Rosiglitazone: Opening Pandora’s Black Box?

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The nephrologist who cares for the patient with diabetic nephropathy is only too aware of the high cardiovascular risk that the disease entails. In the United Kingdom Prospective Diabetes Study (UKPDS), for instance, a prospective study of patients who had newly diagnosed type 2 diabetes and a mean age of 52 yr, the annual cardiovascular death rates were 2.0% in those with microalbuminuria, 3.5% in those with macroalbuminuria, and 12.1% in those who had serum creatinine >175 μM or were receiving renal replacement therapy (1). Accordingly, in addition to antihypertensive management and blockade of the renin-angiotensin system, the optimization of plasma lipids has become an integral part of the patient visit. Although glycemia management has traditionally been left to the endocrinologist or internist, a recently published study has placed the choice of antihyperglycemic drug therapy at center stage for all those who care for patients with diabetes.

On May 21, 2007, the New England Journal of Medicine published on-line a meta-analysis that indicated a 43% increase in myocardial infarction (MI; 95% confidence interval [CI] 1.03 to 1.98; P = 0.03) among recipients of the thiazolidinedione (TZD) rosiglitazone when compared with those who were treated with either a sulfonylurea, metformin, or placebo (2). In isolation, this study, with the weaknesses described in the accompanying editorial and elsewhere, may have been dismissed by an audience long educated on the problems of meta-analyses (3,4); however, another meta-analysis that was preformed by the manufacturer had also raised similar concerns (5), and a Cochrane review (6) provided little reassurance. In response to the controversy, an interim analysis of the rosiglitazone-based Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, in which the primary outcome was cardiovascular death or hospitalization, was performed (7). For the primary outcome and for MI, the hazard ratios were 1.08 (95% CI 0.89 to 1.31; P = 0.43) and 1.16 (95% CI 0.75 to 1.81), respectively, for patients who received rosiglitazone versus those who were treated with a combination of metformin and sulfonylurea. Although inconclusive on its own, the hazard ratio for MI in RECORD, like those in two other large prospective trials of rosiglitazone published in the past 12 mo (8,9), trended toward an increase in MI rather than the diminution that had been hoped for.

The 5 wk between the New England Journal of Medicine’s publication of the meta-analysis and the Food and Drug Administration (FDA) Advisory Panel review on July 30 were filled with a barrage of publicity, editorial commentary, statements from eminent societies, and, above all, distressed telephone calls from patients. Although we have yet to hear the FDA’s final pronouncement, the joint panel of the Endocrinology and Metabolic Drugs and the Drug Safety and Risk Management Advisory Committees voted by a margin of 20 to 3 that the available data support the conclusion that rosiglitazone increases the risk for cardiac ischemia in patients with type 2 diabetes (10). They also agreed by 22 to 1 to recommend that rosiglitazone be kept on the market but that it should have a black box warning for specific subgroups of patients (10).

Over the years, we had grown accustomed, with BP reduction and LDL cholesterol lowering, to seeing our understanding of cardiovascular pathophysiology translate into health benefits. More recently, however, this link has been broken, not only with hormone replacement therapy for the secondary prevention of coronary artery disease (11) but also with the Cholesterol Ester Transfer Protein inhibitor torcetrapib, which, although substantially elevating HDL, was associated with an excess of major adverse cardiovascular events (12). Such findings implore us to review—first to re-explore the pathophysiology and second to determine whether “off-target” effects of the drug, such as the increase in BP with torcetrapib, might account for the apparent paradox. Regardless, we are left with an uncertain feeling about basing treatment decisions on surrogate markers for disease outcome. For insulin and sulfonylureas, we have evidence from UKPDS that a 0.9% reduction in glycylated hemoglobin reduces the microvascular complications of diabetes by 25% over 10 yr (13). For MI, the same study reported a 16% risk reduction with insulin and sulfonylureas, of borderline significance (P = 0.052) (13), although, in an overweight group, monotherapy with metformin resulted in a statistically significant 39% risk lowering (14). By examining the relationship between glycemic control and outcome, the UKPDS estimated that a 1% reduction in glycylated hemoglobin should translate to a 14% reduction in MI (15); however, this relationship, applicable to UKPDS and the drugs used therein, may not be generalizable to a broader context. This may be particularly important for new agents such as the TZD, which have a myriad of non–glucose-related effects (16). Indeed, the complexities of TZD actions make it hard to predict what their
effects on atherosclerotic disease might be, with some studies showing potential antiatherogenic activity (17) and others suggesting proatherogenic effects (18,19).

