

Metformin plus rosiglitazone had more effective glycemic control than metformin alone in 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 Apr 5;283:1695-702.

QUESTION

What is the effectiveness and safety of combination therapy with metformin and rosiglitazone in patients with type 2 diabetes mellitus that is poorly controlled by metformin alone?

DESIGN

Randomized {allocation concealed*}†, double-blind,* placebo-controlled trial with 26-week follow-up.

SETTING

36 outpatient centers in the United States.

PATIENTS

348 patients between 40 and 80 years of age (mean age 58 y) with type 2 diabetes who had a fasting plasma glucose (FPG) level between 7.8 and 16.7 mmol/L, a fasting C-peptide level ≥ 0.27 nmol/L, a body mass index between 22 and 38 kg/m², and a weight change of $\leq 10\%$ between screening and baseline and who were receiving therapy with metformin, 2.5 g/d. Exclusion criteria were renal or hepatic disease, angina, cardiac insufficiency, symptomatic diabetic neuropathy, an abnormal electrocardiogram, abnormal laboratory test results, long-term insulin

therapy, participation in any rosiglitazone-related study, or use of any investigational drug within 30 days of the study. Follow-up was 83%.

INTERVENTION

Patients were allocated to receive metformin, 2.5 g/d, plus 1 of the following 3 regimens: rosiglitazone, 4 mg/d ($n = 119$) or 8 mg/d ($n = 113$), or placebo ($n = 116$) once daily for 26 weeks.

MAIN OUTCOME MEASURES

Hemoglobin (Hb) A_{1c} level, FPG level, and adverse events.

MAIN RESULTS

Analysis was by intention to treat. At 26 weeks, mean HbA_{1c} levels decreased from baseline in both rosiglitazone groups: reductions were 0.56% and 0.78% in the 4 mg/d and 8 mg/d rosiglitazone groups, respectively ($P < 0.001$). In contrast, mean HbA_{1c} levels increased from baseline by 0.45% ($P < 0.001$) in the metformin-plus-placebo group. Mean HbA_{1c} levels were lower in patients who received metformin plus rosiglitazone, 4 mg/d or 8 mg/d, by 1.0% and 1.2%, respectively ($P < 0.001$), than in those who received metformin plus placebo.

No changes from baseline in mean FPG levels were seen in the metformin-plus-placebo group. Mean FPG levels were lower in patients who received metformin plus rosiglitazone, 4 mg/d or 8 mg/d, by 2.2 mmol/L and 2.9 mmol/L, respectively ($P < 0.001$), than in those who received metformin plus placebo. The only change in reported adverse events was a slight increase in edema. However, total cholesterol levels and body mass index were higher in the rosiglitazone groups than in the placebo group ($P < 0.001$).

CONCLUSION

Once-daily metformin plus rosiglitazone improved glycemic control more effectively than did treatment with metformin alone in patients with poorly controlled type 2 diabetes mellitus.

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*See Glossary.

†Information provided by author.

COMMENTARY

This study by Fonseca and colleagues had a weakness in design leading to potential bias: Before entry, approximately half of the patients were on unspecified combination therapy. All were then transferred to metformin monotherapy; those who were randomized to rosiglitazone were restored to a combination therapy, whereas approximately 23% of those who were randomized to placebo remained on reduced treatment. Conversely, 40% of patients on rosiglitazone switched from monotherapy to combination therapy. Therefore, the observed differences in glycemic control may have been exaggerated.

The major efficacy outcome was HbA_{1c} level, which is a widely accepted surrogate end point for glycemia, particularly because of the U.K. Prospective Diabetes Study (1), which suggests that using this as an end point leads to better outcomes. However, controversy exists about this conclusion (2), and surrogate end points need to be regarded with caution, as the experience with doxazosin on blood pressure lowering in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) has shown (3) (see page 86 of this issue).

What about the safety of rosiglitazone? Liver function did not change, but this study cannot completely exclude toxicity effects. Anemia and weight gain occurred, and some of these cases required

further investigation. A deterioration in plasma lipid levels also occurred in the patients who were treated with rosiglitazone. Levels remained within guideline targets overall, but the effect on large numbers of patients treated for prolonged periods is still uncertain. The effect of glycemic improvement on cardiovascular mortality is modest (1); any benefit might thus be negated in the long term.

What should the clinician conclude? The combination of rosiglitazone with metformin has a sound theoretical, and now a tentative clinical, basis in patients who are both obese and diabetic. The alternative is either a sulfonylurea or insulin regimen, both of which can cause hypoglycemia and weight gain while possibly not improving outcomes (2). However, careful monitoring for possible toxicity and long-term studies with cardiovascular end points are essential.

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References

1. UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-53.
2. McCormack J, Greenhalgh T. *BMJ*. 2000;320:1720-3.
3. Lasagna L. *JAMA*. 2000;283:2013-4.