

Rimonabant Improves Cardiovascular Risk Profile

BY BRUCE JANCIN
Denver Bureau

NEW ORLEANS — Evidence is mounting that rimonabant, shown effective for weight loss and smoking cessation, independently improves patients' cardiovascular risk profiles, F. Xavier Pi-Sunyer, M.D., reported at the annual scientific sessions of the American Heart Association.

In the wake of the highly favorable results of the Rimonabant In Obesity–North America (RIO-NA) trial that were presented, the company plans to file for marketing approval for the investigational drug in the second quarter of 2005, a Sanofi-Synthelabo spokesman told this newspaper.

A total of 3,040 obese patients participated in RIO-NA, a 2-year randomized double-blind trial conducted at 72 U.S. and Canadian centers. Subjects were randomized to rimonabant at 20 or 5 mg/day or to placebo in a 2:2:1 ratio for the first year. Those on rimonabant were then re-randomized to the same dose of the drug or placebo for the second year. All patients were also prescribed a mildly hypocaloric diet designed to create a 600 kcal/day deficit relative to energy requirements.

Patients on rimonabant at 20 mg/day

experienced significant reductions in body weight and abdominal fat well in excess of what can be achieved with currently available weight-loss medications. They also developed an improved cardiovascular risk profile and a sharply decreased prevalence of the metabolic syndrome, said Dr. Pi-Sunyer, professor of medicine at Columbia University and chief of the department of endocrinology, diabetes, and nutrition at St. Luke's-Roosevelt Hospital, New York City.

Mean weight loss at 1 year was 8.7 kg in the 20 mg rimonabant group, compared with 2.8 kg with placebo. At 2 years the rimonabant group weighed a mean of 7.4 kg less than at baseline; the placebo group weighed 2.3 kg less. A total of 62.5% of patients on high-dose rimonabant lost more than 5% of their initial body weight and 32.8% lost more than 10%, compared with 33.2% and 16.4%, respectively, of the subjects on placebo.

After 2 years on rimonabant at 20 mg/day, mean waist circumference was

reduced by 3.1 inches, compared with 1.9 inches on rimonabant 5 mg/day and 1.5 inches on placebo. HDL levels rose by a mean of 24.5%, while triglyceride levels fell by 9.9% in the 20 mg rimonabant group, compared with a 13.8% rise in HDL and 1.6% decline in triglycerides in the placebo

arm, reported Dr. Pi-Sunyer, principal investigator for RIO-NA.

At baseline, 34.8% of patients met criteria for the metabolic syndrome. After 2 years on rimonabant at 20 mg/day,

the prevalence of metabolic syndrome fell to 22.5%, a greater than one-third reduction. In contrast, there was no meaningful change in the prevalence of metabolic syndrome in the placebo arm.

Statistical analysis indicated that about half of the improvements in HDL cholesterol, triglycerides, insulin sensitivity, and fasting insulin seen with rimonabant were attributable to the weight loss, while the other half could be traced to an independent effect of the medication, he continued.

Depression, anxiety, irritability, and nausea were slightly more common in the rimonabant groups than the placebo group. But the three study arms did not differ significantly in terms of serial scores on the Hospital Anxiety and Depression Scale.

RIO-NA was the largest and longest study in a drug-development program, totaling more than 6,600 obese or overweight patients in phase III trials. First-year results of RIO-NA were remarkably consistent with those reported earlier in the year-long RIO-Europe and RIO-Lipids trials.

Discussant Robert H. Eckel, M.D., president-elect of the AHA, noted that rimonabant is the prototype of a new drug class targeting the endocannabinoid receptor within the brain's pleasure centers. More agents will likely follow.

"Rimonabant is of particular interest to me because the HDL effect appears to be much greater than would be expected from the amount of weight loss that occurred," said Dr. Eckel, professor of medicine at the University of Colorado, Denver.

Although the 2-year data show very encouraging evidence of both safety and efficacy, the effects of longer-term therapy directed at the brain's pleasure center remain a question mark, he added. ■



Patients on rimonabant at 20 mg/day had a sharply decreased prevalence of the metabolic syndrome.

DR. PI-SUNYER

Niacin, Psyllium Fiber May Augment Statins' Risk Reduction

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW ORLEANS — Pairing niacin or psyllium fiber with a statin can enhance the regimen's ability to reduce a patient's cardiovascular risk factors, according to the results of two independent, controlled studies reported at the annual scientific sessions of the American Heart Association.

In one study of 167 patients, adding 1 g/day of niacin to an existing statin regimen boosted serum HDL cholesterol levels, reduced triglyceride levels, and slowed the progression of atherosclerosis as measured by carotid intima-media thickness. In the second, 67-patient study, adding a daily dose of psyllium fiber to a standard statin dose cut serum LDL cholesterol levels as much as did doubling the statin dose.

