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Editor's Note

Another Pill for Weight Reduction

Key words: cannabinoid receptor antagonist, weight loss, obesity

Introduction

There is no question that the population of the world is becoming overweight. The new enemy is our appetites. One of every four persons on earth is too fat. Fat people now outnumber hungry people in the world, amounting to 1.7 billion people who could lose weight. Thus, there is a great need for weight reduction. Obesity isn't the only factor, but it does contribute to hypertension, hyperlipidemia, and diabetes, the three major components of the metabolic syndrome.

In 2004, three trials, entitled RIO-Lipids, RIO-Europe, and RIO-North America (RIO-NA), were presented at national and international meetings. All three trials tested the effectiveness of a drug called rimonabant, a selective cannabinoid type 1 (CB_1) receptor antagonist, a new class of therapeutic agents. Rimonabant targets the endocannabinoid system. The drug's mechanism of action is to mute appetite alarms in the brain, stomach, and fatty tissue that promote smoking and eating. Rimonabant works by blocking endogenous cannabinoid binding to neuronal CB_1 receptors. Activation of these receptors by endogenous or exogenous cannabinoids increases appetite. A selective endocannabinoid receptor antagonist thus offers a novel approach to appetite control and weight reduction. In addition, the drug has potential as a treatment for smoking cessation because the endocannabinoid system is also involved in the body's response to tobacco dependence.

RIO Clinical Trials

All RIO trials were double-blind placebo-controlled trials.

In RIO-Lipids, patients with abdominal obesity and abnormal lipid profiles were treated with rimonabant for one year; results were presented at the American College of Cardiology Annual Scientific Session in March 2004.

RIO-Europe was a study of the weight-reducing effect and safety of rimonabant in obese patients with or without comorbidities and was presented at the European Congress of Cardiology in September 2004.

RIO-North America (RIO-NA) was presented at the November 2004 American Heart Association Annual Scientific Sessions in New Orleans by Xavier Pi-Sunyer, on behalf of the other investigators. Enrollees numbered 3,040 and mean follow-up was two years. The primary endpoint was change in weight from baseline to one year and the prevention of weight regain after re-randomization through the second year. Other secondary endpoints were weight loss relative to baseline weight, waist circumference, and change in metabolic parameters. Patients entered into the RIO-NA trial had body mass index of ≥ 30 km/m^2 or > 27 associated with a comorbidity such as hyperlipidemia or hypertension. Diabetic patients were excluded.

RIO Clinical Trial Results

In the RIO-Lipids trial, 20 mg rimonabant resulted in a significant weight loss of 58.4% compared with 30% for rimonabant 5 mg/day and 19.5% for placebo. In addition, 20 mg rimonabant resulted in a 23% high-density lipoprotein cholesterol increase and a 15% decrease in triglycerides, but no significant difference in low-density lipoprotein cholesterol levels.

Results of the RIO-Europe trial reveal that rimonabant at 20 mg/day resulted in 8.6 kg weight loss at one year compared with 4.8 kg for rimonabant 5 mg/day and 3.6 kg weight loss for placebo.

In the RIO-North America trial, patients randomized to 20 mg rimonabant and who remained on that dose for a full two years had a 7.4 kg weight loss versus 2.3 kg for placebo. Similarly, waist circumference reduction of 8 cm was accomplished in patients taking 20 mg for two years compared with 3.8 cm for placebo.

Increases in HDL of 24.5% were seen in patients randomized to 20 mg rimonabant for two years versus 13.8% in the placebo group. Triglycerides were also reduced in the 20-mg patient group and were increased 1.6% in the placebo group. Metabolic syndrome was reduced 22.5% in the 20-mg rimonabant group.

The RIO-North America investigators conclude that among obese patients treated with the CB_1 receptor antagonist rimonabant there is greater reduction in weight, waist circumference, and presence of metabolic syndrome at one year compared with placebo. Weight loss through two years was maintained in patients who continued to receive high-dose rimonabant. The results of this latest trial are quite similar to those of RIO-Europe and RIO-Lipids.

Adverse Effects of Rimonabant

The major concern regarding the drugs that have been prescribed so far for weight reduction is safety. No agent is free of adverse events, but those adverse events must be balanced against the benefit of weight reduction. Those who have experience with rimonabant indicate that there may be some neuropsychiatric events, including depression and anxiety, and some patients have complained of nausea. If this drug is eventually approved by the Federal Drug Administration for use, its use will not be limited only to patients who have satisfied clinical trial entry criteria; it will also probably be used in patients who are mildly depressed. This may be the type of patient that would be more susceptible to unwanted side effects.

Conclusions

If this agent is as good as it seems to be, the cardiovascular community will have a potent agent to deal with the multiple problems secondary to obesity. This new class of drug, that is, cannabinoid -1 receptor antagonists, may not solve the problem completely, but in combination with hypocaloric diets and favorable modulation of risk factors, it may provide a start. I seriously doubt that it will replace bariatric surgery as a therapy for morbidly obese patients requiring 150 pounds of weight reduction, but who knows?

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