HEART OF THE MATTER

Lessons From Rosiglitazone

As the sun sets on the most recent chapter in the rosiglitazone saga, one may search for a "teaching moment" we can all profit from. Unfortunately, the rosiglitazone experience stands out as a unique example of how *not* to behave in clinical trials, and how *not* to introduce a new drug therapy and to maintain its clinical benefit in the eyes of patients and physicians. What is of particular concern is that the story paints a dismal picture of all the players, including industry, clinical scientists, and the federal government.

BY SIDNEY GOLDSTEIN, M.D.

In the beginning, the Food and Drug Administration did not demand rigorous assessment of cardiovascular outcomes in the studies which approved thiazolidinediones, even though the major expression of diabetes over time is heart disease. The rosiglitazone uproar that began in 2007 led the FDA to require such assessments in 2008, and that error has now been corrected. One could argue that the important changes in the agency's approval process stands as the one positive outcome of this story.

In order to understand the cardiovascular outcomes of one of the TZDs, a meta-analysis—a research tool that is messy and imprecise at best—examined rosiglitazone using the clinical data that were available at that time in regard to the cardiovascular effects of the drug (N. Engl. J. Med. 2007;356:2457-71). Although carried out in a spirit of the search for clinical truths in drug therapy, it gravitated into a confrontation between GlaxoSmithKline (GSK) and the authors of the meta-analysis when significant increases in adverse cardiovascular events were reported. This led to what appeared to many as an overt attempt by GSK to cover up any negative information about the drug. Much of the "backstory" comes from a variety of sources in the press and documents obtained as part of a Senate investigation, which described in a January 2010 report a corporate environment at GSK bent on suppressing any information that could implicate adverse cardiovascular outcomes with the drug and that could impact on its sales of more than $2 billion annually.

The publication of the rosiglitazone meta-analysis led to the premature unblinding of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) study, which was at the time not quite two-thirds through its planned 6-year test of the cardiovascular effects of rosiglitazone against other non-TZD diabetes drugs. For reasons that appeared to be related more to marketing pressures than clinical knowledge, the medical leadership of the trial and the sponsor GSK agreed to publish the unplanned interim results of RECORD (N. Engl. J. Med. 2007;357:28-38). This seriously compromised the data analysis and the responsibilities of the investigators to the patients in the study. If it had been allowed to continue to conclusion without the interim analysis, it could have provided the needed clinical data to answer some of the concerns about the drug. At the behest of the FDA, a new 16,000 patient study, Thiazolidinedione Intervention With Vitamin D Evaluation (TIDE) sponsored by GSK, to compare rosiglitazone and pioglitazone to placebo, has begun. The presumption is that patients can be recruited in this trial in the light of the publicity reports from the recent meeting of the FDA's Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees in the lay and professional press.

In that 2-day meeting, which left us exactly where we started, the lack of leadership from the FDA was astounding, with members of its staff providing contradictory information and opinions. And of the 33 member panel made up of cardiologists, endocrinologists, statisticians, and patient representatives, 12 voted to have rosiglitazone withdrawn, 17 to restrict the use of the drug with an increased patient and physician warning, 3 to leave it unchanged, and 1 abstained. It seems to this observer that at times some of the committee members were more concerned about the welfare of GSK than the safety of diabetes patients.

One could make a case for the continued use of rosiglitazone to treat diabetes if it were the only option, but with the plethora of other drugs available it does not seem to be in the patients' best interest to continue to use a drug that is potentially unsafe. Even more dubious is the argument for the continuation of the TIDE trial, which turns the drug approval process upside down and seems to be little more than a marketing effort. It is hard to imagine that patients will agree to participate in a randomized trial given the FDA advisory committee coverage and the potential risks of rosiglitazone expressed in it.

At a time when the clinical trials industry (and it has become an industry) is at the threshold of testing new complex clinical strategies for previously untreated conditions like Alzheimer's disease, we should be able to manage our research with intelligence and a sense of the primacy of our responsibility to patient care. It is critical to create an environment in which both patients and physicians believe that we are living up to those goals. The rosiglitazone saga leaves us far short of meeting that challenge. ■

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POSTMASTER Send changes of address (with old mailing label) to CARDIOLOGY NEWS Circulation, 60 Columbia Rd., Bldg. B, 2nd flr., Morristown, NJ 07960.

CARDIOLOGY NEWS (ISSN 1544-8800) *is published monthly by Elsevier Inc., 60 Columbia Rd., Bldg. B, 2nd flr., Morristown, NJ 07960, 973-290-8200, fax 973-290-8250. Subscription price is $109.00 per year.*

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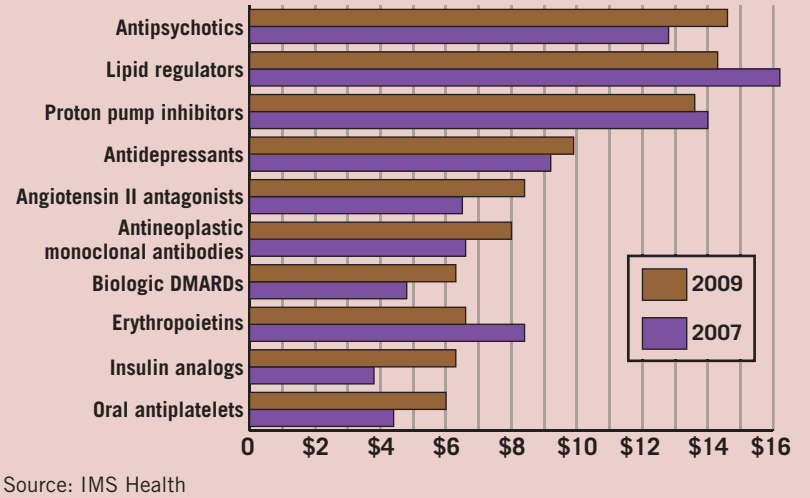

Source: IMS Health