Repaglinide/Troglitazone Combination Therapy

Improved glycemic control in type 2 diabetes

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OBJECTIVE — This multicenter open-label clinical trial compared the efficacy and safety of repaglinide/troglitazone combination therapy, repaglinide monotherapy, and troglitazone monotherapy in type 2 diabetes that had been inadequately controlled by sulfonylureas, acarbose, or metformin alone.

RESEARCH DESIGN AND METHODS — Patients with type 2 diabetes ($n = 256$) who had inadequate glycemic control ($HbA_{1c} \geq 7.0\%$) during previous monotherapy were randomly assigned to receive repaglinide (0.5–4.0 mg at meals), troglitazone (200–600 mg once daily), or a combination of repaglinide (1–4 mg at meals) and troglitazone (200–600 mg once daily). After a 4–6 week washout period, the trial assessed 22 weeks of treatment: 3 weeks (weeks 0–2) of forced titration, 11 weeks of fixed-dose treatment (weeks 3–13), and 8 weeks (weeks 14–21) of titration to maximum dose. Changes in HbA_{1c} and fasting plasma glucose (FPG) values were measured.

RESULTS — The combination therapy showed a significant reduction in mean HbA_{1c} values (-1.7%) that was greater than with either type of monotherapy. Repaglinide monotherapy resulted in a reduction of HbA_{1c} values that was significantly greater than troglitazone (-0.8 vs. -0.4%) ($P < 0.05$). Combination therapy was more effective in reducing FPG values (-80 mg/dl) than either repaglinide (-43 mg/dl) or troglitazone (-46 mg/dl) monotherapies. Adverse events were similar in all groups.

CONCLUSIONS — Combination therapy with repaglinide and troglitazone leads to better glycemic control than monotherapy with either agent alone. Repaglinide monotherapy was more effective in lowering HbA_{1c} levels than troglitazone monotherapy. Repaglinide/troglitazone combination therapy was effective and did not show unexpected adverse events.

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T he pathogenesis of type 2 diabetes may involve dual metabolic defects of inadequate β-cell function as well as reduced sensitivity of insulin target tissues. Patients typically show a declining response to oral hypoglycemic agents over time. The recent availability of new oral agents with varying mechanisms of action has increased the possibility of meaningful combination therapy that can be superior to the use of these agents as monotherapy. Several studies have reported improved glycemic control with such combination therapy (1–3).

Repaglinide is the first oral agent of the meglitinide class to become available for the treatment of type 2 diabetes (4) and has a mechanism of β-cell stimulation that differs from sulfonylureas (5). Repaglinide is chemically unrelated to sulfonylureas or any other currently available class of oral hypoglycemic agents (6). Rapid absorption and clearance of repaglinide make this agent a suitable choice for the management of meal-related blood glucose surges.

Troglitazone is a thiazolidinedione, which is a class of drugs that improves insulin sensitivity in peripheral tissues. By increasing both the supply and physiological effectiveness of circulating insulin in patients with type 2 diabetes, such a secretagogue/sensitizer combination therapy regimen may be an improvement on the efficacy of either agent used as a monotherapy. Repaglinide offers an unusually short elimination half-life (~1 h) and meal-time dosing administration, which results in an insulin stimulation that is maximal during postprandial periods when it is most needed, unlike even short-acting sulfonylureas. The safety profile of repaglinide is a key factor to weigh when combining treatments that may each contribute to adverse events. Because repaglinide has a shorter duration of action than sulfonylureas and offers the simple option of skipping the dose for missed meals, repaglinide may involve less risk of hypoglycemic episodes than other available secretagogues.

This clinical trial was designed to compare the efficacy and safety of a combination of repaglinide/troglitazone, repaglinide monotherapy, and troglitazone monotherapy in the glycemic management of type 2 diabetes in patients who had previously shown an inadequate glycemic response to monotherapy with either sulfonylureas, acarbose, or metformin.

