

Rosiglitazone drama has internists scratching their heads

By Jessica Berthold

A flurry of troubling studies and label changes on rosiglitazone (Avandia) in recent months has left internists wondering how to handle treatment with the diabetes drug. To recap events: Last May, a meta-analysis of 42 studies suggested rosiglitazone raised the risk of myocardial infarction (MI) by 43%, and cardiovascular death risk by 64%; the study was in the June 14 *New England Journal of Medicine*. In July, an FDA panel voted not to pull rosiglitazone from the market, however, noting that most of the studies had lasted only six months and there were relatively few myocardial events overall.

In August, the makers of drugs in the thiazolidinedione class [i.e., rosiglitazone and pioglitazone (Actos)] agreed to an FDA suggestion to add a boxed warning saying the drugs may cause or worsen heart failure. Then, another study found a higher risk of MI with rosiglitazone, but not a higher risk for cardiac death; it was published in the Sept. 12 *Journal of the American Medical Association*. In November, the maker of rosiglitazone agreed, at the behest of the FDA, to revise its boxed warning to include the potential of increased MI risk. Separately, in February and March of 2007, the FDA issued safety alerts for rosiglitazone and pioglitazone, saying studies suggested the drugs may increase fracture risk among female diabetic patients.

E. Victor Adlin, FACP, an endocrinologist at Temple University School of Medicine in Philadelphia, discussed how the rosiglitazone drama has affected internists' prescribing habits, and how he regards the evidence thus far.

Q: What are your thoughts on the rosiglitazone meta-analysis published last June?

A: A number of observers have identified methodologic problems with the study, including the unevenness of the small effect size, the fact that it's unclear whether you should include studies that didn't show any effect, and how it will distort the frequency of unwanted effects if you don't. The study has also become quite controversial because of other studies that have shown much less of an effect or no effect.

Q: Avandia sales were down 38% in the third quarter of 2007. How have you seen recent events influencing the way internists use rosiglitazone for treatment?

A: I think most endocrinologists take the attitude that if a patient is already on rosiglitazone and is doing very well with it, there may be a greater risk in switching him and hoping he can do as well with some other drug regimen. On the other hand, I always have in the back of my mind that there is this possible increased cardiovascular risk, so if I have a choice of starting rosiglitazone, versus some other choice that I think is

equally advantageous, I'm more likely to choose the other option than I used to be. I would guess other internists are doing the same.

Q: Has the study had a spillover effect on the way people prescribe pioglitazone?

A: While the (meta-analysis) really didn't tell us anything new about pioglitazone, it reminds us that this whole class of drugs has side effects that are well recognized, namely, fluid retention that can lead to edema and congestive heart failure, or can worsen congestive heart failure; and more recently, an effect on bone density and some increase in risk of fractures. So it may very well have increased the reluctance of some doctors to use this entire class of drugs, all other things being equal.

Q: When dealing with a new patient who needs to go on a diabetes medication, how would you decide whether to prescribe metformin, a sulfonylurea or a glitazone?

A: Metformin would commonly be chosen as the first drug: it doesn't cause hypoglycemia, it's inexpensive, and it is not associated with any weight gain. If glucose is still high or GI side effects develop—which is fairly common—I would add or substitute one of the sulfonylureas, which are also fairly inexpensive and pretty reliable, though they may cause low blood sugar. Also, if an individual has an elevated serum creatinine, then there would be a contraindication to metformin but the person could still use sulfonylureas.

Q: What happens if a patient is on metformin and sulfonylureas, and glucose control is still inadequate?

A: That was the subject of a recent "clinical decisions" article in the Jan. 18 *New England Journal of Medicine*. The three choices were to add pioglitazone, insulin or exenatide. All three choices had their advocates. It's common that you would start with metformin and a sulfonylurea, and then a drug like Avandia or Actos could be added if necessary. But many would prefer to add insulin at this point.

