

EDITORIAL



Rosiglitazone and Cardiovascular Risk

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In this issue of the *Journal*, Nissen and Wolski¹ report the results of a meta-analysis of treatment trials of rosiglitazone, as compared either with other therapies for type 2 diabetes or with placebo. Eligible studies included randomized trials that lasted for at least 24 weeks. The prespecified primary end points of interest were myocardial infarction and death from cardiovascular causes. The authors identified 42 eligible studies, many of which were small or short-term trials, that included a total of 158 myocardial infarctions and 61 deaths from cardiovascular causes. They used the Peto method to combine data from the trials. In this meta-analysis, rosiglitazone was associated with a significant increase in the risk of myocardial infarction (odds ratio, 1.43; 95% confidence interval [CI], 1.03 to 1.98; $P=0.03$) and a borderline-significant finding for death from cardiovascular causes (odds ratio, 1.64; 95% CI, 0.98 to 2.74; $P=0.06$).

The meta-analysis has a number of strengths. Among these were the effort to include unpublished studies, the prespecified analysis plan, the use of major cardiovascular events as the primary outcome, and an analysis in which rosiglitazone was compared with placebo. In the latter analysis, the odds ratio for myocardial infarction was 1.80 (95% CI, 0.95 to 3.39; $P=0.07$), and the odds ratio for death from cardiovascular causes was 1.22 (0.64 to 2.34; $P=0.55$).

The study also has a number of weaknesses. Only summary trial-level data (rather than patient-level data) were available, so it was not possible to conduct time-to-event analyses or to evaluate the time course of risks. Data were not adequate to conduct dose-response analyses. The eligible trials included both placebo and active-treatment

control groups. Across the trials, there was no standard method for identifying or validating outcomes; events in eligible or ineligible trials may have been missed or misclassified. The total number of events was relatively small, with the result that there was little or no power to detect potential differences among the trials if they were present. Although, in general, these limitations are likely to move estimated odds ratios toward the null, the weaknesses, which are largely related to the quality of the available data, are nonetheless substantial. A few events either way might have changed the findings for myocardial infarction or for death from cardiovascular causes. In this setting, the possibility that the findings were due to chance cannot be excluded. In their discussion, the authors properly emphasize the fragility of their findings.

Rosiglitazone, a thiazolidinedione, is an agonist of peroxisome-proliferator-activated receptors (PPARs), primarily γ receptors, in the cell nucleus.² These ligand-activated nuclear transcription factors activate the transcription of genes that affect glucose and lipid metabolism.³ Rosiglitazone increases hepatic and peripheral insulin sensitivity⁴ and reverses insulin resistance, a prominent feature of type 2 diabetes.² Approved in 1999 for the treatment of hyperglycemia in type 2 diabetes, rosiglitazone has been shown in small, short-term trials to reduce levels of fasting glucose and glycated hemoglobin.² At usual doses, the thiazolidinediones decrease glycated hemoglobin levels by an average of about 1 percentage point or less, but they are also associated with increases in body weight, adverse effects on lipids, fluid retention, and anemia.² The product label for rosiglitazone, which summarizes the

results of randomized trials lasting 26 weeks, lists many of these adverse effects in the section on warnings.

The thiazolidinediones represent an interesting and potentially important class of drugs. The current epidemic of obesity in the United States has spawned an epidemic of type 2 diabetes, with 1.5 million new cases per year.⁵ The complications of diabetes, both microvascular and macrovascular disease, are directly related to levels of fasting glucose and glycated hemoglobin. Even in older adults, elevated levels of fasting glucose are directly and strongly associated with major cardiovascular events, and the attributable risk of an elevated glucose level is second only to elevated systolic blood pressure in this population.⁶ In patients with type 1 diabetes, intensive insulin treatment is associated with a reduced risk of cardiovascular events.⁷ A treatment that simultaneously reduces insulin resistance, improves glycemic control, and decreases the risk of cardiovascular events would be a major therapeutic advance for type 2 diabetes.