RESEARCH DESIGN AND METHODS

Patients
A total of 256 patients (30–86 years of age) with type 2 diabetes were randomly

Table 1—*Demographics and baseline characteristics**

Characteristics	Repaglinide	Troglitazone	Repaglinide/troglitazone
Total patients treated	83	85	88
Age (years)	58.7 ± 11.2	57.0 ± 11.2	59.0 ± 10.0
Sex (M/F)	53/30	59/26	54/34
Ethnic origin			
Caucasian	64 (77)	64 (75)	69 (78)
Black	9 (11)	9 (11)	7 (8)
Other	10 (12)	12 (14)	12 (14)
BMI (kg/m^2)	29.1 ± 4.5	29.6 ± 5.0	30.4 ± 5.4
Duration of diabetes (years)	7.5 ± 6.2	5.6 ± 5.6	6.4 ± 6.3
HbA$_{1c}$ (%)	8.8 ± 1.0	8.7 ± 1.0	8.7 ± 1.0
FPG (mg/dl)	217.0 ± 46.6	214.7 ± 47.6	208.5 ± 44.8
C-peptide (nmol/l)	1.3 ± 0.5	1.4 ± 0.7	1.4 ± 0.6

Data are *n*, means ± SD, or *n* (%). *Includes all patients randomized in clinical trial.

assigned to receive 1 of 3 treatment regimens (repaglinide, troglitazone, or a combination of repaglinide and troglitazone) in this open-label clinical trial at 20 sites. Enrolled patients had an HbA$_{1c}$ value between 7.0 and 10.5% and a fasting plasma C-peptide concentration >0.2 nmol/l while receiving treatment with sulfonylureas, acarbose, or metformin as monotherapy. Patients were excluded if they had abnormal renal or hepatic function or had cardiac disease within the last 12 months. A total of 83 patients (53 men and 30 women) were randomly assigned to receive repaglinide for 22 weeks, 85 patients (59 men and 26 women) received troglitazone, and 88 patients (54 men and 34 women) received a combination of repaglinide and troglitazone. The protocol was approved by the institutional review boards of all study sites, and patients gave their informed consent.

Study design

Forced titration: weeks 0–2. After a 4- to 6-week washout period when previous drug therapy was discontinued, patients received 0.5 mg repaglinide 0–30 min before each meal, or 200 mg troglitazone once daily, or a combination of both repaglinide (0.5 mg at meals) and troglitazone (200 mg once daily). The dose of repaglinide was increased to 1.0 mg at meals after 1 week (after week 0) and was further increased to 2.0 mg after 2 weeks of treatment. The dose of troglitazone was increased to 400 mg once daily after 2 weeks of treatment. Patients in the combination therapy group received 1.0 mg repaglinide and 200 mg troglitazone after 1 week (after week 0), 2.0 mg repaglinide and 200 mg troglitazone after 2 weeks, and 2.0 mg

repaglinide and 400 mg troglitazone at the end of third week of treatment.
Fixed-dose treatment: weeks 3–13. The dosage levels of all treatments were then maintained for 11 weeks from the beginning of week 3 until the end of week 13. However, the clinical trial protocol called for a reduction in dosage in the event of persistent levels of fasting plasma glucose (FPG) <80 mg/dl and/or repeated major hypoglycemia. Such dose reduction was to be achieved by reversing the last step of the dose increment schedule. FPG and HbA$_{1c}$ levels were measured at weeks 0, 10, and 14, and circulating liver transaminase levels were measured at weeks 0, 4, 7, 10, and 14.
Titration to maximum dose: weeks 14–21. After 14 weeks of treatment, FPG values

were used to assess the need for further escalation of the dose. If the FPG value was >120 mg/dl, then the patient was titrated toward the maximum dose of the drug (e.g., 4.0 mg repaglinide at meals or 600 mg troglitazone once daily). For the combination therapy group, the dose of repaglinide was first increased to 4.0 mg at meals, and FPG was measured after an additional week. If FPG values remained >120 mg/dl, then the dose of troglitazone was increased to 600 mg once daily. If necessary, a reduction in dose could also occur as described during the forced titration phase of this study. At week 22 of treatment, both FPG and HbA$_{1c}$ values were assessed for therapeutic response. Levels of liver transaminases were measured every 4 weeks.

