Heart of the Matter

The Ashes of Rosiglitazone

As the smoke settles over the firestorm created by the recent rosiglitazone revelations, many questions remain and much can be learned from the public discourse in both the medical and lay press. So what can be said about how the story evolved and ultimately reached a nonconclusion?

BY SIDNEY GOLDSTEIN, M.D.

Rosiglitazone (Avandia, GlaxoSmithKline), a thiazolidinedione (TZD) was approved by the Food and Drug Administration for use in 1999 as an effective agent for lowering blood sugar. A modest amount of clinical data indicates that lowering blood sugar can have a beneficial effect on the microvascular changes associated with diabetes mellitus. Lowering blood sugar became a surrogate end point in the judgment of the FDA for a presumed clinical benefit in diabetes.

Some information existed to suggest that although rosiglitazone did indeed lower blood sugar, it might have some adverse effects on coronary heart disease. In fact, in September 2006, the European Medicines Agency had placed a warning label on rosiglitazone about the risk of cardiac ischemic events. In the United States, the FDA was in the process of reevaluating its judgment on this issue when along came the recent meta-analysis published by Dr. Steven Nissen and Kathy Walski (N. Engl. J. Med. 2007;356:2457-71).

One had to be impressed with the speed at which the authors, editorial writers, and the New England Journal of Medicine achieved major national and international headline exposure from a meta-analysis based on the meager and disparate data created from widely variable event classification.

The fact that a trial aimed at elucidating the potential mortality/morbidity effects of the drug was already underway in Europe and Australia was particularly unfortunate. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial was about halfway through its 6-year follow-up when the uproar occurred. RECORD randomized 4,447 patients to rosiglitazone or placebo in addition to standard oral diabetic agents. Even though its design was flawed by its unblinded nature, it surely might have provided some information relative to the risks of rosiglitazone. With the release of its interim 3-year follow-up data (N. Engl. J. Med. 2007, 357[doi:10.1056/NEJMoa073394]), it now seems almost impossible to imagine anything of value coming from it. Even so, the data provided little conclusive information either way. The observation of no significant benefit or risk for mortality mixed in with ankle edema and questionable heart failure does not address all the problems. Ankle edema, a problem which has been seen with both pioglitazone (Actos) and rosiglitazone, has been an issue for some time. Whether or not this is heart failure, as some would suggest, or just an effect similar to that observed with calcium entry blockers, is uncertain.

All of this played out in an atmosphere in which the FDA has been recently taking its hits. The direction the FDA was taking regarding rosiglitazone is not entirely clear. Records suggest that it was under consideration and that one FDA reviewer was chastised for proposing restriction of its use. The slow and possibly flawed response by the FDA can hardly be countenanced. More importantly, the practice of the FDA to accept surrogate data in cardiovascular disease evaluation is a continuing problem. The FDA's approval of a drug based solely on its ability to lower blood sugar, without consideration of major cardiovascular safety and efficacy, is unacceptable.

Whether all of this could have been achieved without all the brouhaha is not certain. It is clear that the authors of the New England Journal paper were in discussion with members of Congress long before its publication. Whether there were discussions with the FDA is not clear. It does suggest that there was an attempt to "get to" the FDA or at least influence its policies. The possible contamination of science by politics is disturbing. Politics needs to be confined to the editorial pages, not in the meat of a scientific manuscript and its publication.

The ultimate decision forced by Congress on GSK and Takeda, the maker of the similar drug pioglitazone, could well have been achieved if cooler heads had been in charge. In addition we might still hold our scientific journals in high regard. ■

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