COMMENTS AND RESPONSES

Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Response to Cobitz and Ambery

We are not surprised that GlaxoSmithKline, the manufacturer of rosiglitazone (Avandia), is not happy with the recommendation of the consensus group (1) that rosiglitazone not be used in the treatment of type 2 diabetes (2). Drs. Cobitz and Ambery argue that the consensus group used data selectively, did not consistently apply criteria for selecting interventions, and unfairly dismissed the use of rosiglitazone. They note the absence of conclusive data regarding the safety of rosiglitazone, citing meta-analyses, including one by the U.S. Food and Drug Administration (FDA), that, according to Cobitz and Ambery, reported "no increase in cardiovascular ischemic risk with rosiglitazone," and state that the FDA and European Medicines Agency have "maintained the availability of rosiglitazone to patients."

With regard to the absence of conclusive data to judge the safety of rosiglitazone, we have decried the absence of definitive studies to address this important issue (3). However, the evidence proffered by GlaxoSmithKline that, according to Cobitz and Ambery, we "overlooked" and that exonerates rosiglitazone is disingenuous at best. The cited meta-analysis by Lago et al. was restricted to an examination of cardiovascular mortality rather than all myocardial infarctions, which were the basis of the original (4) and subsequent (5) meta-analyses that identified the putative cardiovascular risk of rosiglitazone. In addition, Cobitz and Ambery's contention that the FDA meta-analysis did not implicate rosiglitazone as a cardiovascular risk factor is belied by the FDA statistician's conclusion: "Both this reviewer's and the applicant's [GlaxoSmithKline's] analyses produced statistically significant overall estimates of risk of about 1.3 to 1.4 for both total (nonserious plus serious) myocardial ischemic events and serious myocardial ischemic events" (6). Although we agree that the "vagaries" of meta-analyses are problematic, the results of the meta-analyses are much more consistent than GlaxoSmithKline suggests. Moreover, neither A Diabetes Outcome Progression Trial (ADOPT) nor the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial provides reassurance regarding rosiglitazone's safety. RECORD is the only study of rosiglitazone that has been aimed directly at cardiovascular disease outcomes, with the hypothesis that rosiglitazone was noninferior to comparators. Although the interim analysis was grossly underpowered, the direction of the preliminary results suggested a trend toward more, not fewer, cardiovascular events with rosiglitazone.

The consensus group strongly felt that it could not ignore the accumulating data questioning the safety of rosiglitazone. Although rosiglitazone remains available, it is now accompanied by a black box warning regarding congestive heart failure and myocardial ischemia, a fact conveniently ignored by Cobitz and Ambery. As noted in a previous editorial, "The jury may still be out with regard to the cardiotoxicity of rosiglitazone, but when it comes to patient safety, 'first do no harm' should outweigh any presumption of innocence" (7). Given the other options available, the consensus group agreed unanimously to withdraw our previous recommendation of rosiglitazone.

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