Efficacy and safety assessments
HbA$_{1c}$ values were measured by a central clinical laboratory (UCT International, Farmingdale, NY). HbA$_{1c}$ levels were determined by a high-performance liquid chromatography method with a normal laboratory range of 4.7–6.4%.

During the course of the study, patients were monitored for any abnormality in vital signs or changes in weight. Symptoms of hypoglycemia and corresponding self-assessed blood glucose readings were also recorded, with particular emphasis on any events accompanied by blood glucose readings <45 mg/dl. A physical examination, funduscopy, and 12-point electrocardiogram (ECG) were performed at the beginning and end of the clinical trial.

Table 2—*Study completion status and selected adverse events during treatment*

	Repaglinide	Troglitazone	Repaglinide/troglitazone
Patients treated	83 (100)	85 (100)	88 (100)
Completed week 22*	74 (89)	61 (72)	70 (80)
Did not complete week 22	9 (11)	24 (28)	18 (20)
Reasons for discontinuation			
Adverse event: hyperglycemia	1 (1)	2 (2)	0
Adverse event: other	1 (1)	4 (5)	5 (6)
Noncompliance	3 (4)	1 (1)	7 (8)
Inadequate glycemic control (lack of efficacy)	3 (4)	14 (16)	0
Other	1 (1)	3 (4)	6 (7)
Adverse events			
Patients with serious adverse events	7 (8)	9 (11)	6 (7)
Patients with elevated liver function test values†	1 (1)	1 (1)	3 (3)
Patients with hypoglycemic episodes‡	3 (4)	1 (1)	7 (8)

Data are *n* (%). *Between-treatment *P* value = 0.026; †>2 times upper limit of normal value; ‡symptoms of hypoglycemia with blood glucose values <45 mg/dl.
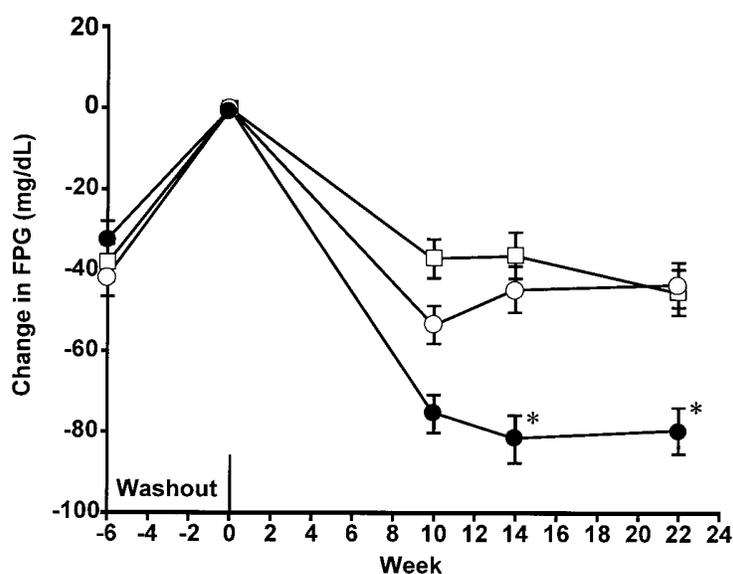
Figure 1—*Changes in FPG values during treatment. Baseline FPG values (at week 0): troglitazone group (□), 204.2 mg/dl; repaglinide group (○), 216.2 mg/dl; and repaglinide/troglitazone combination therapy group (●), 210.5 mg/dl. *P < 0.05 for combination therapy vs. troglitazone or repaglinide monotherapy.*

In the repaglinide/troglitazone combination therapy group, HbA_{1c} values decreased significantly from baseline by the week 22 visit (Fig. 2) from 8.7 to 7.0% ($P < 0.05$). Combination therapy was more effective in reducing HbA_{1c} (-1.7%) compared with repaglinide (-0.8%) or troglitazone (-0.4%) monotherapy. Repaglinide monotherapy resulted in a significantly greater reduction in HbA_{1c} compared with troglitazone monotherapy ($P < 0.05$).

