New Drugs Aim to Raise HDL in Short, Long Term

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW YORK — Although drug treatments that raise serum levels of HDL cholesterol are already available, several potentially better, more targeted treatments are moving through the development pipeline, H. Bryan Brewer Jr., M.D., said at an international symposium on triglycerides and HDL.

The new treatments are in a range of development stages, from preclinical animal studies to phase III clinical trials, and they span several different treatment strategies, said Dr. Brewer, director of lipoprotein and atherosclerosis research at the Washington Hospital Center.

Short-term treatments to raise HDL-cholesterol levels are geared to treating patients with acute coronary syndrome who need rapid plaque stabilization. This approach includes infusion of exogenous apolipoprotein A_1, the main protein component of HDL cholesterol, delipidation of HDL, or infusion of an apo A_1 mimetic peptide.

Long-term treatments are also in the works, which would be better suited to reducing coronary and cardiovascular disease risk on a chronic basis. This strategy includes oral treatment with an apo A_1 mimetic peptide or treatment with an agent that inhibits the cholesterol ester transfer protein (CETP), which is involved in regulating the size of cholesterol particles. Reduced CETP activity is antiatherogenic. Dr. Brewer summarized where these treatments now stand:

► **Apo A_1 infusion.** The first of the new wave of HDL cholesterol treatments used a recombinant, variant apo A_1 protein, apo A_1 Milano, derived from people who lived in a village in northern Italy. Five weekly infusions of apo A_1 Milano to a total of 36 patients with acute coronary syndrome led to an average drop in their atheroma volume of about 1%, a significantly better reversal of atherosclerosis than what was seen in a control group of 11 patients (JAMA 2003;290:2292-300). The results of this "landmark" study showed that rapid regression of atherosclerosis was possible and that acute apo A_1 infusions could be given to patients with acute coronary syndrome, said Dr. Brewer. Further clinical testing is ongoing.

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► **HDL delipidation.** In this process, a patient undergoes plasmapheresis, and cholesterol is removed from the patient's existing HDL particles using an organic solvent. The delipidated HDL is then returned to the patient. This treatment, which takes about 4 hours, can increase cholesterol efflux about 20-fold, said Dr. Brewer. The treatment has progressed through animal safety and efficacy testing, and is scheduled to start in clinical testing in late 2005. Dr. Brewer is also chief scientific director for Lipid Sciences Inc., the company that is developing this treatment.

► **Synthetic apo A_1 mimetic peptide.** Researchers have produced an 18-amino-acid peptide that mimics the structure of a portion of the amphipathic, helical peptide that forms apo A_1. In vitro and animal studies indicate that the 18-amino-acid peptide can remove cholesterol from cells without cytotoxicity. Animal studies are continuing with this agent, which is administered intravenously.

► **CETP inhibitors.** The most advanced of these agents is torcetrapib. In a pilot, uncontrolled study with 19 patients, treatment with 120 mg torcetrapib once daily for 4 weeks boosted serum levels of HDL cholesterol by an average of about 50% (N. Engl. J. Med. 2004;350:1505-15). Torcetrapib's clinical efficacy is now being tested in a study that will follow atherosclerosis regression using intravascular ultrasound, similar to the apo A_1 Milano study. But, in a controversial move, Pfizer, which is developing torcetrapib, is now studying it clinically only in combination with atorvastatin. Another CETP inhibitor, JTT-705, is being developed by Roche and is also in clinical studies.

► **Oral synthetic apo A_1 mimetic peptide.** The D-4F peptide is similar in concept to the other synthetic apo A_1 mimetic peptide under study, except itis made exclusively from D-amino acids, is not digested, and is orally active. The D-4F peptide is in early-phase human testing. ■