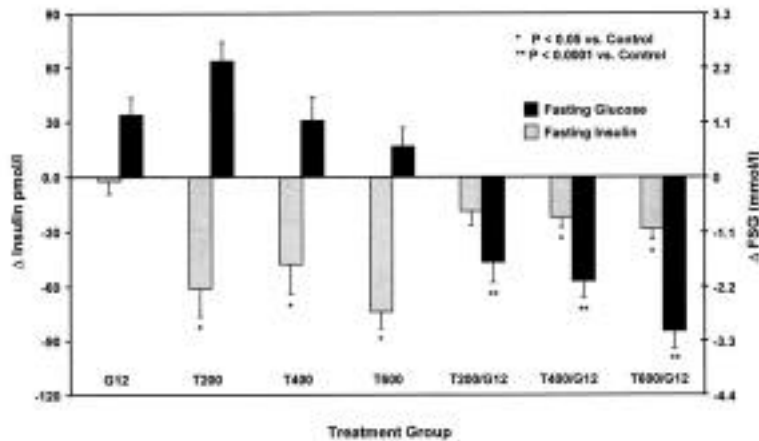


Figure 3—Mean change from baseline to week 52 in FSG and insulin.

baseline in body weight for the T200, T400, and T600 groups were -2.5 , -1.2 , and -0.2 kg (-5.6 , -2.6 , and -0.5 lb), respectively; the decrease for the T200 group was significant compared with the control group ($P \leq 0.05$). Changes from baseline in body weight observed in the combination groups were 2.6 , 3.5 , and 5.9 kg (5.8 , 7.7 , and 13.1 lb) for the T200/G12, T400/G12, and T600/G12 groups, respectively ($P \leq 0.05$).

Safety assessment and patient withdrawal

Of the 552 patients randomized to the double-blind phase, 318 (58%) completed all 52 weeks of the study. Completion rates were highest for the combination groups (71–85%) and lowest among the troglitazone monotherapy groups (28–46%); 57% of the patients in the G12 group completed the study. The rates of withdrawal due to lack of efficacy for the combination groups

(4–14%) were lower than those for patients treated with either troglitazone alone (40–55%) or micronized glyburide alone (25%, Table 4). Withdrawal due to lack of efficacy in the combination groups correlated inversely with troglitazone dose, from 14% in the T200/G12 group to only 4% in the T600/G12 group. Withdrawals due to adverse events were similar across all treatment groups (6–11%). The most common adverse events noted in the study are listed in Table 4.

Troglitazone was well tolerated whether administered as monotherapy or in combination with micronized glyburide. Serious adverse events occurred in 8, 6, and 8% of the monotherapy, combination, and G12 groups, respectively. The incidences of associated serious adverse events (as assessed by the reporting investigator) were 1, 4, and 3% in monotherapy, combination, and micronized glyburide groups, respectively. Gastrointestinal adverse events occurred in 3, 4, and 1% of patients in the monotherapy, combination, and G12 groups, respectively.

The overall incidence of true hypoglycemic events (defined as symptomatic and/or biochemical events documented with a blood glucose level <55 mg/dl measured by a laboratory or home monitor,

Table 3—Mean changes from baseline values for lipid parameters after 52 weeks of treatment (intent to treat population with last observation carried forward)