As shown in Fig. 3, at the beginning of treatment, all groups had a similar makeup in terms of the percentage of patients with poor glycemic control ($HbA_{1c} > 8\%$) or moderate glycemic control ($7\% < HbA_{1c} \leq 8\%$). During 22 weeks of treatment, patients in both the repaglinide and troglitazone monotherapy groups demonstrated a therapeutic response, with 19% of the repaglinide group and 13% of the troglitazone group achieving good glycemic control ($HbA_{1c} \leq 7\%$). However, repaglinide/troglitazone combination therapy achieved this desirable level of glycemic control in 62% of patients after 22 weeks, which was a substantially greater therapeutic response. Only 7% of patients treated with the repaglinide/troglitazone combination regimen continued to show poor glycemic control at the end of the 22-week treatment period.

Statistical analysis

The sample size was chosen to ensure 80% power to detect superiority of the combination therapy versus monotherapy, where superiority was defined as treatment period decreases in HbA_{1c} values that were at least 0.6% greater for combination therapy. To test the overall treatment effects on HbA_{1c} values, analysis of variance was performed with treatment and center included in the model.

RESULTS — Patients in all 3 treatment groups were comparable regarding age, BMI, FPG, C-peptide, and HbA_{1c} values (Table 1). A total of 205 (80%) patients completed the study: 74 (89%) in the repaglinide group, 61 (72%) in troglitazone group, and 70 (80%) in the repaglinide/troglitazone combination therapy group (Table 2). In the troglitazone monotherapy group, the major cause of discontinuation of treatment was inadequate glycemic control (14 patients, 16%). Only 3 repaglinide-treated patients discontinued treatment because of lack of efficacy, and no discontinuations of combination treatment occurred for this reason.

Glycemic control and metabolic indexes

Changes in mean FPG values during treatment are shown in Fig. 1. For combination therapy, FPG values decreased significantly from baseline by week 22 from 207.1 ±

45.6 to 130.6 ± 38.6 mg/dl ($P < 0.05$, mean values for all patients with postbaseline data). Combination therapy resulted in a significantly greater ($P < 0.05$) reduction in FPG values (-80 mg/dl) compared with repaglinide (-43 mg/dl) or troglitazone (-46 mg/dl) monotherapy.
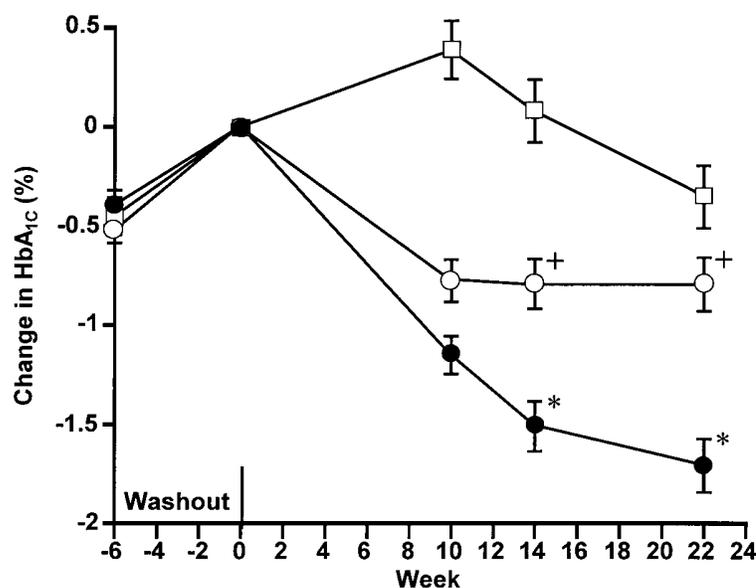