When choosing glitazones, you have to worry about fluid retention, heart failure and a potential bad effect on bone density; also, these drugs are more expensive, and are likely to cause weight gain. And nowadays you must add to that long list of negatives that it is unknown to what extent the glitazones may add to the risk of cardiovascular disease. On the other hand, an obvious advantage of the glitazones is that they can be taken orally, while insulin and exenatide must be injected.

Q: Are there any circumstances under which would you

choose to prescribe a glitazone first, over other treatments?

A: There may be occasions where I would not want to use metformin initially, for example if the patient had borderline renal function, or was already bothered by diarrhea or dyspepsia. But I would still choose a sulfonylurea over a glitazone as initial therapy in most cases.


Q: Have you heard of any situations where doctors are recommending rosiglitazone but patients won't take it?

A: Well, that is probably going to be a bigger problem for patients who are already on rosiglitazone, because the alert patient who reads about it in the newspaper is very likely to call his provider and ask "Does this apply to me; should I stop the drug?" But yes, some patients not already taking rosiglitazone may remember the doubts that have been raised and resist their doctor's suggestion to start taking the drug.

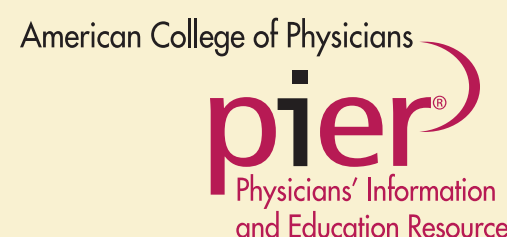
Q: Was it a good call by the FDA to keep the drugs on the market but add a boxed warning?

A: Yes. Their decision agrees with the expert opinions of The Endocrine Society and the American Diabetes Association. It seems to be a consensus right now that we shouldn't panic and remove rosiglitazone from the market. Hopefully additional studies will show more clearly whether rosiglitazone adds significantly to cardiovascular risk in patients with diabetes.

Q: How would you advise internists on the use of rosiglitazone?

A: Every case should be judged individually. We should probably keep in mind that there is a potential, though unproved, increase in cardiovascular risk, and that should affect our thinking, but there are many other factors. Those include the extent to which the patient can tolerate rosiglitazone and other drugs, how badly the patient needs improved control of diabetes, and whether the patient responds to alternatives or is at risk more than the average for cardiovascular disease. 

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Oral drug therapies for treating type 2 diabetes

Drug	Mechanism	Hb A _{1c} Reduction	Notes
Biguanides (metformin)	Suppresses hepatic glucose production; decreases intestinal absorption of glucose; improves insulin sensitivity	1%–2%; may also reduce lipid and blood pressure levels, although blood pressure effect may not be clinically significant	No weight gain; gastrointestinal side effects; increase in risk for lactic acidosis (avoid if creatinine level >1.4 mg/dL in women and >1.5 mg/dL in men, decompensated congestive heart failure, liver failure, or heavy alcohol use)
Sulfonylureas (glimepiride, glipizide, glyburide, acetohexamide, chlorpropamide)	Increases pancreatic secretion of insulin	1%–2%	Possible initial weight gain; potential for hypoglycemia
Thiazolidinediones (rosiglitazone and pioglitazone)	Increases sensitivity to insulin	1%–2% as monotherapy or when added to other agents	Weight gain and edema; avoid in New York Heart Association class III or class IV heart failure
α-Glucosidase inhibitors (acarbose and miglitol)	Decreases postprandial hyperglycemia by reducing gastrointestinal carbohydrate absorption	0.5%–1%	Gastrointestinal side effects; acarbose contraindicated in cirrhosis and requires liver function monitoring
Meglitinides (repaglinide and nateglinide)	Increases pancreatic secretion of insulin through a different glucose-binding site than used by sulfonylureas	0.5%–2%	Compared with sulfonylureas: shorter onset of action and half-life; greater decrease in postprandial glucose level; lower risk for hypoglycemia

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