A Prospective, Randomized Comparison of the Metabolic Effects of Pioglitazone or Rosiglitazone in Patients With Type 2 Diabetes Who Were Previously Treated With Troglitazone

MEHMOOD A. KHAN, MD[1]
JOHN V. ST. PETER, PHARMD[2,3]
JAY L. XUE, DVM, PHD[4]

OBJECTIVE — To characterize potential differences in glycemic control, plasma lipid level, and weight in a cohort of patients previously treated with troglitazone (TROG) who were switched to either pioglitazone or rosiglitazone.

RESEARCH DESIGN AND METHODS — After a 2-week washout from TROG, 186 patients were randomly assigned to receive either pioglitazone (PIO) or rosiglitazone (ROSI). Weight, HbA_{1c}, and fasting lipid profile were documented before discontinuing TROG and at 4 months after starting either pioglitazone or rosiglitazone. Secondarily, the effect of concurrent medications on study outcomes was assessed.

RESULTS — A total of 127 patients completed follow-up: 67 individuals in the PIO group (32 women, 35 men) and 60 individuals in the ROSI group (33 women, 27 men). There were no significant differences in gender mix, age, weight, fasting lipid profile, or HbA_{1c} between the ROSI and PIO groups. After 4 months of randomized treatment, no change in HbA_{1c} from baseline between or within groups was noted. Both groups experienced an equal and significant increase in weight from baseline of ~2.0 kg. Thiazolidinedione and HMG-CoA reductase inhibitor therapy had significant and independent effects on lipid profile ($P < 0.005$). Significant improvements in lipid profile were noted in the PIO group ($P < 0.01$), whereas none were detected with conversion to ROSI. Specifically, the PIO group experienced an average decrease in total cholesterol of ~20 mg/dl.

CONCLUSIONS — Differing effects on lipid profile were apparent after random conversion from TROG to either PIO or ROSI, despite similar weight increase and glycemic control. The clinical significance of these differences remains to be determined, and further comparative research is warranted.

Diabetes Care 25:708–711, 2002

From the [1]Division of Endocrinology, Mayo Clinic, Rochester, Minnesota; the [2]Division of Endocrinology, Metabolism and Nutrition, Hennepin County Medical Center, Minneapolis, Minnesota; the [3]College of Pharmacy, University of Minnesota, Minneapolis, Minnesota; and the [4]Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota.

Address correspondence and reprint requests to John V. St. Peter, PharmD, BCPS, Department of Medicine, Division of Endocrinology, Metabolism and Nutrition, Hennepin County Medical Center, 701 Park Avenue, #865-B, Minneapolis, MN 55415-1829. E-mail: stpet003@umn.edu.

Received for publication 12 November 2001 and accepted in revised form 7 December 2001.

M.A.K. has received honoraria and consulting fees from Takeda Pharmaceuticals America and SmithKline Beecham, and J.V.S.P. has received honoraria for speaking engagements from Takeda Pharmaceuticals America.

Abbreviations: PIO, pioglitazone; ROSI, rosiglitazone; TROG, troglitazone.

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

Rosiglitazone (ROSI), pioglitazone (PIO), and troglitazone (TROG) are all thiazolidinediones used in the management of diabetes. TROG has been withdrawn from the market because of concerns over hepatotoxicity, which is presumed to be idiosyncratic. These drugs all have effects on glucose and lipid metabolism as well as body weight (1–4). There are demonstrated differences in pharmacological effects of these drugs in vitro (5–7). However, there is little comparative data available on their relative clinical effects (8–11). The removal of troglitazone from the market provided a unique opportunity to assess possible differences in clinical response with conversion to either PIO or ROSI. Therefore, we designed and implemented a protocol to assess several routine clinical end points in our TROG-treated patients after random assignment to PIO or ROSI.

