SEAS
Simvastatin + Ezetimibe in Aortic Stenosis

Press Release

EMBARGO: 18.00/6pm BST, Monday 21 July 2008

Results from the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study

The SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study has investigated the effects of intensive cholesterol lowering with the combination of simvastatin (40 mg daily) and ezetimibe (10 mg daily) in patients with aortic stenosis.

Aortic stenosis (which involves partial blockage of the aortic valve in the heart) is a relatively common disease among older people in Western populations. Left untreated, it can progress to death from heart failure or cardiac arrest. Aortic valve replacement for severe symptoms is the second most frequent type of heart surgery. Apart from surgery, there is no medical therapy known to prevent or heal this condition. Population studies and other scientific research indicate that a high blood level of LDL-cholesterol (so called “bad” cholesterol) is a risk factor for developing aortic stenosis and may be involved in the pathological process. Treatment to lower LDL-cholesterol in many other types of patient has been shown to produce substantial reductions in the rates of heart attacks, strokes and other adverse outcomes.

The SEAS study is the first large-scale randomised trial to assess the effects of lowering LDL-cholesterol in patients with aortic stenosis. The study was initiated and designed by academic researchers in Scandinavia, and carried out at 173 clinical centres in Norway, Denmark, Sweden, Finland, Germany, UK and Ireland. It included 1873 patients with mild to moderate aortic stenosis without symptoms who were not considered to have a clear indication for treatment with cholesterol-lowering drugs. Patients were randomly assigned to receive either intensive cholesterol lowering with the combination of simvastatin (40 mg daily) and ezetimibe (10 mg daily) or matching placebo. The first patient was included in 2001. The study was completed according to the study plan when the last patient included had been followed for 4 years (March 2008). Vital status at the end of the study was established for all patients. All data have been checked for completeness and the data file for analysis was closed on 30 June 2008.

The scientific leadership of the study was a Steering Committee consisting of 14 academic representatives of centres in each of the participating countries and two members (a statistician and a coordinator) representing the funders. The SEAS study is funded by the pharmaceutical companies Merck Sharp & Dohme (MSD) and Schering-Plough who market the drugs being tested. All clinical endpoint events were adjudicated by an independent committee that was blinded to the study treatment allocation. The study was monitored by an independent Data Safety and Monitoring Board. Data collection was performed by MSD, and the data were analyzed by statisticians at Ullevål University Hospital in Oslo, Norway, and at MSD.

The primary endpoint of the SEAS study was “major cardiovascular events”, which is the composite of events associated with aortic valve disease and with atherosclerotic disease. The secondary endpoints were the two separate components of the primary endpoint: “aortic valve disease events” (surgical valve replacement, hospitalization because of heart failure, and cardiovascular death); and “atherosclerotic disease events” (non-fatal myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention, hospitalization because of unstable angina pectoris, non-haemorrhagic stroke and cardiovascular death). Subsidiary outcomes included echocardiographic evidence of aortic stenosis progression and safety.

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Compared with placebo, the combination of simvastatin and ezetimibe reduced LDL-cholesterol by about two-thirds, corresponding to a reduction of about 2 mmol/L (76 mg/dl), and this effect was sustained throughout the study. 688 patients had one or more primary endpoint events. No significant difference was observed between the treatment groups for the combined primary endpoint (333 patients with an event on LDL-lowering treatment versus 355 on placebo; hazard ratio [HR] 0.96; 95% confidence interval [CI] 0.83 to 1.12). Nor was there a significant difference for the secondary endpoint of aortic valve disease events alone (308 versus 326; HR 0.97; 95% CI 0.83 to 1.14). The combination of simvastatin and ezetimibe did, however, produce a statistically significant 22% (95% CI 3% to 37%; p=0.02) proportional reduction in the secondary endpoint of atherosclerotic events alone: 148 (15.7%) in the simvastatin plus ezetimibe group versus 187 (20.1%) in the placebo group.

The study therapy was generally well tolerated, with no significant differences between the treatment groups in the proportions of patients who stopped taking study treatment (irrespective of whether it was active or placebo). In the subsidiary safety analyses, a total of 158 patients were recorded with an adverse event attributed to cancer. More of these events were observed among patients assigned the combination of simvastatin and ezetimibe than among those assigned placebo (93 [9.9%] versus 65 [7.0%]; unadjusted p=0.03), and there were also slightly more cancer deaths (39 [4.1%] versus 23 [2.5%]; unadjusted p=0.05). These apparent differences were not related to any particular type of cancer and did not become significantly larger with more prolonged treatment.

The observed differences in cancer in the SEAS study are based on small numbers and could have occurred as a result of chance. In order to assess their relevance, the SEAS data have been provided to an independent academic group for combined analysis with data on cancer from the two other large trials of simvastatin and ezetimibe, which are still in progress. The SHARP (Study of Heart and Renal Protection) study is a randomized placebo-controlled trial of simvastatin and ezetimibe in 9400 patients with chronic kidney disease. The IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) study is a randomized double-blind trial of simvastatin and ezetimibe compared to simvastatin alone which has recruited 12,000 of a planned 18,000 patients with acute coronary disease.

In combination, the SHARP and IMPROVE-IT studies involve about 4 times as many cancers (in both treatment groups combined) as in the SEAS study. The analysis of SHARP and IMPROVE-IT does not support the suggestion of an increase in cancer that was raised by the subsidiary analyses of the relatively small numbers of cancers in the SEAS study. Independent analysis of these data was initiated and has been conducted and interpreted by the Clinical Trial Service Unit (CTSU) at the University of Oxford, UK. The CTSU also designed and is conducting the SHARP trial, which is funded by a research grant to the University of Oxford from MSD and Schering-Plough academic. Both the SHARP study and the analyses of cancer data have been conducted by the CTSU independently of the pharmaceutical companies.

In conclusion, the SEAS study has found that intensive LDL-cholesterol lowering with the combination of simvastatin and ezetimibe in patients with mild to moderate aortic stenosis does reduce the risk of coronary artery disease events (as has been shown for many other types of patient in previous trials) but not the rate of progression of aortic valve disease. The use of simvastatin and ezetimibe in such patients was generally well tolerated and safe.

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For more information, please, refer to the press release issued by the CTSU today.