	Troglitazone monotherapy (mg)			Troglitazone/glynase combination (mg/mg)			Micronized glyburide (mg)
	200	400	600	200/12	400/12	600/12	12
FFAs (mEq/l)							
Baseline	0.74 ± 0.04	0.86 ± 0.06	0.81 ± 0.10	0.72 ± 0.04	0.79 ± 0.05	0.70 ± 0.03	0.76 ± 0.06
Change from baseline	-0.09 ± 0.04	-0.17 ± 0.06	-0.19 ± 0.10	-0.12 ± 0.04	-0.15 ± 0.04	-0.08 ± 0.03	-0.05 ± 0.06
Triglycerides (mmol/l)							
Baseline	3.1 ± 0.6	3.1 ± 0.4	3.2 ± 0.3	3.2 ± 0.5	3.0 ± 0.2	2.9 ± 0.3	2.5 ± 0.2
Change from baseline	-0.4 ± 0.5	-0.1 ± 0.4	-0.1 ± 0.4	-0.4 ± 0.3	-0.4 ± 0.2	-0.6 ± 0.2	0.2 ± 0.2
Total cholesterol (mmol/l)							
Baseline	5.9 ± 0.2	5.6 ± 0.1	5.6 ± 0.1	5.4 ± 0.1	5.6 ± 0.1	5.5 ± 0.1	5.6 ± 0.1
Change from baseline	0.5 ± 0.2*	0.6 ± 0.1*	0.7 ± 0.1*	0.4 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.2 ± 0.1
HDL cholesterol (mmol/l)							
Baseline	0.95 ± 0.03	0.98 ± 0.05	0.97 ± 0.05	0.95 ± 0.03	0.99 ± 0.06	0.91 ± 0.03	0.92 ± 0.02
Change from baseline	0.02 ± 0.02	0.08 ± 0.04	0.12 ± 0.07*	0.04 ± 0.04	-0.05 ± 0.06	0.12 ± 0.05	0.00 ± 0.02
LDL cholesterol (mmol/l)							
Baseline	3.5 ± 0.1	3.3 ± 0.1	3.4 ± 0.1	3.1 ± 0.1	3.3 ± 0.1	3.2 ± 0.1	3.4 ± 0.1
Change from baseline	0.5 ± 0.1*	0.3 ± 0.1	0.4 ± 0.1*	0.4 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.1 ± 0.1
Apo B (mg/dl)							
Baseline	135 ± 6.8	124 ± 4.7	118 ± 5.1	117 ± 3.6	124 ± 3.4	118 ± 2.8	125 ± 3.1
Change from baseline	6.4 ± 6.2	3.4 ± 5.8	3.1 ± 6.4	6.3 ± 2.7	0.1 ± 3.1	-0.7 ± 2.6	2.9 ± 3.4

Data are means ± SEM. * $P \leq 0.05$ compared with control subjects. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.02586.

Table 4—Patient withdrawal and adverse events by treatment group

	Troglitazone monotherapy (mg)			Troglitazone/glycylase combination (mg/mg)			Micronized glyburide (mg)
	200	400	600	200/12	400/12	600/12	12
<i>n</i>	78	81	78	78	76	82	79
Total withdrawn	56 (72)	45 (56)	44 (56)	22 (28)	22 (29)	12 (15)	33 (42)
Because of lack of efficacy	43 (55)	32 (40)	34 (44)	11 (14)	7 (9)	3 (4)	20 (25)
Because of adverse events	6 (8)	7 (9)	6 (8)	5 (6)	8 (11)	5 (6)	6 (8)
Because of noncompliance	3 (4)	2 (3)	3 (4)	0 (0)	1 (1)	2 (2)	1 (1)
Other	4 (5)	3 (4)	1 (1)	6 (8)	6 (8)	2 (2)	6 (8)
Most frequent adverse events							
Infection	13 (17)	16 (20)	12 (15)	23 (29)	27 (36)	25 (30)	26 (33)
Pain	5 (6)	10 (12)	9 (12)	9 (12)	11 (14)	14 (17)	7 (9)
Accidental injury	7 (9)	9 (11)	7 (9)	10 (13)	10 (13)	13 (16)	9 (11)
Rhinitis	4 (5)	7 (9)	4 (5)	6 (8)	11 (14)	12 (15)	7 (9)
Flu syndrome	4 (5)	5 (6)	11 (14)	9 (12)	4 (5)	8 (10)	10 (13)
Back pain	2 (3)	10 (12)	5 (6)	7 (9)	11 (14)	5 (6)	4 (5)
Diarrhea	5 (6)	2 (2)	11 (14)	5 (6)	7 (9)	6 (7)	8 (10)
Urinary tract infection	7 (9)	6 (7)	5 (6)	5 (6)	5 (7)	8 (10)	6 (8)
Headache	4 (5)	5 (6)	6 (8)	8 (10)	4 (5)	6 (7)	2 (3)
Sinusitis	2 (3)	6 (7)	5 (6)	10 (13)	5 (7)	5 (6)	5 (6)
Rash	4 (5)	4 (5)	6 (8)	6 (8)	5 (7)	7 (9)	4 (5)

Data are *n* (%).

or events requiring emergency assistance) was low, occurring in 1 of the 237 patients (<1%) who received troglitazone monotherapy, in 6 of the 236 (3%) given the combination therapy, and in 1 of the 79 (1%) treated with G12. Four of the eight incidents were considered treatment-related, but none required emergency treatment. The G12 dosage was reduced in one patient, and none of these patients discontinued the study.

Elevated serum alanine aminotransferase >3 times the upper normal limit was noted in 1, 3, 0, 5, 4, 5, and 5% of the G12, T200, T400, T600, T200/G12, T400/G12, and T600/G12 groups, respectively. At investigators' discretion, a total of seven patients receiving troglitazone monotherapy or combination were discontinued from the study because of liver enzyme elevations without any clinical manifestations; all were followed, and enzyme levels returned to either baseline level or normal range.