RESEARCH DESIGN AND METHODS

Study design

This was an open-label, randomized comparison of PIO and ROSI in patients previously stabilized on TROG in combination with various other glucose-lowering medications. All patients were derived from a single diabetes center associated with a major teaching hospital serving a large metropolitan, Midwestern city. As outlined by the Declaration of Helsinki and Title 21 of the U.S. Code of Federal Regulations, the center's Human Subjects Research Committee reviewed and approved the protocol. Participating subjects gave written informed consent. Any patient currently taking TROG and with stable liver function assessed by liver enzymes (alanine and aspartate aminotransferase) was eligible to participate. Information regarding standard demography and concurrent medications

Table 1—*Baseline characteristics of patients completing the protocol*

	ROSI	PIO	*P* value
Gender (male/female)	27/33	35/32	0.42
Age (years)	57.1 ± 12.1	57.8 ± 11.0	0.73
Weight (kg)	103.2 ± 24.8	101.4 ± 24.2	0.67
BMI (kg/m^2)	35.6 ± 7.4	35.2 ± 7.4	0.76
HbA_{1c}	7.9 ± 1.9	8.0 ± 1.7	0.58
Cholesterol (mg/dl)	190.7 ± 44.1	196.9 ± 44.5	0.43
HDL cholesterol (mg/dl)	45.3 ± 15.2	44.7 ± 15.6	0.83
LDL cholesterol (mg/dl)	105.9 ± 29.7	116.2 ± 38.0	0.10
Triglyercide (mg/dl)	236.0 ± 222.0	181.0 ± 110.1	0.19
HMG-CoA reductase inhibitor use	35 (58)	40 (60)	0.88
Metformin use	16 (27)	22 (33)	0.45
Insulin use	25 (42)	39 (58)	0.06
Sulfa use	40 (67)	41 (61)	0.52

Data are means ± SD or *n* (%).

at the time of randomization was compiled in all participants. Before stopping TROG therapy, baseline assessment of weight and clinical laboratory values were completed. These measures were repeated after 4 months of randomized therapy with either PIO or ROSI and included liver enzymes (alanine and aspartate aminotransferase), HbA_{1c}, and fasting plasma lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides). Concurrent lipid-lowering therapy was held constant during the 4-month study period. Daily thiazolidinedione dose conversion was accomplished using each manufacturer's marketed dosage forms and the knowledge that all three compounds demonstrated relatively linear, dose-dependent pharmacokinetics (1,2,12). For patients currently taking TROG 600 mg/day, either PIO 45 mg/day or ROSI 4 mg b.i.d. was used; patients taking TROG 400 mg/day were given either PIO 30 mg/day or ROSI 4 mg/day; and patients taking TROG 200 mg/day were given either PIO 15 mg/day or ROSI 2 mg/day.

Measurements

The major end points of this study were weight, HbA_{1c}, and plasma lipids. Total cholesterol and triglycerides were measured on a Vitros 950 (Ortho Clinical Diagnostics, Rochester, NY); HDL cholesterol and LDL cholesterol (when required) were analyzed using a Dimension RXL (Dade, Wilmington, DE). LDL cholesterol concentrations were estimated using the Friedewald equation when triglyceride levels were <300 mg/dl (13). LDL cholesterol was measured directly when triglycerides exceeded 300 mg/dl. HbA_{1c} was analyzed using the DCA2000 latex immunoglutination inhibition system (Bayer, Tarrytown, NY)

Statistical analysis

Univariate analysis of baseline and follow-up demography and clinical laboratory end points, both between and within the PIO and ROSI treatments, were accomplished using Pearson χ^2, unpaired, or paired Student's *t* test where appropriate. Changes in HbA_{1c}, weight, triglyceride, total cholesterol, LDL cholesterol, and HDL cholesterol over time were computed as values at month 4 minus baseline values. General linear models (SAS, Cary, NC) were used to assess the impact and potential interactions of various independent variables on the change in the outcome measures listed above. Independent variables included gender, age, thiazolidinedione (PIO or ROSI), thiazolidinedione dose, days exposed to TROG, and concurrent medication present or absent HMG-CoA reductase inhibitor, insulin, sulfonylurea, and/or metformin). Initial models screened for the significance of independent variables and their interaction in the models. Final models contained only those factors identified as

