

# Comparison of the Glycemic Effects of Rosiglitazone and Pioglitazone in Triple Oral Therapy in Type 2 Diabetes

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To date, there have been few comparison studies between rosiglitazone and pioglitazone (1,2) and none of the two thiazolidinediones (TZDs) as a third agent in triple oral therapy. In February 2003, pioglitazone replaced rosiglitazone as the TZD on the pharmacy formulary at our hospital. This gave us the opportunity to compare the effectiveness of rosiglitazone and pioglitazone added to type 2 diabetic patients already on maximum (tolerated) doses of metformin and a sulfonylurea agent whose HbA<sub>1c</sub> (A1C) levels did not meet the American Diabetes Association goal of <7.0%.

## RESEARCH DESIGN AND METHODS

Our diabetes clinic treatment algorithm mandates starting small doses of either a sulfonylurea agent or metformin and increasing the dose every 2 weeks until either a fasting plasma glucose (FPG) concentration of <130 mg/dl is attained or a maximal (tolerated in the case of metformin) dose is reached. If the FPG concentration remains >130 mg/dl, the alternate drug is added and also increased every 2 weeks. When the FPG goal is achieved, further therapeutic decisions are based on A1C levels measured 2–3 months later. Only when both agents are maximized and either the FPG concentration 2 weeks after the last increase remains >130 mg/dl or an A1C level is  $\geq 7.0\%$  2–3 months after the FPG goal is reached, or at any time thereafter, is a maximal dose of a TZD added. The maximal dose is used because it can take

up to 4 months to see a maximal response. If lower TZD doses are used initially and titrated upward, the patient can remain out of control for up to a year before insulin is started.

Four months after adding the TZD, we decided whether triple oral therapy had been successful. We chose an A1C level of  $\leq 7.5\%$  to designate success and not start insulin (which necessitates significant lifestyle changes) because there was only a slight increase in the development or progression of retinopathy and/or nephropathy in patients with mean A1C levels between 7 and 8% (3–7). Only when A1C levels exceeded 7.5% (measured 4 months after starting the TZD or subsequently) was bedtime insulin started.

The study design was a retrospective chart review of 104 adult type 2 diabetic patients followed in our diabetes clinic. The criterion for inclusion was taking a TZD for at least 4 months in patients who had failed maximal (tolerated) doses of metformin and a sulfonylurea agent. Comparisons were made in patients at 4 months, and those with successful outcomes (A1C  $\leq 7.5\%$ ) were followed for 8 more months. The responses of 56 consecutively treated patients, in whom 45 mg pioglitazone was added, were compared with 48 patients receiving 8 mg rosiglitazone, as reported previously (8).

**RESULTS**— Fifty-six patients on pioglitazone (24 men and 32 women, aged

$54.1 \pm 7.7$  years [mean  $\pm$  SD], diabetes duration  $8.3 \pm 5.9$  years, and BMI  $33.2 \pm 7.4$  kg/m<sup>2</sup>) were studied. There were 42 Latinos, 11 African Americans, 2 Caucasians, and 1 Asian Pacific Islander. At baseline, 55 patients were taking maximal doses of glyburide (20 mg) or glipizide (40 mg), with 1 patient on a submaximal dose because of daytime hypoglycemia. Fifty-three patients were taking maximal doses of metformin (2 g) (3 had increased serum creatinine concentrations). The initial A1C level was  $9.5 \pm 2.1\%$ , which decreased to  $7.4 \pm 1.1\%$  4 months later. Thirty-five (62%) patients achieved A1C levels <7.5% at 4 months. Of these 35 patients, 22 (63%) were still responding at 1 year. Of those patients controlled at 4 months but not on pioglitazone at 1 year, A1C levels rose to >7.5% in seven patients (21%) and six patients (17%) were lost to follow-up.

We compared the above results to a prior study of rosiglitazone added to maximal (tolerated) doses of metformin and a sulfonylurea agent (8) in 48 patients with similar baseline characteristics (17 men and 31 women, aged  $51 \pm 12.7$  years, diabetes duration  $7.7 \pm 6.1$  years, and BMI  $31.2 \pm 7.4$  kg/m<sup>2</sup>). Their baseline A1C level was  $9.3 \pm 1.5\%$ , which decreased to  $7.5 \pm 1.5\%$  4 months later. Of these 48 patients, 31 (65%) achieved A1C levels <7.5% at 4 months. Of the 31 patients controlled at 4 months, 19 (61%) were still responding at 1 year. Of those patients not on rosiglitazone at 1 year, A1C levels rose to >7.5% in eight patients (26%), edema developed in two patients (6%), and two patients (6%) were lost to follow-up.

Individual responses to both TZDs are shown in Fig. 1.

