

## Efficacy and Safety of Lovastatin in Adolescent Males With Heterozygous Familial Hypercholesterolemia: A Randomized Controlled Trial

Stein et al report the experience of 132 patients recruited from 14 different centers to participate in a study evaluating the safety and efficacy of lovastatin treatment in children with heterozygous familial hypercholesterolemia (HeFH). Adolescent boys aged 10 to 17 years who had followed the American Heart Association (AHA) pediatric diet for at least 4 months were recruited in this randomized, placebo-controlled study. The inclusion criteria for HeFH were: (1) low-density lipoprotein cholesterol (LDL-C) values of at least 4.9 mmol/L (189 mg/dL) and no more than 13.0 mmol/L (503 mg/dL) and at least 1 parent had an LDL-C value of at least 4.9 mmol/L (189 mg/dL); or (2) LDL-C values of at least 5.7 mmol/L (220 mg/dL) and no more than 13.0 mmol/L (503 mg/dL) and a parent who had died of coronary artery disease (CAD) with no available lipid values. These LDL-C entry criteria had to be met prebaseline. Both groups in the study were similar as to age, height, weight, smoking rate, blood pressure, testicular volume, and baseline serum lipid profile.

Prior to randomization, all eligible participants received placebo during the last 4 weeks of an 8-week stabilization period in addition to the AHA diet. After randomization, they were administered either placebo or lovastatin immediately prior to the evening meal during the following 24 weeks (period 1). Lovastatin was started at 10 mg/d and increased at 8 and 16 weeks to 20 and 40 mg/d, respectively. During the second 24-week period (period 2), lovastatin was given at 40 mg/d. Those who received placebo during period 1 continued receiving placebo during period 2. Subjects were followed every 4 weeks during period 1 and every 6 weeks during period 2. Clinical assessment, including growth assessment and serum cholesterol, triglyceride, LDL-C, high-density lipoprotein cholesterol, apolipoprotein B (Apo B), transaminases, and creatine kinase levels, were determined at every visit. Total protein, albumin, ferritin, glucose, and vitamins A, D, and E serum levels also were determined to evaluate nutritional status.

There was a positive family history for familial hypercholesterolemia in 74% of the 132 randomized subjects. In 56% the mother was affected while in 44% the father was affected. The mean age of onset of CAD of the affected parents was 37 years. Lovastatin had no significant effect on growth parameters

throughout the study. Sexual maturation progressed similarly in both groups. Baseline total cholesterol, LDL-C, and Apo B serum concentrations were elevated, as expected in individuals with HeFH. Lovastatin reduced total cholesterol and LDL-C levels at all dosages and Apo B at 40 mg/dL during period 1 (Apo B was not measured during treatment with lower dosages). Continued therapy with lovastatin reduced LDL-C and Apo B levels 25% and 22%, respectively, during period 2. Although a gradual upward trend from baseline levels in alanine aminotransferase was noted, no significant differences were found between groups at week 48. Biochemical measurements to assess nutritional status did not show differences at baseline or after 48 weeks of lovastatin treatment except for a reduced tocopherol level.

The authors concluded that lovastatin did not affect growth and effectively reduced serum LDL-C and total cholesterol levels.

Stein EA, et al. *JAMA* 1999;281(2):137-144.

**Editor's comment:** *Familial hypercholesterolemia is a worrisome genetic condition that requires aggressive lipid-lowering therapy. Failure to control hypercholesterolemia has been associated with high mortality and frequent life-threatening cardiovascular episodes, often seen early in life. Thus, this interesting report demonstrates the importance of these therapeutic interventions in the pediatric population. The study itself demonstrates modest reductions (21%) in serum lipid level after 48 weeks of intense therapy. This reduction occurred with the help of a low-fat, low-cholesterol diet without alterations in growth and development while other nutritional indexes remained intact. This is important since dietary restrictions to lower serum cholesterol may result in a decreased growth rate. This paper also remarks on the significance of the potential prevention of the high morbidity associated with increased serum cholesterol levels. However, long-term studies are necessary to corroborate the safety and effectiveness of lipid-lowering therapies for prolonged periods beginning in childhood.*

Fima Lifshitz, MD

## Weight Control and Risk Factor Reduction in Obese Subjects Treated for Two Years With Orlistat: A Randomized Controlled Trial

A randomized, double-blind, placebo-controlled study using orlistat, a gastrointestinal lipase inhibitor, to promote weight loss is reported by Davidson et al. A total of 1,187 obese subjects older than 18 years with a body mass index of 30 to 43 kg/m<sup>2</sup> and absence of weight loss in the previous 3 months were recruited from 18 different research centers in the United States. Qualified subjects received a controlled-energy diet that provided 30% of energy intake as fat during a 4-week lead-in period. Individual energy intake was calculated according to the estimated daily maintenance energy requirement (1.3 x calculated basal metabolic rate) minus 2,100 to 3,360 kJ/d. After the 4-week lead-in period, 892 subjects, who

had a treatment compliance rate of  $\geq 75\%$ , were randomly assigned to receive placebo (25% of the subjects, n=224) or orlistat 120 mg (75% of the subjects, n=668) for 52 weeks. Subjects who received placebo in the first year who had a  $\geq 70\%$  compliance rate received placebo for an additional 52 weeks. Orlistat-treated subjects who completed 1 year with a compliance rate of  $>70\%$  received placebo, orlistat 120 mg, or orlistat 60 mg for an additional 52 weeks. Medical history, body weight determination, clinical chemistry, thyroid function, fasting lipid levels, fasting glucose and insulin, and 3-hour glucose tolerance tests were performed at the time of randomization and at the end of years 1 and 2.