Experts Discuss Options For Rosiglitazone Use

BY MIRIAM E. TUCKER
Senior Writer

CHICAGO — Until the controversy surrounding rosiglitazone has been resolved, physicians might consider the advice offered by three diabetes specialists during a panel discussion held during the annual scientific sessions of the American Diabetes Association.

The 2-hour session drew an overflow crowd despite being a last-minute addition to the already jam-packed ADA program. It featured presentations from Dr. Steven E. Nissen and Dr. Philip D. Home, along with panelists Dr. David M. Nathan, Dr. Barry J. Goldstein, and Dr. John B. Buse.

Dr. Nissen, of the Cleveland Clinic, reviewed the results of his meta-analysis of 42 trials that revealed a significant increase in the risk of myocardial infarction with rosiglitazone (N. Engl. J. Med. 2007;356: 2457-71).

Dr. Home, of Newcastle University, Newcastle upon Tyne, England, then summarized the inconclusive findings of the 3.75-year analysis of data from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study, designed as a 6-year trial to assess the safety of rosiglitazone. The unplanned interim analysis had been published rapidly in response to the media attention (N. Engl. J. Med. 2007 June 5 [Epub doi:10.1056/NEJMoa073394]) and Congressional scrutiny garnered by Dr. Nissen's report.

Dr. Nathan, who is chief of the Diabetes Center at Massachusetts General Hospital, Boston, and who wrote editorials for both Dr. Nissen's and Dr. Home's articles, remarked, "There are insufficient data to come to any conclusions that would convince us all. That has given rise to this enormous controversy."

A joint meeting of the Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, scheduled for July 30, is likely to bring forth more data.

In the meantime, Dr. Buse, Dr. Goldstein, and Dr. Nathan offered advice about how they would approach the following three clinical scenarios:

►**A patient with diabetes in poor control who is not currently taking rosiglitazone.** Dr. Buse and Dr. Nathan agreed that they would not start a patient on rosiglitazone (Avandia) at this point, at least until more data become available.

"I think at this time, I wouldn't personally choose to start someone on Avandia therapy de novo until these issues are settled to the extent that they're likely to be settled in the next few months," Dr. Buse said.

Dr. Nathan pointed out that the well-known adverse lipid profile of rosiglitazone, compared with pioglitazone, already made it a less attractive option. Indeed, he said, the data on fluid retention and heart failure—combined with the newer data on fractures and decreased bone density—render the whole thiazolidinedione (TZD) class less attractive than other agents. "I don't understand why people would, given the choice of other agents to lower glycemia, start anyone on rosiglitazone," he said.

But Dr. Goldstein suggested that rosiglitazone in low doses might still play a role in combination therapy in patients with insulin resistance. He advised following the ADA's treatment algorithm, published in 2006, which recommends metformin as first-line therapy with the TZDs as a possible add-on in patients who don't achieve glycemic goals (Diabetes Care 2006;29: 1963-72).

"There's no reason to start with a TZD as monotherapy unless the patient is intolerant to metformin. But at a lower dose, they can be used in combination," said Dr. Goldstein, director of endocrinology, diabetes, and metabolic disease at Jefferson Medical College, Philadelphia.

►**A patient with diabetes who is in good control on a regimen that includes rosiglitazone.** All three panelists felt that they wouldn't rock the boat in this situation. "If [hemoglobin] A_{1c}, LDL cholesterol, triglycerides, and [HDL cholesterol] are all controlled, I think there would be more risk to switching someone … over the next 1.5-2 months … until we know everything we're going to know for the next 2 years," when the RECORD results are available, Dr. Buse said.

Dr. Goldstein said that such a patient "should certainly stay on either [TZD] until we learn more." And, said Dr. Nathan, "I would think twice about changing someone who's achieving all the other goals."

►**A patient with diabetes who is taking rosiglitazone but is not in good control.** All three felt that consideration should be given to stopping rosiglitazone in this situation. Dr. Buse remarked, "If you're going to have to rethink the regimen, I think it's appropriate to rethink the Avandia as well." But even then, he added, it might be difficult to take a patient off the drug because of either personal preference or formulary issues.

Dr. Goldstein noted that such patients are often taking several oral glucose-lowering agents, most commonly metformin and a sulfonylurea in combination with a TZD, and that insulin is generally considered to be the next step. Given that it's rare for patients to be on insulin combined with three oral agents, and that the weight gain and fluid retention problems associated with TZDs are often exacerbated by insulin, "the TZD is often the one that's dropped when insulin is added."

But Dr. Nathan was more direct: "If the patient is not achieving goals, I would stop Avandia and change the regimen."

Dr. Buse disclosed no financial ties with either GlaxoSmithKline Inc., maker of rosiglitazone, or Takeda Pharmaceutical Co., maker of pioglitazone. Dr. Goldstein has ties to both, whereas Dr. Nathan has received research support from GSK. All three have relationships with makers of other diabetes drugs. ■

Pages 18a—18b◊