Bromocriptine Add-On Benefits CVD Outcome

BY MIRIAM E. TUCKER
Senior Writer

SAN FRANCISCO — An investigational quick-release formulation of bromocriptine mesylate produced a 42% reduction in a prespecified combined end point of myocardial infarction, stroke, coronary revascularization, or hospitalization for heart failure or angina in a 52-week study of more than 3,000 patients with type 2 diabetes.

The data come from the Cycloset safety trial, a prospective, randomized, double-blind, placebo-controlled study in which quick-release (QR) bromocriptine was given as add-on therapy to patients already taking one or two oral hypoglycemic agents with or without insulin, as well as cardiovascular medications. The beneficial reduction in the prespecified cardiovascular composite end point was seen even among patients with good glycemic control at baseline, Dr. Richard Scranton reported at the annual scientific sessions of the American Diabetes Association.

Subgroups of patients who failed oral diabetes therapies at baseline experienced a mean 0.7% reduction in HbA_{1c} in favor of bromocriptine-QR.

Cycloset, developed by VeroScience LLC, is a novel quick-release formulation of the dopamine-2 receptor agonist that is given once daily in the morning. The time of administration is critical, because circadian neuroendocrine rhythms in the hypothalamus are key to the regulation of peripheral metabolism, said Dr. Scranton, chief medical officer of VeroScience.

In animals that undergo marked annual cycles of metabolism, seasonal shifts from the obese, insulin-resistant condition to the lean, insulin-sensitive state are driven by shifts in the circadian phase relations of hypothalamic neurotransmitter levels. By mimicking this neurophysiological shift pharmacologically, it is possible to produce a shift in metabolism. Available evidence suggests that bromocriptine-QR acts centrally to reset hypothalamic centers regulating postprandial insulin-mediated glucose and lipid metabolism, thereby reducing postprandial hyperglycemia and hyperlipidemia.

"The time-of-day–dependent impact of dopamine upon circadian hypothalamic regulation of metabolism is a key component to the drug's mechanism of action," Dr. Scranton explained.

In three previous phase III clinical trials, Cycloset significantly reduced hyperglycemia among obese individuals with type 2 diabetes (Expert Opin. Investig. Drugs 1999;8:1683-707). Based on those data, the Food and Drug Administration issued an "approvable" letter for the agent for the treatment of type 2 diabetes, conditional in part on the completion of a large, placebo-controlled, randomized trial in patients with type 2 diabetes in order to evaluate drug-related adverse events fully. Those data are provided by the current study, Dr. Scranton said.

A total of 3,095 patients from 74 U.S. centers were randomized 2:1 to receive bromocriptine-QR starting at 0.8 mg and titrating up to 4.8 mg, taken once daily in the morning, or placebo. Concomitant diabetes medications were adjusted to maintain ideal glucose control. The final intent-to-treat analysis included 2,054 patients who received bromocriptine-QR and 1,016 who received placebo.

At baseline, the patients had a mean age of about 60 years, mean hemoglobin A_{1c} (HbA_{1c}) of 7.0%, and mean diabetes duration of 8 years. Most were on at least one oral glucose-lowering agent, about a third were on two oral agents, and about 15% were on insulin. They were typical of type 2 patients, with a mean body mass index of 32 kg/m^2, mean LDL cholesterol of about 97-98 mg/dL, and mean systolic blood pressure of 128-129 mm Hg. Three-fourths had hypertension and hypercholesterolemia, and about 41% had hypertriglyceridemia. Two-thirds were taking statins and more than half were on angiotensin-converting enzyme inhibitors.

The treatment and placebo groups were comparable in all baseline characteristics except history of revascularization surgery, in 10% vs. 13%, respectively.

Discontinuations from any cause were 41% with bromocriptine-QR and 26% on placebo. Discontinuations because of adverse events occurred in 24% with bromocriptine-QR, compared with 10.5% on placebo, including four deaths among those receiving bromocriptine-QR and two in the placebo group (0.2% of each group). Nausea, occurring mainly during the initial dose-escalation phase of the study, was the primary reason for both the increased discontinuations and the adverse event reports in the treatment group. For most patients, the nausea was mild to moderate and lasted less than 2 weeks, Dr. Scranton said in a follow-up interview.

In prespecified analyses of glycemic control, subgroups of patients who failed oral diabetes therapies (HbA_{1c} at or above 7.5%) at baseline experienced on average a 0.7 % reduction in HbA_{1c} in favor of bromocriptine-QR, relative to both placebo and to baseline.