CONCLUSIONS — In this study, glycemic control achieved by adding troglitazone to current sulfonylurea treatment was superior to maintaining patients on sulfonylurea alone or switching them to troglitazone monotherapy. In terms of reaching clinical practice guidelines, 40% of patients treated with T600/G12 achieved the opti-

mal ADA target of HbA_{1c} ≤7%, and 60% achieved an HbA_{1c} ≤8%, the level above which action is advised. These results support the use of troglitazone in combination with sulfonylurea to achieve the ADA recommended guidelines for glycemic control. For patients not achieving acceptable glucose control with combination therapy, treatment with a combination of troglitazone and insulin, other agents indicated for combination therapy with insulin, or insulin alone should be considered.

Consistent with the mechanism of action of troglitazone, the concomitant decreases in HbA_{1c} and FSG levels along with reduced plasma insulin levels suggest improved insulin sensitivity (Fig. 3). The observed significant reductions in glucose AUCs and concomitant trends in insulin AUCs in the MTT subset provide additional support for this interpretation.

In contrast, the data of patients maintained on G12 (the active control group) suggest a progression of β-cell failure consistent with a secondary failure of sulfonylurea treatment. In this group, both HbA_{1c} and FSG levels increased over the course of this study, while insulin levels decreased. These changes are more likely indicative of diminished secretory capacity rather than improved insulin sensitivity.

The switch from current sulfonylurea to troglitazone monotherapy provided no

significant improvement in glycemic control. The net gain in insulin sensitivity with troglitazone was only marginally higher than the net loss in insulin secretion caused by the withdrawal of sulfonylurea. Given the slower-acting properties of troglitazone and the acute effect of sulfonylureas on insulin secretion, the detrimental effects of sulfonylurea withdrawal were not immediately compensated for by the benefits of troglitazone treatment. This imbalance resulted in an interim state of hyperglycemia and glucose toxicity that may have hindered the action of troglitazone. This effect is also reflected by the high rate of withdrawals in the troglitazone monotherapy groups due to lack of efficacy, the majority of which took place during the first 12 weeks of treatment.

Hypoglycemic events were rare in this study, partially due to the sulfonylurea dose-reduction algorithm implemented in the study for FSGs <4.4 mmol/l (80 mg/dl). Consistent with the experience in this study, the dose of the concomitant hypoglycemic agent should be reduced gradually as glucose levels fall below normal values. In this study, sulfonylurea dose reductions were necessary as early as 2–4 weeks of treatment after the addition of troglitazone.

Lipid changes observed in this study appear to reflect a correlation between hyperglycemia and dyslipidemia. Statisti-

cally significant but modest increases in total and LDL cholesterol were observed in the troglitazone monotherapy groups but not in the combination groups that had significant improvement in glycemic control. Nevertheless, no significant changes were observed in apo B, indicating no increase in atherogenic risk (23). Although a notable change (-0.6 mmol/l or -50.5 mg/dl) in triglycerides was observed in the T600/G12 group, it did not reach statistical significance because of the inherent variability of triglyceride measurements. Similarly, the magnitude of decreases in circulating FFA and increases in HDL cholesterol did not reach statistical significance; however, they mirror the changes observed in previously reported studies and are consistent with improved insulin sensitivity resulting from troglitazone treatment (17–19,24). In this study, changes in body weight correlated with improved glycemic control ($P < 0.05$). Similar correlations were noted in the DCCT, where weight gain was statistically related to the degree of glycemic improvement and not to the dose of insulin (25). The increases in body weight observed in the combination therapy groups but not in the monotherapy groups suggest that factors other than troglitazone therapy contributed to the weight gain. Such factors may include 1) reduction of glycosuria associated with improved glycemic control and 2) the weight-maintenance diet implemented in this study rather than a weight-reduction diet recommended for management of overweight diabetic patients. Diet and exercise are fundamental approaches to the management of type 2 diabetes and should be emphasized even when pharmacological interventions are added.

Overall, the adverse event and serious adverse event profiles for troglitazone monotherapy and combination therapy were similar to those of the control arm. Nevertheless, the infrequency of laboratory abnormalities associated with troglitazone therapy further supports its favorable adverse events profile. Although hepatic dysfunction has been reported with troglitazone treatment, a complete review of hepatic dysfunction associated with troglitazone in controlled studies is detailed elsewhere (26). Combination therapy with troglitazone and sulfonylurea appears to be safe and well tolerated. The effectiveness of troglitazone in ameliorating insulin resistance and acting synergistically with a sulfonylurea to restore glycemic control has important clinical

implications, specifically in reaching ADA treatment goals in a patient population with limited therapeutic options.

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