Whether the concerns raised over rosiglitazone also apply to the other marketed TZD, pioglitazone, are unclear. It has been neither subjected to the same sort of published meta-analysis as rosiglitazone nor reviewed in the same detail by the July 30 FDA Advisory Panel; however, unlike rosiglitazone, for which studies showed a trend to increase MI, the large pioglitazone-based Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study provided a more favorable trend (20). In this prospective, randomized trial, 5238 patients with type 2 diabetes and evidence of macrovascular disease were randomly assigned to receive either pioglitazone (15 to 45 mg) or placebo, in addition to their other medications. Although not meeting their primary composite end point, patients who received pioglitazone did have a NS reduction in nonfatal MI when compared with placebo (hazard ratio 0.83; 95% CI 0.65 to 1.06). It is, however, uncertain, whether these findings might be due to chance alone, be due to a direct antiatherogenic effect of pioglitazone, or be a consequence of the favorable effects that pioglitazone had on glycemic control and LDL:HDL cholesterol.

Apart from the issue of rosiglitazone and MI, three other adverse effects, common to both marketed TZD, need to be considered in patients with diabetic nephropathy. Patients with diabetes and nephropathy are at substantially higher risk for vision-threatening macular edema when compared with those without kidney disease (21). Accordingly, the recent reports that both pioglitazone and rosiglitazone have been associated with, albeit uncommonly, new-onset and/or worsening of macular edema are of concern (22,23). Similarly, the reductions in bone density and increased fracture rates that are associated with TZD use (24) may be particularly worrisome in patients who are already at increased risk as a consequence of renal bone disease; however, it is the association of TZD with not only peripheral edema but also a two-fold increase in hospitalization for heart failure (7,25) that calls into question the use of TZD in patients with diabetic nephropathy, who are already at high risk. In the Irbesartan Diabetic Nephropathy Trial (IDNT), for instance, even though patients with a history of symptomatic heart failure were excluded (26), >10% were hospitalized for heart failure during a median follow-up period of 2.6 yr, despite renin-angiotensin system blockade (27). Because TZD do not cause myocardial dysfunction (28), one might speculate that heart failure from TZD-induced fluid overload would respond well to diuretic therapy and be associated with a more benign prognosis; however, in the absence of long-term, prospective trial data indicating this, the use of TZD in patients who are at high risk for heart failure, such as those with diabetic nephropathy, should be undertaken with considerable caution.

In light of recent events, initiation of rosiglitazone in patients with diabetic nephropathy will likely be less frequent; however, for those who are already taking it, some physicians, on considering the data, may say, “Better the devil you know...” whereas others will retort, “Primum non nocere.” For a patient who has stable renal function that has been well controlled on rosiglitazone without significant fluid retention, the option of changing to pioglitazone might seem the simplest, pending further data on this drug’s cardiovascular safety. Alternatively, a change of drug class might be considered. Although metformin, α glucosidase inhibitors, and some sulfonlureas, such as glyburide, are best avoided in patients with stage 3 or higher chronic kidney disease, there are many other agents in the US pharmacopoeia that, according to NKF-KDOQI Clinical Practice Guidelines, do not require dosage adjustment, even in patients who are on dialysis. These include the second-generation sulfonlureas glipizide and gliclazide, the meglitinide insulin secretagogue repaglinide, and the incretin mimetic exenatide. For the newest antihyperglycemic drug, the dipeptidyl-peptidase IV inhibitor sitagliptin, a 50–75% dosage reduction is suggested for patients with a GFR of 30 to 50 or <30 ml/min per 1.73 m², respectively (29). In some patients, insulin may be the preferred treatment; however, although exogenous insulin is degraded by the kidney such that its half-life can be prolonged with nephropathy, there are no evidence-based guidelines to assist in the choice of insulin treatment in patients with chronic kidney disease. Nevertheless, the usual practice of initiating and escalating dosages cautiously should substantially diminish the likelihood of hypoglycemia in all patients.

With much of the dust now settling, the opportunity for a less heated review of the place of rosiglitazone in treating patients with diabetes is welcome. All things considered, we are fortunate to have had an early alert, a timely review, and numerous alternative therapies.

Disclosures

Dr. Gilbert has been a member of advisory boards for Glaxo Smith Kline, Eli Lilly and Co., Merck, and Servier, manufacturers of drugs mentioned in this article.

References