**CONCLUSIONS**— One head-to-head, randomized, blinded clinical trial that compared maximal doses of rosiglitazone and pioglitazone in drug-naïve type 2 diabetic patients showed similar glycemic control after 24 weeks (2). “Troglitazone switch studies,” in which patients who had been previously treated with troglitazone were switched to either

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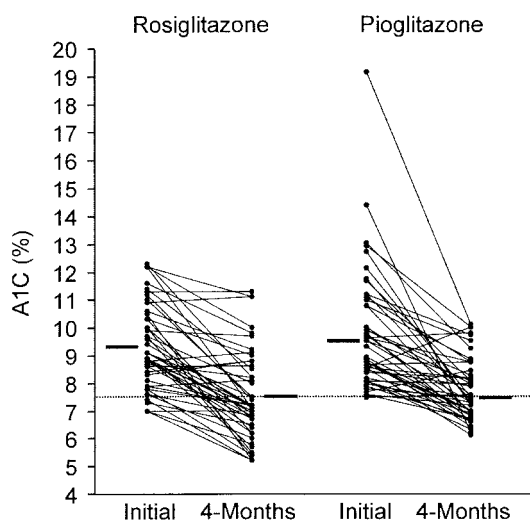
**Abbreviations:** FPG, fasting plasma glucose; TZD, thiazolidinedione.

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

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**Figure 1**—A1C levels before and 4 months after adding either 8 mg rosiglitazone (8) or 45 mg pioglitazone to type 2 diabetic patients taking maximal (tolerated) doses of metformin and a sulfonylurea agent who had failed to achieve an A1C level of  $<7.0\%$ . The mean A1C values at each time are depicted as bars and the 4 month A1C goal for triple oral therapy as a dotted line.

rosiglitazone or pioglitazone (9–13), and retrospective medical record analyses (1,12,14,15) demonstrated that changes in glycemic control were similar with rosiglitazone and pioglitazone.

We have now shown that adding a maximal dose of TZD to patients in whom maximal (tolerated) doses of metformin and a sulfonylurea agent failed to achieve the American Diabetes Association's A1C goal level of  $<7\%$  lowers the value from 9.5 to 7.4% (pioglitazone) vs. 9.3 to 7.5% (rosiglitazone) after 4 months. Using a goal A1C level of  $\leq 7.5\%$  for our triple oral therapy for reasons cited above, 62% of pioglitazone-treated patients and 65% of rosiglitazone-treated patients were successfully treated after 4 months. Of these, 63% of pioglitazone-treated patients and 61% of rosiglitazone-treated patients were still responding at 1 year. Deteriorating control (A1C  $>7.5\%$ ) was the main reason for patients failing triple therapy and starting insulin.

In conclusion, rosiglitazone and pioglitazone are equally effective in triple oral therapy. Approximately two-thirds of patients on maximal (tolerated) doses of metformin and a sulfonylurea agent initially responded to a maximal dose of either rosiglitazone or pioglitazone at 4 months, and  $\sim 60\%$  of those were still at goal at 1 year. Although most patients on triple oral therapy may eventually require insulin, we prefer to keep patients on oral medications to minimize their changes in

lifestyle as long as appropriate control can be maintained. We do not hesitate to start insulin once that is no longer possible.

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## References

- Boyle PJ, King AB, Olansky L, Marchetti A, Lau H, Magar R, Martin J: Effects of pioglitazone and rosiglitazone on blood lipid levels and glycemic control in patients with type 2 diabetes mellitus: a retrospective review of randomly selected medical records. *Clin Ther* 24:378–396, 2002
- Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, Tan MH, Khan MA, Perez AT, Jacober SJ: A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 28:1547–1554, 2005
- The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure ( $HbA_{1c}$ ) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995
- Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized
- prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
- Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 332:1251–1255, 1995
- Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R: Role of glycaemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care* 21:116–120, 1998
- Warram JH, Scott LJ, Hanna LS, Wantman M, Cohen SE, Laffel LMB, Ryan L, Krolewski A: Progression of microalbuminuria to proteinuria in type 1 diabetes: nonlinear relationship with hyperglycemia. *Diabetes* 49:94–100, 2000
- Roy R, Navar M, Palomeno G, Davidson MB: Real world effectiveness of rosiglitazone added to maximal (tolerated) doses of metformin and a sulfonylurea agent (Letter). *Diabetes Care* 27:1741–1742, 2004
- Davidson PC, Sabbah HT, Steed RD, Richardson P, Robertson DG, Bode BW: Pioglitazone versus rosiglitazone therapy in randomized follow-up patients previously treated with troglitazone (Abstract). *Diabetes* 50 (Suppl. 2):A109, 2001
- Khan M, St. Peter J, Xue J: A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care* 25:708–711, 2002
- Gegick C, Altheimer M: Comparison of effects of thiazolidinediones on cardiovascular risk factors: observations from a clinical practice. *Endocr Pract* 7:162–169, 2001
- Yates SW: Comparative effects of available thiazolidinediones: a review of the literature. *Pharm Ther* 29:584–588, 2004
- Rosenblatt SI, Yoder CL, Albert JE: Actos vs. Avandia: comparison of conversion from Rezulin on significant clinical parameters (Abstract). *Diabetes* 51 (Suppl. 2):A143, 2002
- King A: A comparison in a clinical setting of the efficacy and side effects of three thiazolidinediones (Letter). *Diabetes* 23: 557, 2000
- Peters Harmel A, Kendall D, Buse J, Boyle P, Marchetti A, Lau H: Impact of adjunctive thiazolidinedione therapy on blood lipid levels and glycemic control in patients with type 2 diabetes. *Curr Med Res Opin* 20:215–223, 2004