On the basis of this meta-analysis, however, the possibility of cardiovascular benefit associated with the use of rosiglitazone seems remote. We are not aware of data showing that rosiglitazone prevents microvascular disease. In view of the potential cardiovascular risks and in the absence of evidence of other health advantages, except for laboratory measures of glycemic control, the rationale for prescribing rosiglitazone at this time is unclear. Unless new data provide a different picture of the risk-benefit profile, regulatory action by the Food and Drug Administration (FDA) is now warranted. If patients using rosiglitazone are concerned about the findings of this meta-analysis, they should discuss them with their physicians and not unilaterally stop taking the medication. Ongoing trials using rosiglitazone may provide important new data, but for a drug approved in 1999, the delay in obtaining information about health outcomes has already been considerable.

During the market life of rosiglitazone, tens of millions of prescriptions for the drug have been written for patients with type 2 diabetes. Insofar as the findings of Nissen and Wolski represent a valid estimate of the risk of cardiovascular events, rosiglitazone represents a major failure of the drug-use and drug-approval processes in the United States.

Physicians who chose to prescribe rosiglitazone perhaps focused on the single dimension of glycemic control. The underlying assumption represents a kind of linear “physiological” argument: high levels of glycated hemoglobin increase risk, so a reduction in glycated hemoglobin will automatically translate into improved health outcomes for patients. This perspective ignores the many actions of the genes activated by PPAR- γ agonists, only some of which are currently known. Many physicians did not require proof of health benefits as a criterion for selecting rosiglitazone as a therapy for type 2 diabetes.

Had practicing physicians required this higher standard, they would have been at a loss for evidence from large, long-term trials. Rosiglitazone was approved on the basis of short-term studies of the surrogate end point of glycemic control. The use of surrogate end points in the drug-approval process has been problematic.⁸ Muraglitazar, another PPAR agonist,⁹ and torcetrapib, a cholesteryl ester transfer protein inhibitor that raises levels of high-density lipoprotein cholesterol,¹⁰ are two recent examples. Indeed, at the time of approval of rosiglitazone, the evidence from 26-week studies of expected health benefits was at best mixed. For a lifelong condition such as diabetes, how do the risks of weight gain, edema, and adverse changes in lipids play out against the benefits of improved glycemic control? For a drug that activates a large set of genes, what is the overall balance of risks and benefits? Rofecoxib, whose biologic actions early on suggested the possibility of both gastrointestinal benefit and cardiovascular harm,¹¹ represented a similar regulatory failure to insist on large trials of public health importance in a timely fashion.¹²

The current approach to drug approval involves an intensive, high-quality evaluation in the preapproval setting. For many sponsors, approval marks the transition from research to marketing.¹³ The FDA’s Adverse Event Reporting System is not capable of discerning the risk of events as common as coronary disease. The FDA frequently requires phase 4 trials to address some of the unanswered efficacy or safety questions at the time of approval. But sponsors propose the designs, which sometimes compare their products with inferior treatments or doses.¹⁴ During the period from 1998 through 2003, only about a quarter of the required phase 4 trials were completed,¹⁵ and as of September 30, 2006, a total

of 899 phase 4 studies remain pending.¹⁶ This desultory approach to postmarketing studies necessarily leads to an incomplete evaluation in the postapproval setting. If the FDA approves a drug on the basis of surrogate end points for the long-term treatment of conditions such as diabetes, large, long-term, randomized clinical trials, completed as soon as possible after approval, are essential to identify the health benefits and risks associated with treatment. In the long run, this approach is likely to be in the interests of sponsors, the FDA, and the health of the public.

On May 10, 2007, the Senate passed the Food and Drug Administration Revitalization Act.¹⁷ Although the Senate bill has many strengths, including the allocation of new authority to the FDA, none of its provisions would necessarily have identified the cardiovascular risks of rofecoxib or rosiglitazone in a timely fashion. One section of the bill (title II, subtitle A) focuses largely on the mitigation of known risks at the time of approval. In contrast, a true life-cycle approach, as advocated by the Institute of Medicine,¹⁸ would continue the evaluation of both efficacy and safety after approval, convert surrogate end points into clinically meaningful outcomes,¹⁹ integrate new information about health benefits and risks, and communicate those findings effectively to patients and physicians. The health of the public would benefit from additional revisions to the drug-safety legislation as it moves through the House of Representatives.

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