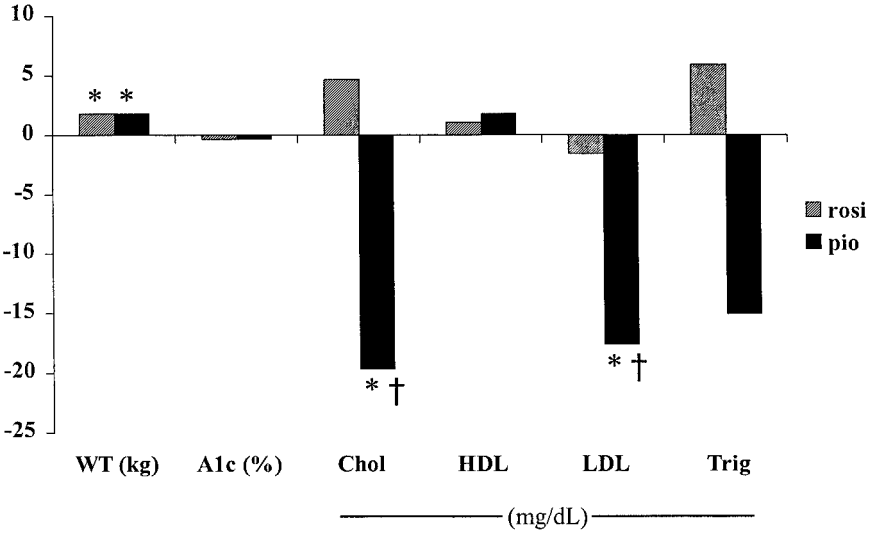

Figure 1—*Average changes from baseline through month 4 of randomized treatment after conversion from TROG to either PIO or ROSI. Units for each factor are listed. Hatched bars represent ROSI; black bars represent PIO.* * P < *0.01, within group comparison, baseline versus value at 4 months;* † P < *0.01; PIO versus ROSI.*

Table 2—*General linear model with change in cholesterol from baseline as the dependent variable*

Factor	*P* value
Gender	0.257
Age (years)	0.630
Thiazolidinedione*	0.004
Thiazolidinedione dose	0.767
Days exposed to TROG	0.788
Concurrent HMG-CoA reductase inhibitor*	0.001
Concurrent insulin	0.076
Concurrent sulfa	0.893
Concurrent metformin	0.686

*No statistical interaction detected between thiazolidinedione and HMG-CoA reductase inhibitor.

significant from the initial models. One-way ANOVA (SPSS, Chicago, IL) using the Dunnett C procedure was used to assess significance of change in cholesterol from baseline in four subgroups: those taking either thiazolidinedione alone (PIO or ROSI) or in combination with an HMG-CoA reductase inhibitor. Statistical significance was considered at $P < 0.05$.

RESULTS — After withdrawal of TROG and after a 2-week washout period, a cohort of 186 TROG-treated patients were randomized to either PIO or ROSI therapy. An equal number of patients from each assigned group subsequently refused to start randomized treatment, stopped thiazolidinedione therapy of their own accord, switched care to a different clinic, or were withdrawn before completing the protocol (14 patients in the PIO group, 16 patients in the ROSI group). Many of these patients ascribed their actions to concern about potential liver toxicity with their new therapy. Other participants (17 patients in the PIO group, 12 patients in the ROSI group) were excluded because of incomplete or unusable data (i.e., did not complete baseline assessment, follow-up assessment, or both and/or nonfasting blood draw). A total of 127 randomized patients (67 in the PIO group, 60 in the ROSI group) completed follow-up and had usable data. After review and based on available data, this group did not seem to be significantly different from those who were excluded from analysis.

The baseline characteristics of this cohort are listed in Table 1. There was no significant difference in gender mix, age, weight, fasting plasma lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), or HbA_{1c} between the ROSI and PIO groups. Additionally, no differences in the proportions of concurrent medications used by the patients in these groups were apparent (Table 1). Maximal PIO dose (45 mg/day) was used in 76.1% (51 of 67 patients) of the PIO cohort; similarly, ROSI (4 mg b.i.d.) was used in 76.7% (46 of 60 patients) of the ROSI cohort. The midrange PIO dose (30 mg/day) was used in 22.4% (15 of 67 patients) of the PIO group, and the midrange ROSI dose (4 mg/day) was used in 16.7% (10 of 60 patients) of the ROSI group. The remaining subjects in each group received the low dose of each drug. The mean ± SD exposure to randomized therapy for the PIO and ROSI groups was 138.8 ± 30.4 and 134.0 ± 30.1 days, respectively ($P > 0.3$).

The mean changes from baseline for weight, HbA_{1c}, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides are shown in Fig. 1. Both groups experienced significant weight gain versus their baseline starting point ($P < 0.01$). No change in glycemic control was apparent at the 4-month assessment point when compared with initial HbA_{1c}. Changes in lipid profile were detected; however, these were only significant for the PIO group versus baseline and when compared with changes noted in the ROSI group.