Figure 2—*Changes in HbA_{1c} values during treatment. Baseline HbA_{1c} values (at week 0): troglitazone group (□), 8.5%; repaglinide group (○), 8.8%; and repaglinide/troglitazone combination therapy group (●), 8.7%. *P < 0.05 for combination therapy vs. troglitazone or repaglinide monotherapy; +P < 0.05 for repaglinide monotherapy vs. troglitazone monotherapy.*
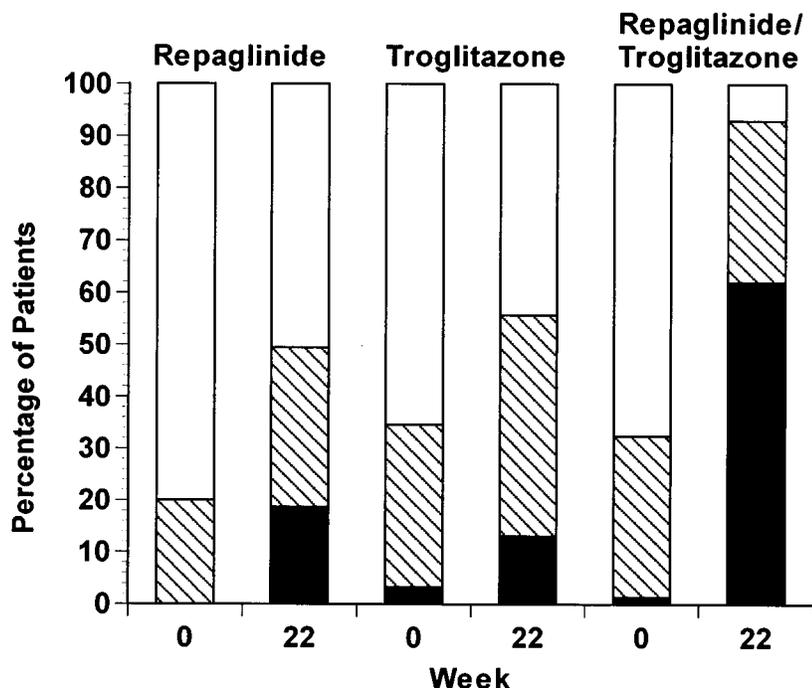
Figure 3—*Patient response categorized by degree of glycemic control.* □, *HbA*$_{1c}$ >8.0%; ◨, 7.0% < *HbA*$_{1c}$ ≤ 8.0%; ■, *HbA*$_{1c}$ ≤7.0%.

Safety evaluations

All of the patients treated with trial medication were included in the safety analysis. Careful review of the adverse event profiles of patients failed to reveal any notable trends or differences between the 3 treatment groups. A total of 22 patients had serious adverse events, 7 (8%) in the repaglinide group, 9 (11%) in the troglitazone group, and 6 (7%) in the repaglinide/troglitazone combination therapy group (Table 2). These events included chest pain (2 patients in the repaglinide group and 1 in the troglitazone group), cerebrovascular disorders (2 patients in the repaglinide group), malignancies (1 patient each in the troglitazone and combination therapy groups), arrhythmia (1 patient in the troglitazone group), and increased aspartate aminotransferase levels (1 patient in the troglitazone group). Chest pain and cerebrovascular disorders occurred in patients who did not have evidence of hypoglycemia that may have possibly contributed to such events. An additional 3 patients (2 in the repaglinide group and 1 in the combination therapy group) had clinically significant ECG findings at the end of the study that were classified as nonserious myocardial infarction adverse events.

