Older Type 2 Drugs as Effective as Newer Ones

BY BARBARA J. RUTLEDGE
Contributing Writer

Metformin and second-generation sulfonylureas appear to be as safe and effective as the newer, more expensive oral diabetes drugs in the treatment of type 2 diabetes in adults, according to Dr. Shari Bolen of Johns Hopkins University, Baltimore, and colleagues.

The researchers analyzed safety and efficacy data from 216 controlled clinical trials and cohort studies of oral diabetes agents, along with two systematic reviews. The studies and reviews were selected from published reports in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases, and from unpublished reports from industry and the Food and Drug Administration.

"Each oral diabetes agent is associated with adverse events that counterbalance its benefits," wrote Dr. Bolen and colleagues in a report published online in advance of its inclusion in the September 18 print edition of Annals of Internal Medicine. "Overall, metformin seemed to have the best profile of benefit to risk." The American Diabetes Association favors metformin as initial pharmacotherapy for type 2 diabetes, although the choice of therapy often depends upon patient comorbidities.

Metformin and second-generation sulfonylureas were generally as effective as newer agents in improving intermediate outcomes. As monotherapy, all oral diabetes agents had similar effects on glycemic control, with an absolute reduction in hemoglobin A_{1c} levels of approximately 1 percentage point. The effects on glycemic control were additive when oral diabetes agents were used in combination therapy. The various agents did not differ significantly in their effect on blood pressure.

Only thiazolidinediones improved HDL cholesterol levels, with a relative mean increase of 0.08-0.13 mmol/L, compared with treatment with other agents. However, thiazolidinediones also increased LDL cholesterol levels by a relative mean increase of 0.26 mmol/L. Metformin improved LDL cholesterol levels by a mean decrease of 0.26 mmol/L.

Metformin treatment was not associated with weight gain, compared with other agents or placebo. Acarbose treatment also did not lead to weight gain, compared with placebo. Weight gains ranging from 1 to 5 kg were seen with most other oral diabetes medications: thiazolidinediones, repaglinide, and second-generation sulfonylureas. Hypoglycemic episodes occurred more frequently with second-generation sulfonylureas and repaglinide than with metformin or thiazolidinediones, although there was wide variation in the risk levels reported from the different clinical trials.

In short-term randomized trials, greater risk of congestive heart failure was seen with thiazolidinediones, compared with second-generation sulfonylureas or metformin. The absolute risk of congestive heart failure ranged from 0.8% to 3.6% for thiazolidinediones and from 0% to 2.6% for other oral diabetes agents. In placebo-controlled trials and cohort studies neither second-generation sulfonylureas nor metformin showed increased risk of congestive heart failure.

Because few studies have analyzed major clinical outcomes, data were insufficient for a thorough comparison of the effects of various oral diabetes agents on cardiovascular morbidity and mortality, microvascular outcomes, neuropathy, or death from any cause. "Large, long-term comparative studies on major clinical end points, such as myocardial infarction, chronic kidney disease, and cardiovascular mortality, are needed to determine definitively the comparative effects of the oral diabetes agents, especially in light of recent controversy regarding rosiglitazone," wrote the authors.

Dr. Zachary Bloomgarden of Mount Sinai School of Medicine in New York disagreed with the analytical design used by the study authors and disputes some of the study's findings.

"The authors are correct in their conclusion that the various agents have similar glucose-lowering events," Dr. Bloomgarden said in an interview. However, he challenged their conclusion that metformin is not associated with increased risk of lactic acidosis, citing toxicology evidence from numerous animal studies.

The question of whether thiazolidinediones might have a beneficial effect in improving cardiovascular outcome was not thoroughly examined, according to Dr. Bloomgarden. The review "appears not to address much of the relevant information on this immense topic," he said. "I would question whether its conclusions should be considered accurate."

Dr. Bloomgarden has served as a consultant for Merck and on speaker panels for Takeda, GlaxoSmithKline, Novo Nordisk, Eli Lilly, Amylin, Merck, and Novartis. ■

Metformin Rated a 'Best Buy' For Type 2 Diabetes Patients

Older type 2 diabetes treatments such as metformin, glipizide, and glimepiride provide the same benefits as newer drugs but at a lower cost, according to Consumer Reports Best Buy Drugs.

"The evidence shows that lower-cost, older medicines work just as well for most people," Consumer Reports Best Buy Drugs Project Director Gail Shearer said in a statement.

The report is based primarily on an analysis of effectiveness, risks, and estimated costs of 10 diabetes drugs conducted by the Agency for Healthcare Research and Quality.

Metformin, glipizide, and glimepiride are identified as "best buy" drugs by Consumer Reports, which points out those products cost only $10 to $60 a month, less than half the cost of rosiglitazone (Avandia, $131-$262), pioglitazone (Actos, $142-$221), or sitagliptin (Januvia, approximately $200).

While Consumer Reports also lists glipizide and glimepiride as best buys, the report "recommends that most people newly diagnosed with diabetes talk to their doctor about taking metformin first."

Similarly, an executive summary of the AHRQ report notes that "physicians and patients can feel comfortable using older medications such as metformin and second-generation sulfonylureas, as monotherapy or in combination, before newer diabetes medications such as thiazolidinediones or meglitinides, especially when cost is a factor."

Metformin was found in the AHRQ analysis to be as effective as other medications but was not associated with weight gain. "Weight increased by 1-5 kg with most of the oral diabetes medications (thiazolidinediones, second-generation sulfonylureas, and repaglinide), but not for metformin and acarbose [Precose], which had no effect on weight in placebo-controlled trials," according to AHRQ.

The AHRQ report, combined with the promotion of metformin by Consumer Reports, could spell trouble for the already maligned thiazolidinedione drug class.

Rosiglitazone in particular has been under scrutiny since a meta-analysis published in the New England Journal of Medicine found a statistically significant increase in the risk of myocardial infarction and an increase in the risk of death from cardiovascular cases in patients treated with the drug. The AHRQ review was completed prior to the release of the meta-analysis.

The drug's manufacturer, GlaxoSmithKline, also is looking at cardiovascular outcomes in the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes trial. The company has reported that the Food and Drug Administration considers the interim results from RECORD to be promising and suggested that they may contradict the observed safety signal.

According to the AHRQ analysis, "these new studies substantiate our call for more vigorous postmarketing surveillance and long-term comparative assessments of major clinical outcomes."

—Brooke McManus

Brooke McManus is a staff writer for Elsevier's "The Pink Sheet."