Landmark Trials in Lipid Management

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Statins have emerged as first line treatment in management of patients with coronary artery disease. Inspite of treatment with statins, patients continue to have higher incidence of recurrent cardiovascular events. So there has been a continuous search for newer targets and better drugs. Recently few trials have been published that hold promise in our fight against cardiovascular disease.

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events. ODYSSEY LONG TERM trial

Jennifer G. Robinson, Michel Farnier, Michel Krempf, et al. N Engl J Med 2015;372:1489-99.

Alirocumab is a monoclonal antibody to proprotein convertase subtilisin–kexin type 9 (PCSK9). It has been shown to reduce low-density lipoprotein (LDL) cholesterol levels in phase 2 studies lasting 8 to 12 weeks in patients who are being treated with statins. This trial was conducted to assess long term efficacy and safety outcome.

The ODYSSEY LONG TERM trial is a phase 3, randomized, double-blind, placebo-controlled study which was conducted at 320 sites in 27 countries. The study was funded by Sanofi and Regeneron Pharmaceuticals. 2341 patients were randomly assigned in a 2:1 ratio to receive alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks. The patients were at high risk for cardiovascular events who had LDL cholesterol levels of 70 mg per deciliter or more and were receiving treatment with statins at the maximum tolerated dose, with or without other lipid-lowering therapy. The primary efficacy end point was the percentage change in calculated LDL cholesterol level from baseline to week 24.

At week 24, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL level was −62 percentage points (P<0.001). The treatment effect remained consistent over a period of 78 weeks. The rate of major adverse cardiovascular events (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; 95% CI, 0.31 to 0.90; p = 0.02). The alirocumab group had higher rates of injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%).

Perspective

Alirocumab, when added to statin therapy at the maximum tolerated dose, significantly reduced LDL cholesterol levels over 78 weeks. In a post hoc analysis, there was evidence of a reduction in the rate of cardiovascular events with alirocumab.

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events. Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER)

Marc S. Sabatine, Robert P. Giugliano, Stephen D. Wiviot et al. N Engl J Med 2015;372:1500-9.

Evolocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9),

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was found to significantly reduce low-density lipoprotein (LDL) cholesterol levels in short-term studies. OSLER-1 and OSLER-2 were two extension studies to obtain longer-term data.

In these two open-label randomized trials, 4465 patients were enrolled who had completed 1 of 12 phase 2 or 3 studies (parent trials) of evolocumab. Eligible patients were randomly assigned in a 2:1 ratio to receive either evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard therapy or standard therapy alone. Patients were followed for a median of 11.1 months with assessment of lipid levels, safety, and adjudicated cardiovascular events including death, myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure. Data from the two trials were combined.

As compared with standard therapy alone, evolocumab reduced the level of LDL cholesterol by 61%, from a median of 120 mg/dl to 48 mg/dl (P<0.001). Neurocognitive events were reported more frequently in the evolocumab group. The risk of adverse events, including neurocognitive events, did not vary significantly according to the achieved level of LDL cholesterol. The rate of cardiovascular events at 1 year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group, 0.47; 95% CI, 0.28 to 0.78; P = 0.003).

Perspective

During approximately 1 year of therapy, the use of evolocumab plus standard therapy, as compared with standard therapy alone, significantly reduced LDL cholesterol levels and reduced the incidence of cardiovascular events.

Fasting Triglycerides Predict Recurrent Ischemic Events in Patients With Acute Coronary Syndrome Treated With Statins

Gregory G. Schwartz, Markus Abt, Weihang Bao et al.
J Am Coll Cardiol 2015;65:2267–75

Patients with acute coronary syndrome (ACS) face a high risk of recurrent cardiovascular events. It is not clear whether triglycerides predict risk after ACS on a background of statin treatment. The current study examined relationships between fasting triglycerides and cardiovascular risk after ACS in 2 large trials of patients treated with statins(dal-OUTCOMES trial and atorvastatin arm of the MIRACL trial).

Analysis of dal-OUTCOMES included 15,817 patients (97% statin-treated) randomly assigned 4 to 12 weeks after ACS to treatment with dalcetrapib (a cholesteryl ester transfer protein inhibitor) or placebo and followed for a median 31 months. Analysis of MIRACL included 1,501 patients treated with atorvastatin 80 mg daily beginning 1 to 4 days after ACS and followed for 16 weeks. Fasting triglycerides were related to risk of coronary heart disease death, nonfatal myocardial infarction, stroke, and unstable angina in models adjusted for age, sex, hypertension, smoking, diabetes, high-density lipoprotein cholesterol, and body mass index.

Fasting triglyceride levels were found to be associated with both long-term and short-term risk after ACS. In dal-OUTCOMES, long-term risk increased across quintiles of baseline triglycerides ($p < 0.001$). The hazard ratio in the highest/lowest quintile was 1.50 (95% confidence interval: 1.05 to 2.15). In the atorvastatin group of MIRACL, short-term risk increased across tertiles of baseline triglycerides ($p =0.03$), with a hazard ratio of 1.51 (95% confidence interval: 1.05 to 2.15) in highest/lowest tertiles . The relationship of triglycerides to risk was independent of lowdensity lipoprotein cholesterol in both studies.

Perspective

Among patients with ACS treated effectively with statins, fasting triglycerides predict long-term and short-term cardiovascular risk. Triglyceride-rich lipoproteins may be an important additional target for therapy