The Conundrum of Rosiglitazone

Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–71.

Study Overview

Objective. To assess the effect of rosiglitazone on cardiovascular morbidity and mortality.

Design. Meta-analysis of randomized controlled trials.

Methods. 3 sources were searched for trials involving rosiglitazone: the published literature, the U.S. Food and Drug Administration (FDA) Web site, and a clinical trials registry maintained by the manufacturer (GlaxoSmithKline). Of 116 trials evaluated, 42 (26 unpublished) met the inclusion criteria. Studies were selected if they had a duration > 24 weeks, used a randomized control group not receiving rosiglitazone, and reported data for myocardial infarction (MI) and mortality from cardiovascular causes. A total of 15,560 patients were randomly assigned to regimens that included rosiglitazone, and 12,283 were assigned to regimens that did not include rosiglitazone. Only summary data were available for abstraction.

Main outcome measures. Primary endpoints were the tabulated occurrences of MI and deaths from cardiovascular causes.

Main results. The 2 study groups (rosiglitazone, control) had similar demographics; both were mostly white, included more male patients, had a mean age < 57 years, and had a mean baseline glycated hemoglobin level of 8.2%. The rosiglitazone group had 86 MIs (vs. 72 in the control group) and 39 deaths from cardiovascular causes (vs. 22 in the control group). Compared with the control group, the rosiglitazone group had an odds ratio for MI of 1.43 (95% confidence interval [CI], 1.03–1.98; $P = 0.03$) and an odds ratio for death from cardiovascular causes of 1.64 (95% CI, 0.98–2.74; $P = 0.06$).

Conclusion. In this meta-analysis, rosiglitazone was associated with a significantly higher risk of MI and a borderline trend towards higher odds of death from cardiovascular causes.

Commentary

Poor glucose control in diabetic patients is associated with increased cardiovascular morbidity and mortality [1,2]. Thiazolidinediones are oral hypoglycemic drugs used by millions of diabetic patients worldwide to improve glucose control by lowering insulin resistance. Initial trials for rosiglitazone, 1 of 2 thiazolidinediones available in the United States, focused on glycemic control as a surrogate endpoint and did not evaluate cardiovascular outcomes. To date, no trial has specifically evaluated the effect of rosiglitazone on cardiovascular morbidity and mortality. Nissen and Wolski undertook this meta-analysis of existing published and unpublished trials to assess the cardiovascular effects of rosiglitazone use.

The authors found a concerning 43% increase in the risk of MI in diabetic patients in the rosiglitazone group and a strong, although borderline significant, trend toward increased deaths from cardiovascular causes. When considering these outcomes, it is important to be aware of the limitations of this meta-analysis. More than half of the selected studies were not peer reviewed and were listed as unpublished in the manufacturer's clinical trial registry. Further, only 1 study adjudicated MI and death from cardiovascular-related causes, and no patient-level data were available to determine if a patient experienced both events. Given the low number of outcome events, even a small number of misclassified events could dramatically alter the study conclusions.

Importantly, this meta-analysis highlights the problems with using surrogate endpoints in clinical drug trials. The other thiazolidinedione available in the United States, pioglitazone, has had a favorable outcome in a trial designed to prospectively evaluate cardiovascular endpoints [3], suggesting that the increase in cardiac morbidity and mortality seen with rosiglitazone may not generalize across the drug class. A clearer picture of the cardiovascular risk associated with rosiglitazone should emerge from a long-term trial that is currently in progress and specifically addresses cardiovascular outcomes [4].

Applications for Clinical Practice

Clinicians need to discuss with their patients the potential cardiovascular risks involved with rosiglitazone. While it may be prudent to avoid starting patients on rosiglitazone

until more robust trials addressing cardiovascular outcomes are completed, current evidence does not indicate that the thiazolidinedione class as a whole should be avoided.

—Review by Mark S. Horng, MD, MPH

References

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