Niacin is the most effective agent available for treating patients with low levels of HDL cholesterol, said Allen J. Taylor, M.D., director of cardiovascular research at Walter Reed Army Medical Center in Washington. The newest revision of the National Cholesterol Education Program's guidelines flags HDL cholesterol levels as low if they are at or below 40 mg/dL in men and 50 mg/dL in women, but the guidelines do not call for using any drug to treat low HDL cholesterol.

The study enrolled men and women older than 30 years with known coronary disease who were already taking a statin

drug. Patients had to have a serum LDL cholesterol level less than 130 mg/dL and an HDL cholesterol level less than 45 mg/dL. They continued their existing statin regimen and were randomized to 1 g of niacin or placebo daily. The niacin dosage started at 500 mg/day for the first 30 days before being boosted to the maintenance dose; treatment was for 1 year. To minimize problems with flushing, a common effect of niacin, the medication was taken at night along with the patient's usual daily dose of aspirin.

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DR. TAYLOR

All patients had their common-carotid intima-media thickness measured by ultrasound at baseline, and then were re-assessed after 1 year. The study's primary end point was the change in intima-media thickness. The average patient age was 67 years, and at baseline the mean serum HDL level was about 40 mg/dL, the mean LDL level was about 90 mg/dL, and the mean triglycerides level was about 170 mg/dL.

After 12 months of treatment, the 78 patients who remained in the niacin group (out of 87 randomized) had an average HDL cholesterol level of 47 mg/dL and an average serum triglycerides level of 134 mg/dL, both statistically significant changes from baseline. In contrast, the 71 patients who completed the study in the placebo group (out of 80 who started) had no statistically significant change in their levels of HDL cholesterol and triglycerides, said Dr. Taylor. Serum levels of LDL cholesterol showed no significant

change in either treatment group.

The average carotid intima-media thickness increased in both groups. In the niacin-treated patients, it thickened by an average of 0.014 mm, not a statistically significant change compared with baseline. But in the placebo group, it thickened by an average of 0.044 mm, a statistically significant increase from baseline.

Even though flushing occurred in most patients treated with niacin, the drug was well tolerated. Fewer patients withdrew because of adverse drug effects in the niacin group than in the placebo group.

"The first step for managing low levels of HDL cholesterol is to counsel a patient on the need for increased exercise, weight loss, and smoking cessation," said Philip Greenland, M.D., chairman of the department of preventive medicine at Northwestern University, Chicago. "The role of drug therapy in raising HDL cholesterol remains poorly defined, even with these new data." Without a clinical end point in this niacin study, "patient management should not necessarily change based on the results. A study that uses coronary events as the end point seems justified," Dr. Greenland said.

The niacin study was an investigator-initiated project that received an unrestricted research grant from Kos Pharmaceuticals, which markets a formulation of niacin. Dr. Taylor said he has no financial relationship with Kos.

The second study assessed psyllium fiber treatment as an adjunct to statin therapy and enrolled patients who were on statin treatment because of coronary disease risk factors. All patients were withdrawn from statins during a 4-week run-in, and then they were randomized to

three treatment groups: 10 mg/day simvastatin, 20 mg/day simvastatin, or 10 mg simvastatin plus 3.6 g soluble fiber per day. The fiber was consumed as 6 g of Metamucil psyllium fiber t.i.d. At the end of the run-in period, serum levels of LDL cholesterol averaged about 173 mg/dL.

After 8 weeks of treatment, serum LDL levels had dropped by an average of 55 mg/dL in the 23 patients treated with 10 mg/day of simvastatin, and by an average of 63 mg/dL in the 22 patients treated with 20 mg/day simvastatin, as well as the 22 patients who received 10 mg/day simvastatin plus the fiber supplement, reported Abel E. Moreyra, M.D., professor of medicine at Robert Wood Johnson Medical School in New Brunswick, N.J. The difference in the magnitude of the drop in LDL cholesterol between the 10-mg simvastatin group and the two comparator groups was statistically significant.

Thus, treatment with 3.6 g/day soluble fiber had the same incremental impact on lowering LDL cholesterol as did doubling a patient's dosage of simvastatin from 10 mg/day to 20 mg/day, said Dr. Moreyra. In addition, the psyllium fiber dosage used was very well tolerated. This study received no commercial funding.

"Most physicians who treat high cholesterol levels have heard of the benefits of using dietary fiber. These results document the effect," commented Sidney C. Smith Jr., M.D., director of the center for cardiovascular science and medicine at the University of North Carolina at Chapel Hill. "Many patients already use psyllium fiber three times a day to get an extra boost in cholesterol lowering. The question is, are there long-term effects of fiber on the pleiotropic effects of statins?" ■