Equivalent weight gain after conversion from TROG was noted in both the PIO and ROSI groups. However, significant effects of concurrent use of sulfonylurea ($P = 0.027$) and/or metformin ($P = 0.047$) were noted in the final model, using change in weight adjusted for thiazolidinedione, concurrent sulfa, and concurrent metformin. Results from general linear model analysis are shown in Table 2, showing that thiazolidinedione and concurrent HMG-CoA reductase inhibitor had significant effects with respect to change in cholesterol. No significant statistical interaction between thiazolidinedione and HMG-CoA reductase inhibitor was detected. However, somewhat opposite effects on cholesterol were noted between the two groups. Specifically, a much greater effect in both direction and quantity was seen in those treated with PIO alone or with concurrent HMG-CoA reductase inhibitor versus that seen in the respective ROSI groups (Table 3).

CONCLUSIONS — The need to convert patients to either PIO or ROSI because of the withdrawal of TROG from worldwide markets provided a unique opportunity to study potential differential effects of a new class of insulin-sensitizing agents. Other groups have published clinical observations within this same paradigm; however, to date, no studies have randomly assigned patients to either of the alternate therapies (9,10). Our prospective, randomized conversion study demonstrated similar effects of PIO and ROSI with respect to weight gain and glycemic control after conversion from TROG. However, differences in lipid profile were detected. Because a significant number of the study patients were concurrently taking medications that could have had effects on serum lipid levels, further analysis of data were warranted. Using change in cholesterol as the dependent variable, we used statistical models

Table 3—*Change in cholesterol (mg/dl) for each thiazolidinedione group, with or without concurrent HMG-CoA reductase inhibitor*

1. PIO alone	−5.2 ± 3.9*	
2. PIO with HMG-CoA reductase inhibitor	−29.4 ± 8.3†	atorvastatin 31 simvastatin 8 cerivastatin 1
3. ROSI alone	16.8 ± 6.1‡	
4. ROSI with HMG-CoA reductase inhibitor	−4.0 ± 5.8	atorvastatin 30 simvastatin 3 pravastatin 1 lovastatin 1

Data are means ± SEM and *n*. Specific concurrent HMG-CoA reductase inhibitor use and number of subjects is listed. *$P < 0.03$ vs. ROSI alone; †$P < 0.01$ vs. ROSI alone; ‡$P < 0.03$ vs. PIO alone and PIO with HMG-CoA reductase inhibitor.

that adjusted for demographic and comedication factors and demonstrated that two factors studied, use of thiazolidinedione and HMG-CoA reductase inhibitor, had significant effects. Subgroup analysis of HMG-CoA reductase inhibitor use by thiazolidinedione use demonstrated that conversion from TROG to ROSI or PIO resulted in differential lipid profile changes that seem to be influenced by the presence of HMG-CoA reductase inhibitor.

Although our study was not designed to elucidate possible mechanisms underlying these clinical observations, recent studies and clinical case reports implicate one possible mechanism that is consistent with our observations. TROG is known to induce hepatic cytochrome P450 3A (CYP3A), whereas PIO and ROSI seem to lack significant enzyme-induction effects (1,2,14–16). TROG is also known to decrease serum concentrations of many CYP3A substrates, including some of the HMG-CoA reductase inhibitors, atorvastatin and presumably simvastatin (17–21). A short-term, prospective, crossover study in normal volunteers documented significant decreases in atorvastatin serum concentrations with concurrent TROG exposure; however, no change in lipid lowering from atorvastatin was noted (19,20). Conversely, worsening of lipid profile has been noted in dyslipidemic patients when TROG was added to existing atorvastatin or simvastatin therapy (17,18). In these cases, TROG-related CYP3A enzyme induction may have resulted in decreased statin exposure and worsening plasma lipid levels. When considering our study, the opposite situation may have been detected, considering that the preponderance of concurrent statin use in our study participants were CYP3A substrates (Table 3). Loss of enzyme induction with the discontinuation of TROG, in statin-treated patients, may have enhanced the observed reduction in lipids associated with PIO conversion and blunted the increase in lipids seen with conversion to ROSI (see Table 3).

Our project incorporates a randomization step in an attempt to control for potential bias inherent to retrospective or prospective analysis of clinical data. In this context, we report that significant changes in lipid profile were apparent despite similar glycemic control and weight gain when patients were randomly converted from TROG therapy to either PIO or ROSI. These changes were apparent after 4 months of therapy and persisted after adjusting for various demographic and concurrent medication factors. Although the mechanisms and clinical significance of these differences are yet to be defined, future thiazolidinedione studies should consider the potential confounding effects of concurrent medications commonly used in the diabetes patient population.

