Initial Oral Therapy for Patients With Type 2 Diabetes

Reviewed by Michael Pignone, MD, MPH

STUDY

Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group: Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 355:2427–2443, 2006

SUMMARY

Design. Double-blind, randomized, controlled trial comparing initial therapy with rosiglitazone, metformin, or glyburide for patients with type 2 diabetes.

Subjects. A total of 4,360 patients aged 30–75 years with fasting plasma glucose levels from 126 to 180 mg/dl when treated with lifestyle change recommendations alone. Patients with clinically significant liver disease, renal impairment, unstable or severe angina, congestive heart failure, or uncontrolled hypertension were excluded.

Methods. Patients were recruited from 488 centers in North America and Europe between April 2000 and June 2002. Participants received one of three initial regimens: 4 mg of rosiglitazone daily, 500 mg of metformin daily, or 2.5 mg of glyburide daily. Medication dosages were titrated upward at each visit if fasting plasma glucose was > 140 mg/dl. Titrations were based on study protocols with a maximum of 4 mg twice daily for rosiglitazone, 1,000 mg twice daily for metformin, or 7.5 mg twice daily for glyburide. The main outcome of interest was time to "treatment failure," defined as fasting plasma glucose > 180 mg/dl on consecutive study visits after at least 6 weeks on the maximum dose of the agent. Outcomes were adjudicated independently. An independent cardiologist who was unaware of treatment assignment reviewed all potential adverse cardiovascular events; potential cases of heart failure were reviewed by a second independent cardiologist who also was unaware of treatment status.

Results. Median duration of treatment was 4.0 years for rosiglitazone or metformin and 3.3 years for glyburide. The proportion of patients completing the study or reaching a primary end point was 63% for rosiglitazone, 62% for metformin, and 56% for glyburide. Occurrence of adverse events was the most common reason for discontinuation: 12% for rosiglitazone, 12% for metformin, and 15% for glyburide. The incidence of treatment failure at 5 years was 15% for rosiglitazone, 21% for metformin, and 34% for glyburide, a reduction of 32% (95% CI 15–45%) for rosiglitazone compared with metformin and 63% (55–70%) for rosiglitazone compared with glyburide. Failure was also less frequent for metformin compared with glyburide (reduction of 46%, [36–55%]). Hemoglobin A_{1c} (A1C) levels were < 7% for 40% of patients assigned initially to rosiglitazone, 36% for patients assigned to metformin, and 26% for patients assigned to glyburide. The most important adverse events were edema for users of rosiglitazone (14.1 vs. 7.2% with metformin and 8.5% with glyburide); gastrointestinal events with metformin (38.3 vs. 23.0% for rosiglitazone and 21.9% for glyburide) and self-reported hypoglycemia (38.7% with glyburide vs. 9.8% with rosiglitazone and 11.6% with metformin). Weight gain occurred with glyburide (+1.6 kg) and rosiglitazone (+4.8 kg), but not metformin (–2.9 kg). Heart failure was more common with rosiglitazone (1.5%) or metformin (1.3%) than with glyburide (0.6%). Death rates did not differ among groups.

Conclusions. Rosiglitazone was associated with lower rates of primary treatment failure but produced only modest improvements in glycemic control compared with metformin or glyburide as initial treatment for diabetes.

COMMENTARY

ADOPT (A Diabetes Outcome Progression Trial) provides important information for providers and patients initiating pharmacological treatment to improve glycemic control in patients with diabetes and moderately elevated fasting plasma glucose levels. Rosiglitazone was found to lead to fewer treatment failures (defined as consecutive fasting plasma glucose measures > 180 mg/dl) but did not produce major differences in glycemic control as measured by the proportion of patients with A1C < 7.0%. Adverse effects differed among the initial treatments, with more weight gain and fluid retention for rosiglitazone, more gastrointestinal side effects for metformin, and more self-reported hypoglycemia with glyburide. Serious adverse events were similar between groups.

Recently published consensus recommendations have suggested that metformin be used as the initial pharmacological treatment for hyperglycemia, along with lifestyle interventions, based on its efficacy, lack of weight gain or hypoglycemia, and relatively low cost.[1] The findings of the ADOPT study do not appear to warrant modification of this recommendation. Rosiglitazone was associated with slightly better glycemic control as a single agent, but its adverse effects (weight gain, edema) and higher cost make it somewhat less desirable as an initial agent.

If glycemic goals are not reached with metformin and lifestyle interventions, our practice has been to add glipizide, a sulfonylurea with a lower risk of hypoglycemia and low cost. If this two-drug combination therapy is ineffective, we then engage in a shared decision with the patient about whether to add a thiazolidinedione or basal insulin. If we add basal insulin, we usually withdraw the sulfonylurea. We have found this regimen to be effective when implemented within an organized program of diabetes care.[2]

REFERENCES

[1]Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B: Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 29:1963–1972, 2006

[2]Rothman RL, Malone R, Bryant B, Shintani AK, Crigler B, Dewalt DA, Dittus RS, Weinberger M, Pignone MP: A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. *Am J Med* 118:276–284, 2005

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