Symptoms suggestive of hypoglycemia in which blood glucose levels were actually ≥45 mg/dl were reported by 27, 16, and 45% of patients in the repaglinide, troglitazone, and combination therapy groups, respectively. However, only 11 patients (3 [4%] in the repaglinide group, 1 [1%] in the troglitazone group, and 7 [8%] in the combination therapy group) had symptoms of hypoglycemic events accompanied by blood glucose values <45 mg/dl (Table 2). None of the patients with hypoglycemic events required the assistance of another person.

Mean body weight of patients in all treatment groups showed increases of 1–2 kg during treatment. Adverse events of anemia occurred in 4 patients in the combination therapy group and 2 patients in the troglitazone monotherapy group. Treatment-emergent elevations of liver enzymes (>2 times upper normal limit) were reported in 3 patients in the combination therapy group and by 1 patient each in the repaglinide and the troglitazone monotherapy groups. All 5 patients with elevated liver enzymes were discontinued from treatment, and their enzyme levels returned to normal. No other clinically relevant changes in laboratory tests were observed in any of the 3 treatment groups.

CONCLUSIONS — The goal of current strategies for the management of type 2 dia-

betes is to achieve the best glycemic control possible without an unacceptable level of hypoglycemia. The glycemic goal should probably be HbA$_{1c}$ values within the range of persons who do not have diabetes. Both epidemiological and intervention studies have shown the clear relationship between overall glycemic control and the development of complications in patients with type 2 diabetes (7–9). The progressive loss of efficacy of oral hypoglycemic agents when used as monotherapy in diabetes has therefore led to numerous trials using combinations of drugs with different mechanisms of action (1–3). The different and complementary mechanisms of action of repaglinide and thiazolidinediones make these agents a logical combination therapy.

This multicenter open-label randomized clinical trial indicated that combination therapy with repaglinide and troglitazone was effective and safe and achieved improvements in glycemic control in patients with type 2 diabetes who had earlier failed to achieve an adequate response during monotherapy with other oral agents. Repaglinide or troglitazone monotherapy produced a modest therapeutic response as measured by FPG or HbA$_{1c}$ levels, although this response reflected the relatively unresponsive patient population of this clinical trial. Use of repaglinide alone reduced HbA$_{1c}$ levels somewhat more than was the case for troglitazone monotherapy. Combination treatment with a repaglinide/troglitazone regimen produced a pronounced response in terms of FPG or HbA$_{1c}$ values, and this response was greater than that of either drug administered alone. At the end of 22 weeks, only 7% of patients receiving combination therapy had HbA$_{1c}$ levels that would be indicative of poor glycemic control (HbA$_{1c}$ >8%).

A common and difficult problem in controlling diabetes is the large increase in blood glucose that occurs after meals. This blood glucose surge is normally controlled by an early peak insulin secretion in the postprandial period. As part of a combination regimen, mealtime repaglinide improves glycemic control by enhancing postprandial insulin response, while the insulin sensitizer troglitazone enhances the effect of insulin. The actions of such combination therapy can be viewed as therapeutic intervention for both major pathophysiological defects of type 2 diabetes: inadequate insulin production and an inadequate response to available insulin. The synergistic actions of repaglinide in combi-

nation with metformin, another insulin sensitizer, have been previously documented (1), and such use of repaglinide is an approved indication (10). The present study is the first clinical trial report of combination use of repaglinide with an insulin sensitizer in the thiazolidinedione class. Since the time of this clinical trial, the newer thiazolidinediones rosiglitazone and pioglitazone may offer advantages over troglitazone in terms of hepatic safety. The therapeutic benefits demonstrated for the combination use of repaglinide with metformin or troglitazone may likely be generalizable to more recently developed insulin sensitizers as well.

In conclusion, this clinical trial has demonstrated that combination therapy with repaglinide and troglitazone significantly increased the percentage of patients achieving optimal glycemic control. Combination use of repaglinide/troglitazone was significantly superior to monotherapy with either treatment alone in a patient population selected for the declining glycemic response to oral hypoglycemic agents that commonly occurs in the clinical treatment of type 2 diabetes.

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