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Is your patient still using rosiglitazone?

Many doctors stopped prescribing rosiglitazone in 2007, when a study linked it to an elevated MI risk. An update to that study underscores the need to switch patients still taking it to another drug.

Rosiglitazone use has been linked to thousands of myocardial infarctions each year.

PRACTICE CHANGER

Do not initiate rosiglitazone therapy for patients with diabetes, and consider switching those who are already taking it to pioglitazone.[1]

STRENGTH OF RECOMMENDATION

A: Based on a meta-analysis of 56 randomized trials.

Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med.* 2010;170:1191-1201.

ILLUSTRATIVE CASE

A 60-year-old African American man with type 2 diabetes comes in for a follow-up visit. He is currently taking metformin 1000 mg BID, glipizide 10 mg BID, and rosiglitazone 8 mg daily. His glucose levels are well controlled and his last hemoglobin A1c was 6.8%.

Should you discontinue the rosiglitazone?

We have been reluctant to use rosiglitazone for the treatment of type 2 diabetes since 2007, when a meta-analysis found the drug to be associated with a significant elevation in risk for myocardial infarction (MI) and a borderline significant increase in risk for cardiovascular mortality.[2] A US Food and Drug Administration (FDA) advisory committee reviewed the evidence in 2007, but did not recommend removing rosiglitazone (Avandia, manufactured by GlaxoSmithKline [GSK]) from the market.[3] Annual US sales of the drug, which fell by more than 60% over the next 2 years, totaled $408 million in 2009.[4]

Body of evidence grows

Since then, additional evidence of the risk associated with rosiglitazone has come to light. The latest study, reviewed here, is an update of the 2007 meta-analysis.[2] The authors used standard methodology like that of their original study, and added an alternative methodology that enabled them to include more trials.

Two FDA safety advisories have also been issued. The first, in September 2010, notified providers and patients of plans to restrict access to rosiglitazone because of its elevated risk of cardiovascular events. An update followed in February 2011, indicating that the drug label now includes a black box warning of that risk.[5]

STUDY SUMMARY

Expanded meta-analysis highlights MI risk

The new meta-analysis included 56 trials and a total of 35,531 patients. Of these, 19,509 (55%) were randomized to receive rosiglitazone, and 16,022 (45%) were assigned to a comparator group, which could be either placebo or active treatment.

To be included in the meta-analysis, a trial had to have a randomized comparator group, the duration of treatment had to be

similar for all study groups, and participants had to have >24 weeks of drug exposure.[1] Outcomes of interest were MI and cardiovascular mortality. The earlier meta-analysis included 42 studies, all of which had at least one of these outcomes.[2] The alternative methodology used in this study—in which smaller studies were grouped by randomization ratios and larger trials were reviewed individually—made it possible to include studies without any MIs or cardiovascular deaths.

The researchers identified 3 groups of trials for inclusion:

- The first group consisted of 5 studies that GSK submitted to the FDA in 1999 for presentation to the advisory committee, which recommended approval of rosiglitazone. In these 5 trials, 1967 patients were randomly assigned to receive rosiglitazone and 793 patients received either a comparator drug or placebo.
- The second group included 48 trials, which were primarily identified from the GSK clinical trial registry. These trials were not originally published, but a legal court settlement mandated their eventual publication,[6] providing new data not available for the previous meta-analysis. In these 48 trials, a total of 11,231 patients were randomly assigned to receive rosiglitazone and 7473 received either a comparator drug or placebo.
- The third—and smallest—group featured 3 large prospective randomized trials that had been published in major medical journals.[7-9] A total of 6311 patients were randomly assigned to receive rosiglitazone and 7756 patients received comparator drugs.

Fifteen of the 56 trials did not report any MIs, and 30 trials did not report any cardiovascular mortality. The trials without either outcome were not part of the primary analysis, but were included in the alternative analysis.

For the 41 trials with ≥1 MI, rosiglitazone therapy significantly increased the risk of MI (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.02-1.63; *P*=.04), but did not affect cardiovascular mortality (OR, 1.03; 95% CI, 0.78-1.36; *P*=.04).

The results of the alternative analysis were very similar to the primary results, showing an increased risk for MI (OR, 1.28; 95% CI, 1.01-1.62), but no change in cardiovascular mortality (OR, 0.99; 95% CI, 0.75-1.32).

WHAT'S NEW?

A stronger case for a safer alternative

We believe that this meta-analysis strengthens the case against the use of rosiglitazone for the treatment of type 2 diabetes. The number of trials and patients studied is substantial, and the alternative analytic approach allowed the researchers to include all 56 available trials, whether or not any MIs or cardiovascular deaths were reported.

At an FDA advisory committee meeting in July 2010, the recommendation to remove rosiglitazone from the market received a plurality of votes. That recommendation was not carried out, however because 4 other options—all of which involved leaving rosiglitazone *on* the market—taken together, received more votes.[10]

We think this meta-analysis provides substantial doubt about the safety of rosiglitazone. If there is a safer alternative, the decision not to use rosiglitazone becomes even easier. An important question, then, is whether the other thiazolidinedione on the market, pioglitazone (Actos), carries similar risks.

The PROACTIVE trial, a large cardiovascular outcomes study published in 2005,[11] and a patient-level meta-analysis of cardiovascular outcomes published in 2007,[12] assessed the risk of death, MI, and stroke in a diverse population of patients taking pioglitazone. Compared with studies of cardiovascular events associated with rosiglitazone, the PROACTIVE trial and the meta-analysis showed that pioglitazone has a significantly lower risk of death, MI, or stroke.

For patients who are doing well on rosiglitazone, a within-class switch to pioglitazone would appear to decrease coronary artery events. However, it must be noted that both drugs have a black box warning regarding congestive heart failure. (The black box

warning for rosiglitazone now identifies the increased risk of MI, as well).[5]

CAVEATS

Missing data weaken analysis

The authors of the meta-analysis reported here were unable to obtain individual patient outcomes, which would have allowed them to do a more powerful analysis. However, other meta-analyses, including one from the FDA,[13] found similar results.

CHALLENGES TO IMPLEMENTATION

Patients and physicians may be reluctant to switch

Theoretically, a switch to pioglitazone is an easy choice, as it is the same class of medication as rosiglitazone but has a lower risk of MI. The use of rosiglitazone caused about 83,000 excess MIs between 1999 and 2007, the FDA estimated.[14] That number has since been downgraded to up to 6000 excess MIs annually to reflect the reduced usage of the drug.[1,14] But when patients are doing well on a particular medication, neither they nor their doctor may want to change to another drug, especially when the adverse effects of the current medication are uncommon. Nonetheless, reevaluation of their diabetic medication regimen often gives patients an opportunity to ensure that they are taking the best first-line agent—which in many cases is metformin, and not a thiazolidinedione at all.[15] JFP

An in-class switch to pioglitazone appears to decrease cardiovascular events.

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