Rosiglitazone: Failure of oversight or demons imagined?

Hey doc, I hear you're trying to kill me with that diabetes drug you got me on."

So began my conversation with MJ, an overweight man with type 2 diabetes who, despite counseling, resolutely smokes a pack of cigarettes a day.

Perhaps you've had a similar encounter with a patient of yours who's taking rosiglitazone (Avandia). As I write this, the news is awash with reports of the FDA Panel that voted 20-3 that rosiglitazone may increase the chances of a heart attack and 22-1 to keep the drug on the market. Small solace to the 7 million MJs worldwide who see some irony in remaining on a drug that has caused a "virtual public health emergency."[1]

So where do we go from here?

Discussing the matter with patients is not easy, given that the facts are not black and white. Taken together, the data from the original meta-analysis by Nissen,[2] the analysis of the RECORD trial,[3] and GlaxoSmithKline's own analysis[4] do not conclusively demonstrate either cardiovascular risk or benefit from rosiglitazone or provide a robust comparison to a full range of alternative therapies. While most experts believe (as do I) that it is unlikely that rosiglitazone reduces cardiac events in patients with diabetes, what we actually advise individual patients remains more challenging. Consider:

1. **The magnitude of increased risk** and variation of risk for classes of patients is largely unknown. With rosiglitazone's association with congestive heart failure (see the RECORD study), it would seem prudent to steer away from peroxisome-proliferator-activated receptor (PPAR) agonists in patients with existing heart failure, or those who are at high risk.
2. **The unintended consequences** of switching from rosiglitazone to another agent, including factors such as new side effects, nonadherence, or relative worsening of glycemic control may obviate any increased risk in cardiovascular events.
3. **The timing of risk is uncertain.** A more robust time to event analysis is not possible given the data that's available in the public domain. Thus, we do not know if cardiovascular risk is increased early, after a certain time, or if it escalates over time.
4. **There is an alternative.** Another PPAR, pioglitazone (Actos), may reduce macrovascular complications. However, the most robust trial—the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE)[5]—has been criticized for its methodology.

With all of this in mind, I'm going to counsel patients on the risks and benefits of ongoing rosiglitazone use and lean towards switching to another alternative.

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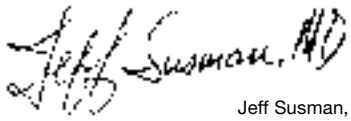
I'm also going to advocate for change. I believe we need to:

- **develop a robust drug surveillance system.** And what better way to uncover drug side effects than equipping every family physician with electronic health records? I say ditch that new bomber, cut industry subsidies, and give us a system for capturing patient level data throughout our healthcare system.
- **stop approving drugs based on surrogate outcomes** such as glycemic control and require patient-oriented outcomes such as cardiovascular events or all cause mortality before giving new drugs the green light. *The Journal of Family Practice* has been a leader in emphasizing patient-oriented outcomes—isn't it time the FDA did the same?
- **require all pharmaceutical companies to publish patient level data** from their trials, including all results (eg, side effects) from preliminary trials. It is clear that at least one other PPAR agonist in development was abandoned because of its association with cardiovascular events. Thus, it should be no surprise that such information might emerge during post-marketing surveillance.
- **stop demonizing pharmaceutical companies** and condemning the FDA, while ignoring the lamentable state of healthcare in the US.

Isn't it time Congress, the FDA, Pharma, our major insurers, big business, and yes—family physicians—unite to foster a health system built on equity, evidence, effectiveness, and efficiency?



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