NIH stops clinical trial on combination cholesterol treatment

May 26 2011

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health has stopped a clinical trial studying a blood lipid treatment 18 months earlier than planned. The trial found that adding high dose, extended-release niacin to statin treatment in people with heart and vascular disease, did not reduce the risk of cardiovascular events, including heart attacks and stroke.

Participants were selected for AIM-HIGH because they were at risk for cardiovascular events despite well-controlled low-density lipoprotein (LDL or bad cholesterol). Their increased risk was due to a history of cardiovascular disease and a combination of low high-density lipoprotein (HDL or good cholesterol) and high triglycerides, another form of fat in the blood. Low HDL and elevated triglycerides are associated with an increased risk of cardiovascular events. While lowering LDL decreases the risk of cardiovascular events, it has not been shown that raising HDL similarly reduces the risk of cardiovascular events.

During the study's 32 months of follow-up, participants who took high dose, extended-release niacin and statin treatment had increased HDL cholesterol and lowered triglyceride levels compared to participants who took a statin alone. However, the combination treatment did not reduce fatal or non-fatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures to improve blood flow in the arteries of the heart and brain.

"Seeking new and improved ways to manage cholesterol levels is vital in

the battle against cardiovascular disease," said Susan B. Shurin, M.D., acting director of the NHLBI. "This study sought to confirm earlier and smaller studies. Although we did not see the expected clinical benefit, we have answered an important scientific question about treatment for cardiovascular disease. We thank the research volunteers whose participation is key in advancing our knowledge in this critical public health area, and the dedicated investigators who conducted the study."

The AIM-HIGH trial, which stands for Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health, enrolled 3,414 participants in the United States and Canada with a history of cardiovascular disease who were taking a statin drug to keep their LDL cholesterol low. Study participants also had low HDL cholesterol and high triglycerides, which meant that they were at significant risk of experiencing future cardiovascular events. Niacin, also known as Vitamin B3, has long been known to raise HDL and lower triglycerides. Eligible participants were randomly assigned to either high dose, extended-release niacin (Niaspan) in gradually increasing doses up to 2,000 mg per day (1,718 people) or a placebo treatment (1,696 people). All participants were prescribed simvastatin (Zocor), and 515 participants were given a second LDL cholesterol-lowering drug, ezetimibe (Zetia), in order to maintain LDL cholesterol levels at the target range between 40-80 mg/dL.

The NHLBI funded the AIM-HIGH study with additional support from Abbott Laboratories, a pharmaceutical company based in Abbott Park, Ill. Abbott also provided Niaspan and Merck Pharmaceuticals, based in Whitehouse Station, N.J., provided Zocor. All drugs used in the study were approved for marketing in the United States and Canada and have been on the market for many years.

Researchers began recruiting participants in early 2006. The study was scheduled to finish in 2012. The average age of the participants was 64

years. Pre-existing medical conditions included coronary artery disease (92 percent); metabolic syndrome, which is a cluster of risk factors for heart disease (81 percent); high blood pressure (71 percent); and diabetes (34 percent). More than half of participants reported having a heart attack prior to entering the study.

The rationale for the AIM-HIGH study was based in part on a large number of observational studies that consistently showed that low HDL cholesterol increases the risk of cardiovascular events in men and women, independent of high LDL cholesterol. In addition, previous small clinical studies showed that relatively high residual cardiovascular risk exists among patients with cardiovascular disease, low HDL cholesterol, and high triglycerides despite intensive management of LDL cholesterol.

However, efforts to find HDL-raising treatments that actually reduce this residual risk have thus far proved disappointing. Fenofibrate, an HDL-raising drug, failed to reduce the rate of cardiovascular events in patients with diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD trial) despite favorable effects on HDL and triglycerides. Another HDL-raising drug, torcetrapib, actually increased the rate of cardiovascular events in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial despite lowering LDL and triglycerides and raising HDL levels, as intended.

Earlier studies of niacin had shown more favorable results. Unlike AIM-HIGH, the earlier studies were not designed specifically to evaluate the impact of raising HDL on the risk of cardiovascular events while maintaining excellent LDL control. Several other trials testing this hypothesis, including a large international trial of high dose, extended-release niacin, are still ongoing.

