Lorcaserin Produced Significant Weight Loss

BY MARY ANN MOON

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Lorcaserin, a serotonin receptor agonist similar to fenfluramine and dexfenfluramine but designed to avoid the serotonin-related valvulopathy associated with those drugs, produces significant weight loss compared with placebo, according to a randomized trial of more than 3,000 subjects.

In conjunction with a behavior modification program, twice-daily lorcaserin enabled twice as many obese or overweight patients to lose 5% or more of their body weight during 1 year compared with placebo. The active drug also helped study subjects maintain their weight loss for a second year, compared with placebo, said Dr. Steven R. Smith of Florida Hospital's Translational Research Institute for Metabolism and Diabetes, Winter Park, and his associates.

However, as with other large studies of weight loss, this trial had a dropout rate of nearly 50% at 1 year, and nearly 40% of those subjects dropped out before 2 years.

VITALS

Major Finding: More obese subjects taking twice-daily lorcaserin (47%) than taking placebo (20%) lost 5% or more of their body weight at 1 year. Subjects taking lorcaserin were more likely to maintain their weight loss for another year.

Data Source: Two-year double-blind multicenter randomized clinical trial comparing lorcaserin with placebo in 3,182 obese or overweight subjects.

Disclosures: The study was supported by Arena Pharmaceuticals, which employed several of the coauthors and was involved in study design, data analysis, data review, and writing and revising of the manuscript.

The investigators reported the results of a prospective clinical trial evaluating the efficacy and safety of lorcaserin, conducted during September 2006–February 2009 at 98 academic and private sites, and involving 3,182 subjects.

The study subjects had a body mass index of 30-45 kg/m^2, or a BMI of 27-45 kg/m^2 plus at least one weight-related condition such as cardiovascular disease, impaired glucose tolerance, or sleep apnea. Patients with existing valvulopathy were excluded, as were those with frank diabetes, hypertension, or depression or other psychiatric disease. Echocardiography was performed to assess valvular disease at five intervals during the course of the study.

Both the active-treatment and the placebo groups attended monthly sessions of individual nutritional and exercise counseling, and were encouraged to exercise moderately for 30 minutes per day and to reduce their daily caloric intake to 600 kcal below their estimated energy requirements.

Significantly more subjects in the lorcaserin group (23%) lost 10% or more of their body weight than in the placebo group (8%).

After 1 year, 47% of the subjects taking lorcaserin had lost 5% or more of their baseline body weight, compared with 20% of those taking placebo, a statistically significant difference. Subjects receiving lorcaserin lost an average of 6% of their body weight, compared with an average 2% weight loss with placebo. Significantly more subjects in the lorcaserin group (23%) lost 10% or more of their body weight than in the placebo group (8%).

Among subjects who achieved a weight loss of 5% or more at 1 year, a greater proportion of those who continued taking lorcaserin in year 2 maintained that weight loss (70%) compared with subjects who were assigned to placebo in year 2 (50%).

Use of lorcaserin also was associated with significant declines in adverse metabolic measures such as fasting glucose levels, insulin levels, and glycated hemoglobin levels; waist circumference; adverse lipid measures such as total cholesterol, LDL cholesterol, and triglycerides; and markers of cardiovascular risk such as C-reactive protein levels, fibrinogen levels, blood pressure, and heart rate.

Both study groups showed improvement in quality of life measures, with a greater improvement in the lorcaserin group, Dr. Smith and his colleagues wrote (N. Engl. J. Med. 2010; 363:245-56).

There were no significant differences between lorcaserin and placebo in the development of valvulopathy (less than 3% in both groups), and no severe mitral or aortic insufficiency was found. The two groups also showed no differences in change in pulmonary-artery systolic pressure.

However, "the actual incidence of [Food and Drug Administration]-defined valvulopathy was below the pretrial estimates; as a result, the trial was slightly underpowered regarding the primary echocardiographic safety end point," the investigators noted.

Rates of serious adverse events were similarly low in both study groups, as were rates of depression, depressive symptoms, depressed mood, and suicidal thoughts.

Rates of headache and nausea were higher with lorcaserin than with placebo, but the symptoms tended to be mild and to resolve even with continued use of the agents.

The study was limited by its high dropout rate. It remains unknown whether the findings are applicable to patient groups that were excluded from the trial such as those with a BMI over 45, an eating disorder, or diabetes. ■

MY TAKE

Studies Needed to Confirm Safety

The history of many pharmacologic therapies for obesity—including rimonabant, sibutramine, fenfluramine, and dexfenfluramine—is characterized by withdrawal from the market after postmarketing discovery of serious adverse effects. Given this history, "the justification for using lorcaserin to manage obesity is not greater efficacy than currently available drugs, but rather an apparently much better safety and adverse-event profile," said Dr. Arne Astrup.

Lorcaserin therapy also was associated with "slight, but clinically relevant, improvements in almost all reported surrogate measures of diabetes and cardiovascular risk. These findings are important in light of the problems with drugs such as rimonabant and sibutramine, which do not produce similar reductions in blood pressure, heart rate, and levels of [LDL] cholesterol that would be expected with the weight loss achieved," he noted.

"Lorcaserin use does not seem to increase the risk of valvulopathy, pulmonary hypertension, depression, or suicidal thoughts, but phase III studies will be required to confirm these initial findings in larger populations of patients," he added.

DR. ASTRUP *is in the department of nutrition at the University of Copenhagen in Frederiksberg, Denmark. He reported being a board member and receiving grants from Novo Nordisk, Neurosearch, and Merck. These comments are taken from his editorial accompanying Dr. Smith's report (N. Engl. J. Med. 2010;363:288-90).*