Medication does not appear to reduce progression of atherosclerosis

March 17 2009

Compared to placebo, the drug pactimibe did not effect certain measures of atherosclerosis for patients with familial hypercholesterolemia (high cholesterol levels), but these patients did have an increased incidence of cardiovascular events such as heart attack and stroke, according to a study in the March 18 issue of *JAMA*.

One proposed method to help prevent cardiovascular disease is to block the action of acyl coenzyme A:cholesterol acyltransferase (ACAT), an enzyme involved in cholesterol accumulation. In theory, inhibition of ACAT-1 (an isoform [different form of the same protein] of ACAT) could slow the progression of atherosclerosis (process in which plaque builds up in the inner lining of the arteries) and prevent the development of vulnerable plaque, according to background information in the article. Treatment with ACAT inhibitors, such as the drug pactimibe, have shown promising results for the prevention of atherosclerosis in various animal tests.

Marijn C. Meuwese, M.D., of the Academic Medical Center, Amsterdam, and colleagues assessed the efficacy and safety of pactimibe in reducing progression of atherosclerosis in 892 patients with a family history of high cholesterol, which is associated with a higher risk for atherosclerosis. The randomized, placebo-controlled study (Carotid Atherosclerosis Progression Trial Investigating Vascular ACAT Inhibition Treatment Effects [CAPTIVATE]) was conducted at 40 clinics in the United States, Canada, Europe, South Africa and Israel between February 2004 and December 2005. Participants received

either 100 mg/d of pactimibe (n = 443) or matching placebo (n = 438), in addition to standard lipid-lowering therapy. Atherosclerosis was assessed by ultrasound measurements of carotid intima-media thickness (CIMT; a measurement of the thickness of the inner wall of a major artery) at the beginning of the study and at 12, 18, and 24 months. Increasing thickness is considered a marker of increasing plaque in the artery. The treatment was discontinued on October 26, 2005, when the parallel ACTIVATE study failed to demonstrate efficacy of pactimibe vs. placebo.

After 6 months of treatment with pactimibe, the average percentage change from baseline of low-density-lipoprotein cholesterol (LDL-C) significantly increased by 7.3 percent compared with 1.4 percent in the placebo group. This increase in LDL-C was observed throughout the study and disappeared after discontinuation of the study drug.

The annual progression of maximum CIMT showed no difference between groups. However, the annual progression of the average CIMT showed a significant difference between groups as relative average CIMT increase was observed in patients receiving pactimibe (difference, –0.014 mm). Average CIMT progressed significantly in the pactimibe group within 1 year, whereas only minor progression of average CIMT was observed in the placebo group.

Serious adverse events were reported more frequently by patients in the pactimibe group than in the placebo group (10.0 percent vs. 7.7 percent). Cardiovascular events (6.3 percent vs. 3.4 percent) as well as the composite of cardiovascular death, heart attack, and stroke (2.3 percent vs. 0.2 percent) occurred more frequently in patients receiving pactimibe vs. placebo.

"… in patients with familial hypercholesterolemia, pactimibe had no effect on atherosclerosis as assessed by changes in maximum CIMT

compared with placebo but was associated with an increase in mean CIMT as well as increased incidence of major cardiovascular events," the authors write.

They add that the findings from this study and findings from other studies lessen "the promise and further development of this class of drugs for cardiovascular prevention."

More information: JAMA. 2009;301[11]:1131-1139

Source: JAMA and Archives Journals (news : web)