Acknowledgments— We thank Marcia Madden, ANP; Jodie Duntley, CNS; Kathleen Hall, MD; Mohammad Fareed, MD; and the staff of the Hennepin Center for Diabetes and Endocrinology for their various contributions to this project. We also thank Leigh Hamersten and Clifford Hill for their contribution with respect to the data collection.

Portions of these data were presented in abstract form at the 61st Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 22–26 June 2001.

References

1. *Pioglitazone Hydrochloride Prescribing Information*. Lincolnshire, IL, Takeda Pharmaceuticals America, 2000
2. *Rosiglitazone Maleate Prescribing Information*. Philadelphia, SmithKline Beecham Pharmaceuticals, 2001
3. Einhorn D, Kipnes M, Glazer NB, Wishner W: Durability of glycemic control with pioglitazone in long-term combination and monotherapy (Abstract). *Diabetes* 50:A110, 2001
4. King AB, Armstrong D: Characteristics of patients who gain weight while on pioglitazone (PIO) treatment (Abstract). *Diabetes* 50:A120, 2001
5. Camp HS, Li O, Wise SC, Hong YH, Frankowski CL, Shen X, Vanbogelen R, Leff T: Differential activation of peroxisome proliferator–activated receptor-γ by troglitazone and rosiglitazone. *Diabetes* 49:539–547, 2000
6. Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, Kurokawa R, Rosenfeld MG, Willson TM, Glass CK, Milburn MV: Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma. *Nature* 395:137–143, 1998
7. Sakamoto J, Kimura H, Moriyama S, Odaka H, Momose Y, Sugiyama Y, Sawada H: Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. *Biochem Biophys Res Commun* 278:704–711, 2000
8. Davidson PC, Sabbah HT, Steed RD, Richardson P, Robertson DG, Bode BW: Pioglitazone versus rosiglitazone therapy in randomized follow-up in patients previously treated with troglitazone (Abstract). *Diabetes* 50:A109, 2001
9. Gegick CG, Altheimer MD: Comparison of effects of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice. *Endocr Pract* 7:162–169, 2001
10. King AB: A comparison in a clinical setting of the efficacy and side effects of three thiazolidinediones. *Diabetes Care* 23:557, 2000
11. King AB, Armstrong D: Comparison of the glucose and lipid effects of rosiglitazone (ROS) and pioglitazone (PIO) following conversion from troglitazone (TRO) treatment (Abstract). *Diabetes* 50:A120, 2001
12. *Troglitazone Prescribing Information*. Morris Plains, NJ, Parke-Davis, 1999
13. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
14. Koup JR, Anderson GD, Loi CM: Effect of troglitazone on urinary excretion of 6β-hydroxycortisol. *J Clin Pharmacol* 38:815–818, 1998
15. Loi CM, Stern R, Koup JR, Vassos AB, Knowlton P, Sedman AJ: Effect of troglitazone on the pharmacokinetics of an oral contraceptive agent. *J Clin Pharmacol* 39: 410–417, 1999
16. Loi CM, Young M, Randinitis E, Vassos A, Koup JR: Clinical pharmacokinetics of troglitazone. *Clin Pharmacokinet* 37:91–104, 1999
17. DiTusa L, Luzier AB: Potential interaction between troglitazone and atorvastatin. *J Clin Pharmacol Ther* 25:279–282, 2000
18. Lin JC, Ito MK: A drug interaction between troglitazone and simvastatin. *Diabetes Care* 22:2104–2106, 1999
19. Loi CM, Sedman AJ: Response to Lin and Ito: Effect of troglitazone on atorvastatin pharmacokinetics and pharmacodynamics. *Diabetes Care* 22: 2105–2106, 1999
20. Loi CM, Stern R, Abel R, Koup JR, Vassos AB, Sedman AJ: Effect of troglitazone on PK and PD of atorvastatin (Abstract). *Clin Pharmacol Ther* 65:186, 1999
21. Prueksaritanont T, Vega JM, Zhao J, Gagliano K, Kuznetsova O, Musser B, Amin RD, Liu L, Roadcap BA, Dilzer S, Lasseter KC, Rogers JD: Interactions between simvastatin and troglitazone or pioglitazone in healthy subjects. *J Clin Pharmacol* 41:573–581, 2001