IDIS Independent Drug Information Service

PEARL:
Prompt Evidence Assessment and Review of the Literature

Now what for patients taking rosiglitazone (Avandia)?

The clinical issue: In 2008, the U.S. Food and Drug Administration (FDA) assigned a black box warning to rosiglitazone (Avandia) because of evidence that this oral hypoglycemic agent can increase the risk of myocardial infarction and heart failure.[1,2] After further review of safety data, **the FDA announced that physicians should restrict the use of rosiglitazone (and its combination products) to patients with Type 2 diabetes whose blood sugar cannot be controlled with other agents**.

The evidence: The current concerns about the safety of rosiglitazone began in 2007 with 2 meta-analyses randomized studies that found patients treated with rosiglitazone had a 43% increase in the risk of heart attack, and twice the risk of heart failure compared to those given other drugs, including placebo.[1,2] These results were confirmed in an updated analysis in 2010.[3] In contrast, the RECORD trial did not report an increased cardiovascular risk associated with rosiglitazone.[4] However, few patients in that trial had cardiovascular events and the study and its analysis had important methodological limitations. As a result, the FDA has required that the trial data be re-analyzed. Several observational studies have also found an increased risk of cardiovascular events from rosiglitazone compared with pioglitazone.[5] In July 2010, a FDA Advisory Committee overwhelmingly voted to restrict use of the drug.

What does the FDA recommend?: Because of ongoing safety concerns, the FDA has required the manufacturer of rosiglitazone to undertake a "Risk Evaluation and Mitigation Strategy" in which **rosiglitazone use is restricted to patients already taking it, or those who cannot achieve glycemic control with other medications and choose not to take pioglitazone (Actos).** Prescribers are required to discuss these risks with their patients and to and document this in the medical record.[6] In explaining its decision to leave rosiglitazone on the market, the FDA argued that the data on risk were not totally consistent, and that the drug could still have potential benefit for some patients. In contrast, the European Medicines Agency completely suspended the marketing of rosiglitazone, requiring all patients to transition off the drug.

What should cliniciansdo?: Given the risks outlined above, **we suggest that all patients be transitioned off rosiglitazone and onto other treatments**. Metformin and the sulfonylureas have a very strong evidence base for preventing end-organ damage and a good safety profile, and are preferred for patients who do not have specific contraindications. They can be safely used in combination. For patients already taking multiple oral agents, insulin should be considered. Although pioglitazone has not been linked to a comparable increased risk of heart attack, it causes both heart failure and fracture,[7] and thus should be considered only in patients with inadequate glycemic control who are already on multiple other agents, are unwilling to take insulin, and for whom there are no other therapeutic options.

References: **1.**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.; **2.**Singh S, Loke YK, Furberg CD. Long-term Risk of Cardiovascular Events With Rosiglitazone: A Meta-analysis. *JAMA.* 2007;298:1189.; **3.**http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143349.htm; **4.**Home PD et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*. 2009;373:2125.; **5.**Graham et al. Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone. *JAMA.*; 2010;304:411.; **6.**Woodcock J, Sharfstein J, Hamburg M. Regulatory Action on Rosiglitazone by the U.S. Food and Drug Administration. *NEJM*. 2010;363:1489.; **7.** Dormuth CR, et al. Risk of Thiazolidinedione-Associated Fracture Should Be Appropriately Assessed—Reply. *Arch Intern Med*. 2010;170:209.

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These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

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