Clinical Update

A new option in oral hypoglycemic therapy for type 2 diabetes mellitus

Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 2000;283:1695-702.

Background

Many patients with type 2 diabetes mellitus require treatment with more than one oral hypoglycemic agent to achieve optimal glycemic control.[1] Traditionally, physicians have combined metformin, which enhances glucose uptake in peripheral tissues and reduces hepatic gluconeogenesis, with a sulfonylurea drug, which stimulates insulin secretion. Because insulin resistance frequently contributes to hyperglycemia in patients with type 2 diabetes, the combination of metformin and a drug that reduces insulin resistance presents a rational alternative to conventional dual oral hypoglycemic therapy. Rosiglitazone, a newly available member of the thiazolidinedione family of oral hypoglycemic agents, is an example of this type of drug.[2]

Question

Is combination therapy with rosiglitazone and metformin as effective as or more effective than metformin therapy alone in achieving glycemic control in patients with type 2 diabetes?

Design

In this double-blind clinical trial,[3] 348 patients in 36 US outpatient sites were randomly assigned to 1 of 3 treatment groups: metformin plus placebo (n = 116), metformin plus rosiglitazone 4 mg/d (n = 119) or metformin plus rosiglitazone 8 mg/d (n = 113). In all patients the dosage of metformin was titrated to the desired maximum of 2.5 g/d during a prerandomization run-in phase. Efficacy was assessed after 26 weeks of treatment by comparing changes from baseline in the levels of fasting plasma glucose and glycosylated hemoglobin ($HgbA_{1C}$) and in indirect measures of insulin sensitivity and pancreatic β-cell function. Safety was assessed by monitoring adverse events, lipid profile and liver enzyme levels.

Results

The subjects were between 40 and 80 years of age and had had diabetes for 7.7 years on average. They were free of clinically significant hepatic or renal disease, symptomatic coronary artery disease and peripheral neuropathy. Baseline characteristics of the 3 treatment groups were comparable, with mean values for fasting plasma glucose, $HgbA_{1C}$ and body mass index of 12 mmol/L, 8.8% and 30.1 respectively.

After 26 weeks the $HgbA_{1C}$ concentration was significantly lower in each of the metformin–rosiglitazone treatment groups than in the metformin–placebo control group, by 1.0% in the group receiving 4 mg/d of rosiglitazone and 1.2% in the group receiving 8 mg/d ($p < 0.001$). The mean fasting plasma glucose levels were also significantly lower in the rosiglitazone groups than in the control group, by 2.2 mmol/L in the group given 4 mg/d of rosiglitazone and 2.9 mmol/L in the group given 8 mg/d ($p < 0.001$). Measures of insulin resistance and beta-cell function showed improvement in the rosiglitazone groups but not in the control group.

Rates of adverse events, including symptomatic hypoglycemia, were comparable in the 3 groups. No elevation of serum transaminase levels beyond 3 times the upper limit of normal was observed. Compared with the control subjects, those in the 2 rosiglitazone groups demonstrated modest but statistically significant increases in serum cholesterol levels (mean change from baseline low-density lipoprotein cholesterol of 0.46 mmol/L among subjects receiving 4 mg/d and 0.53 mmol/L among those receiving 8 mg/d, $p < 0.001$).

Commentary

This study demonstrates that, in patients with type 2 diabetes, combination therapy with metformin and rosiglitazone achieves significantly better glycemic control than metformin alone. The trial was not designed to assess whether rosiglitazone is superior to insulin or a sulfonylurea drug when combined with metformin. As well, because of the relatively short period of observation, the long-term impact of combination therapy on the progression of diabetes and on the incidence of end-organ complications is unknown.

Practice implications

The addition of rosiglitazone to maximum-dose metformin is safe and effective in improving glycemic control in patients with type 2 diabetes. Increasing the dosage of rosiglitazone from 4 to 8 mg/d appears to offer only modest additional benefit. Patients treated with this combination therapy demonstrate an increase in serum cholesterol and should undergo close lipid-profile monitoring. — *Donald Farquhar*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

References

1. Turner RC, Cull C, Frighi V, Holman R, for the UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. *JAMA* 1999;281:2005-12.
2. Saltiel A, Olefsky J. Thiazolidinediones in the treatment of insulin resistance and type 2 diabetes. *Diabetes* 1996;45:1661-9.
3. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 2000;283:1695-702.