

Update on Rosiglitazone Safety Concerns

On May 21, 2007, the New England Journal of Medicine published a meta-analysis online that found an increased risk of myocardial infarction (MI) associated with the use of rosiglitazone (odds ratio 1.43; 95% confidence interval [CI], 1.03-1.98; $p=0.03$).¹ Since then, other information has been published, including an interim analysis of data from the RECORD trial,² and an FDA advisory panel had a hearing on the safety of this antidiabetic medication.³ Rosiglitazone is a thiazolidinedione that has been used to lower blood glucose in patients with type 2 diabetes mellitus (DM) since 1999. It is marketed by GlaxoSmithKline as Avandia® and is also available in combination with metformin (Avandamet®) and glimepiride (Avandaryl®).⁴

Immediately after publication of the meta-analysis, the FDA stated that contradictory data existed concerning the cardiovascular risks of rosiglitazone.⁵ The FDA recommended that patients discuss the risks and benefits of rosiglitazone products with their healthcare provider. Two FDA committees, the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, met on Monday, July 30, 2007, to discuss the cardiovascular risks of thiazolidinediones, with emphasis on rosiglitazone.⁶

The joint committee agreed that there was a risk of ischemic cardiac events with rosiglitazone use; however, the committee also decided to recommend not withdrawing rosiglitazone from the market. The main concerns were that the evidence supporting the increased risk was inconsistent and that the risk appeared to be greater in specific populations. Several committee members suggested that rosiglitazone's indication in patients taking insulin be removed and a black box warning concerning the increased risk in these patients be added.³

Most of the controversy centers on the published meta-analysis. While the authors have been praised for including unpublished

studies, using cardiovascular events as the outcome, and comparing rosiglitazone to placebo, there are several limitations to the meta-analysis.⁷ Trials that did not report MIs or cardiovascular deaths were excluded from the analysis. Included studies used both placebo and active treatments as controls. Most were less than one year in duration, and only five lasted for more than a year. The patient populations in the studies were not homogeneous; most of the studies included patients with type 2 diabetes, but some were poorly controlled on insulin or oral medications, two were in patients with chronic psoriasis, and one was in patients with mild-to-moderate Alzheimer's disease. Only one included study used an adjudication system to identify cases of myocardial infarction and cardiovascular death, so misclassification bias is possible, which could affect the small number of cardiovascular events. This small number of events also meant that differences could not be detected between the included studies.^{1,7}

GlaxoSmithKline and the FDA performed their own analyses of the available data from randomized, controlled trials. The FDA found that rosiglitazone increased the risk of myocardial ischemic events by 40%, and GSK found a 31% increased risk. Both of these results were similar to the 43% increase reported by the meta-analysis.³ However, a large cohort study found no significant difference in the risk for cardiovascular events between rosiglitazone and other treatments (hazard ratio 0.93; 95% CI 0.80-1.10).^{3,8} In addition, the interim analysis from a large, prospective trial also showed no difference in the incidence of cardiovascular events between patients treated with rosiglitazone and either metformin or a sulfonylurea and patients treated with metformin and a sulfonylurea.²

Currently, it is thought that any cardiovascular risk seen with rosiglitazone may not be a class effect.¹ Pioglitazone, the other thiazolidinedione available in the US, did not show an increased risk of all-cause mortality, non-fatal MI, and stroke compared to placebo in patients with type 2 DM at high risk for macrovascular

morbidity and mortality.⁹

When data from multiple studies were analyzed, an increased risk for cardiovascular events was seen with rosiglitazone. However, this meta-analysis had several weaknesses. While different analyses of the same data showed similar results, a large cohort study and an interim analysis of an ongoing trial did not find an increased risk with rosiglitazone use. Because of the conflicting data, an FDA committee recently voted to keep rosiglitazone on the market and suggested increased warning labels.

References:

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