As is customary in clinical trials, the NHLBI established an independent data and safety monitoring board (DSMB) to monitor trial progress and participant safety. At a regularly scheduled meeting on April 25, 2011, the study's DSMB concluded that high dose, extended-release niacin offered no benefits beyond statin therapy alone in reducing cardiovascular-related complications in this trial. The rate of clinical events was the same in both treatment groups, and there was no evidence that this would change by continuing the trial. For this reason, the DSMB recommended that the NHLBI end the study.

The DSMB also noted a small and unexplained increase in ischemic stroke rates in the high dose, extended-release niacin group. This contributed to the NHLBI acting director's decision to stop the trial before its planned conclusion. During the 32-month follow-up period, there were 28 strokes (1.6 percent) reported during the trial among participants taking high dose, extended-release niacin versus 12 strokes (0.7 percent) reported in the control group. Nine of the 28 strokes in the niacin group occurred in participants who had discontinued the drug at least two months and up to four years before their stroke. Previous studies do not suggest that stroke is a potential complication of niacin, and it remains unclear whether this trend in AIM-HIGH arose by chance, was related to niacin administration or some other issue.

All AIM-HIGH study participants have been informed of the results and will be scheduled for clinic visits within the next 2.5 months. Participants will be followed for an additional 12 to 18 months.

"Patients who were not in the AIM-HIGH trial should not stop taking high dose, extended-release niacin without talking to their doctor first," said Shurin.

"The lack of effect on cardiovascular events is unexpected and a striking contrast to the results of previous trials and observational studies," said

Jeffrey Probstfield, M.D., AIM-HIGH co-principal investigator and professor of medicine and epidemiology at the University of Washington, Seattle. "The AIM-HIGH findings do not support the trial's hypothesis that, in the population studied, adding extended-release niacin to simvastatin in participants with well-controlled LDL cholesterol can provide additional clinical benefit."

"The results from AIM-HIGH should not be extrapolated to apply to potentially higher-risk patients such as those with acute heart attack or acute coronary syndromes, or in patients whose LDL cholesterol is not as well-controlled as those in AIM-HIGH," said William E. Boden, M.D., AIM-HIGH co-principal investigator and professor of medicine and preventive medicine at the University at Buffalo, N.Y.

The niacin tested in the study is a proprietary formulation used in doses of 500-2,000 milligrams (mg), manufactured by Abbott Laboratories and approved and regulated by the U.S. Food and Drug Administration. Low doses of niacin, typically 20 to 100 mg, can be found in multivitamin formulations available without a prescription. The FDA regulates the use of high doses of niacin (over 500 mg), which is approved by prescription for helping treat low HDL cholesterol and/or high triglycerides. At prescription-level doses, some people experience flushing. The extended-release formulation of niacin tested in AIM-HIGH was intended to help reduce the likelihood of flushing.

An estimated 1 in 7 Americans has high blood cholesterol. It is a major risk factor for cardiovascular disease, which kills 800,000 Americans a year. Cholesterol can build up in the walls of arteries and cause them to narrow, a condition known as atherosclerosis.

"As we continue to search for new approaches to treating cholesterol problems, it is important to remember the value of existing treatments. The key to treating high cholesterol so patients can reduce their risk of

cardiovascular disease is to lower the level of LDL cholesterol, through well-established drug treatments such as statins and lifestyle changes," said Patrice Desvigne-Nickens, M.D., NHLBI project officer for the AIM-HIGH trial.

The AIM-HIGH investigators will now focus on completing data collection and analysis. The preliminary outcomes of the study are expected to be reported at scientific meetings in the fall of 2011.

More information:
Diseases and Conditions Index: High Blood Cholesterol: www.nhlbi.nih.gov/health/dci/D … /Hbc/HBC_WhatIs.html

AIM-HIGH Information Page www.aimhigh-heart.com/index.shtml

Your Guide to Living With Heart Disease: www.nhlbi.nih.gov/health/publi … uide/living_well.htm

Provided by National Institutes of Health