Real World Effectiveness of Rosiglitazone Added to Maximal (Tolerated) Doses of Metformin and a Sulfonylurea Agent

A systematic evaluation of triple oral therapy in a minority population

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Patients with newly diagnosed type 2 diabetes who have no or only mild symptoms should be started on a regimen of diet and exercise. Unfortunately, as many as 95% of patients do not achieve adequate control after 3 months of nonpharmacologic therapy (1). When medical therapy is initiated, patients are often started on either a low dose of a sulfonylurea agent or metformin. If control is not attained with the maximal dose of one, the second is usually added until adequate control is achieved or a maximal dose is reached. Since glitazones are so expensive, we use them only after maximal (tolerated) doses of metformin and sulfonylurea agents are reached and control remains unsatisfactory. Only a few studies (2–6) have examined the effectiveness of adding a glitazone as the third oral agent. These have used mean A1C levels as the outcome, which does not provide information on the proportion of patients who can be expected to respond.

RESEARCH DESIGN AND METHODS — Our algorithm-based approach mandates starting small doses of either a sulfonylurea agent (lean patients) or metformin (obese patients) and titrating the dose upward in a stepwise fashion 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 likewise titrated upward 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 later remains ≥130 mg/dl or an A1C level is ≥7.0% 2–3 months after the FPG goal is reached or at any time thereafter is a maximal dose of a glitazone added. The maximal dose is used because it can take up to 4 months to see a maximal response. If lower glitazone doses are used initially and titrated upward, the patient can remain out of control for up to a year before insulin is started. Two months later, 4 months after adding the glitazone, we decide whether triple oral therapy has been successful.

Because the next step is insulin, which necessitates significant lifestyle changes, and because in five studies (7–12) in >2,000 type 1 and type 2 diabetic patients lasting for 6–10 years there was only a slight increase in the development or progression of retinopathy and/or nephropathy in those with mean A1C levels between 7 and 8%, we chose an A1C level of ≤7.5% to designate success and not start insulin. A1C levels were measured every 2 months. Only when A1C levels exceeded 7.5%, measured 4 months after starting the glitazone or at subsequent bimonthly intervals, was bedtime insulin started and glitazone discontinued.

These algorithms allow a systematic evaluation of the effect of adding a glitazone as the third agent. The responses of 48 consecutively treated type 2 diabetic patients failing maximal (tolerated) doses of both metformin and a sulfonylurea agent, in whom 8 mg rosiglitazone was added, are the basis of this report. Comparisons of A1C levels at baseline and 4 months after adding rosiglitazone were analyzed by Student's paired *t* test, with significance accepted at the 0.05 level (two tailed).

RESULTS — Forty-eight patients (17 men and 31 women, age 51.0 ± 12.7 years [mean ± SD], diabetes duration 7.7 ± 6.1 years) were studied. Of the patients, 40 were Latino, 7 were African American, and 1 was East Indian. At baseline, 23 patients were taking maximal doses of glyburide and 25 maximal doses of glipizide. Thirty-eight patients were taking maximal doses of metformin, 1 patient a half-maximal dose because of side effects, and 9 did not receive it (8 because of side effects and 1 because of an increased serum creatinine concentration). The initial A1C level was 9.3 ± 1.5% (mean ± SD), falling to 7.5 ± 1.5% 4 months later ($P < 0.001$ by paired *t* test). The decrease in A1C levels did not correlate with the duration of diabetes ($r = 0.14$, $P = 0.33$). Thirty-one (65%) patients achieved A1C levels <7.5% at 4 months (Fig. 1). Of these patients, 19 (61%) were still on 8 mg rosiglitazone at 1 year, whereas 12 were not taking it. In the latter group, the A1C rose to >7.5% in eight, edema developed in two (and the glitazone was discontinued), and two patients were lost to follow-up.

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Abbreviations: FPG, fasting plasma glucose.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

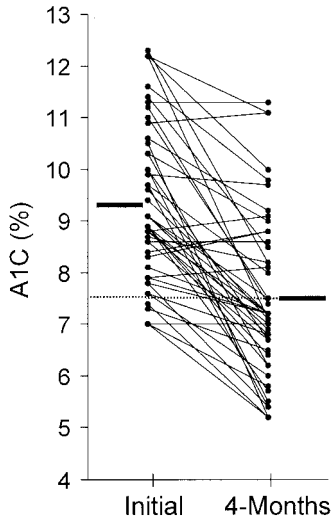

Figure 1—*A1C levels before and 4 months after adding 8 mg rosiglitazone to 48 type 2 diabetic patients failing maximal (tolerated) doses of metformin and a sulfonylurea agent, i.e., those with A1C levels ≥7.0% before adding the glitazone. The mean A1C values at each time are depicted as bars and the 4-month A1C goal as a dotted line.*

CONCLUSIONS — We have shown that the addition of a maximal dose of rosiglitazone (8 mg) to 48 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 9.3 to 7.5% after 4 months. Other published studies (2–6) have mostly used mean A1C levels as the outcome with no stated predetermined target level so that the proportion of patients successfully treated could not be determined. Using a goal A1C level of ≤7.5% for our triple oral therapy for reasons cited above, 65% of our patients were successfully treated 4 months later. Of these, ~60% were still taking it at 1 year. Deteriorating control (A1C level of >7.5%) was the main reason for failing triple therapy and starting insulin. There was no correlation between duration of disease and the change in A1C levels after the glitazone was added. This might have been considered unexpected because β-cell function progressively decreases in type 2 diabetes (13) and the response to oral antidiabetes medications depends on adequate insulin secretion. However, there is a long period of asymptomatic hyperglycemia preceding the diagnosis of diabetes (14), making any estimate of actual duration of disease very inaccurate.

In conclusion, two-thirds of patients on maximal (tolerated) doses of metformin and a sulfonylurea agent initially responded to a maximal dose of rosiglitazone, and 60% were still at goal at 1 year. To maintain near euglycemia, insulin therapy was necessary in a large proportion of patients in our minority population.

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References

1. The UK Prospective Diabetes Study Group: U.K. Prospective Diabetes Study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ* 310:83–88, 1995
2. Yale JF, Valiquett TR, Ghazzi MN, Owens-Grillo JK, Whitcomb RW, Foyt HL: The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin: a multicenter, randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 134: 737–745, 2001
3. Ovalle F, Bell DSH: Triple oral antidiabetic therapy in type 2 diabetes. *Endocr Pract* 4:146–147, 1998
4. Bell DSH, Ovalle F: Long-term efficacy of triple oral therapy for type 2 diabetes mellitus. *Endocr Pract* 8:271–275, 2002
5. Kiayias JA, Vlachou ED, Theodosopoulou E, Lakka-Papadodikima E: Rosiglitazone in combination with glimepiride plus metformin in type 2 diabetic patients. *Diabetes Care* 25:1251–1252, 2002
6. Byrne J, Garg S, Vaidya A, Rajbhandari SM, Wallis SC: Efficacy of triple combination oral therapy using rosiglitazone, metformin, and sulphonylurea in lowering HbA1c. *Pract Diab Int* 20:58–60, 2003
7. DCCT Research Group: The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
8. 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
9. 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 randmized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
10. 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
11. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R: Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care* 21:116–120, 1998
12. 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 relatioinship with hyperglycemia. *Diabetes* 49:94–100, 2000
13. UK Prospective Diabetes Study Group: Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995
14. Harris MI, Klein R, Welborn TA, Knuiman MW: Onset of NIDDM occurs at least 4–7 years before clinical diagnosis. *Diabetes Care* 15:815–819, 1992