The prespecified composite cardiovascular disease (CVD) end point occurred in 1.6% of the bromocriptine-QR group compared with 3.0% of those on placebo. That 42% relative reduction did not change significantly with adjustment for baseline covariables including stroke, coronary revascularization, or center. Analysis of the individual components of the composite suggested benefit for each one, including a 56% relative reduction in myocardial infarction (0.3% vs. 0.8%) and a 63% relative reduction in stroke (0.2% vs. 0.6%). A 55% relative reduction was seen in the combined end point of myocardial infarction, stroke, or CVD death. ■

Exercise Benefit in Diabetes Unaffected by Body Weight

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

SAN FRANCISCO — Even moderate physical fitness appears to confer a significant survival benefit on men with type 2 diabetes, no matter what their body weight, according to Roshney Jacob-Issac, Ph.D.

Her retrospective study, presented at the annual meeting of the Endocrine Society, found an inverse association between mortality and increasing fitness, with normal- and overweight men gaining even more survival benefits as they reached the highest fitness levels. Although obese men didn't reap any extra survival benefit with the top fitness level, moderate fitness decreased their overall risk of death by 52%.

"Increasing physical fitness has a survival benefit in diabetes regardless of body mass index," said Dr. Jacob-Issac of the Veterans Affairs Medical Center, in Washington.

Her retrospective study examined the link between all-cause mortality and exercise capacity in 2,690 men with type 2 diabetes, all of whom were referred for exercise tolerance testing at VA centers in Washington or Palo Alto, Calif. Nearly half of the men (1,196) were obese; 1,088 were overweight, and 406 had a normal BMI.

Peak work load, which was determined via a stress test, was estimated in metabolic equivalents (METs). One MET equals the energy expenditure at rest, or an oxygen consumption of 3.5 mL/kg per minute. Based on peak workload, individuals were categorized as low fit (5 or fewer METs), moderately fit (5.1-8 METs), or highly fit (more than 8 METs). All-cause mortality was assessed at a mean of 7 years.

Overall there were 762 deaths (172 in the normal-weight group, 334 in the overweight group and 256 in the obese group). After adjustment for age, cardiac medications, and cardiovascular disease risk factors, Dr. Jacob-Issac found a strong, graded relationship between increasing fitness and decreasing mortality in all three groups.

In those men with a normal body weight, moderate fitness conferred a 40% reduction in the risk of death and high fitness conferred a 60% risk reduction, compared with low fitness. In overweight men, the risk reduction was 40% for moderate fitness and 65% for high fitness, compared with low fitness.

Among obese men, moderate fitness conferred a 52% reduction in the risk of death, but being highly fit conferred no additional protection.

Dr. Jacob-Issac reported no conflict of interest related to the study. ■

Standard Diabetes Therapies Work in Real-World Settings

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Standard therapies for type 2 diabetes are effective at maintaining glycemic control over at least 5 years in community settings, Dr. James Best reported at the annual scientific sessions of the American Diabetes Association.

Dr. Best, of the University of Melbourne, and his colleagues observed a cohort of 4,900 patients with type 2 diabetes who served as controls for the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial. Community-based family physicians at 63 sites in three countries treated these patients—mean age of 63 years—with diet, sulfonureas, metformin, and insulin in a standard progression.

Over a median of 5 years of follow-up, the patients' median hemoglobin A_{1c} level rose only slightly, from 6.85% to 6.9%. Their median body weight declined slightly, from 86.3 kg (190.3 pounds) at baseline to 85.0 kg (187.4 pounds) at the end of the study. While both of those differences reached statistical significance, it's arguable whether such small changes had clinical significance.

In discussing these results, Dr. Best drew a distinction between "efficacy" and "effectiveness." While any new treatment may show significant efficacy in a clinical trial, it's only truly useful if it proves to be effective in real-world settings.

"I think the glycemic effectiveness of new therapies for type 2 diabetes need to be assessed against what is achievable with standard and widely available current therapy," Dr. Best said. "An HbA_{1c} target of less than 7% is generally safe and generally achievable."

Dr. Best conceded that the patients in the FIELD study were self-selected to a certain extent, which might compromise the generalizability of the results. On the other hand, the FIELD study was intended to evaluate cardiovascular outcomes, not glycemic control, in patients given fenofibrate. "They were fairly representative of patients with type 2 diabetes in the community," he said. And the care they received was representative of the standard diabetes care that type 2 patients would receive anywhere in the community setting.

At the beginning of the study, 1,287 of the control patients were being treated with diet alone. By the end of the 5-year follow-up period, about half of these had been started on one or two oral agents.

Dr. Best said that he had no conflicts of interest related to his presentation. ■