ODYSSEY COMBO II: Alirocumab Significantly Improves Cholesterol Levels in Patients With High CV Risk

Written by Nicola Parry

Christopher P. Cannon, MD, Harvard Clinical Research Institute, Boston, Massachusetts, USA, presented results from the Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With Hypercholesterolemia trial [ODYSSEY COMBO II; NCT01644188]. This phase 3 trial showed that for patients with high cholesterol and existing or increased risk of cardiovascular disease (CVD), alirocumab significantly improved cholesterol levels as compared to ezetimibe, when added to regular statin therapy.

Over the last few decades, statins have been the mainstay of therapy for patients with high levels of low-density lipoprotein cholesterol (LDL-C). However, despite their significant clinical efficacy in most patients, a large residual risk remains for the development of atherosclerotic CVD [Baigent C et al. *Lancet*. 2010].

Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibition represents a promising new strategy for the treatment of hypercholesterolemia that may complement statin therapy [Switzer MP et al. *Cardiovasc Hematol Agents Med Chem.* 2013]. Monoclonal antibodies (mAbs) against PCSK9 have recently been shown to be highly efficacious in lowering LDL-C, with a favorable adverse event profile in early clinical trials. Alirocumab is an investigational mAb that targets and blocks PCSK9 [Roth EM, Diller P. *Future Cardiol*. 2014].

Official Peer-Reviewed Highlights From

ESC CONGRESS BARCELONA 2014

ODYSSEY COMBO II is a double-blind, parallel-group multicenter study being conducted over 104 weeks to evaluate the safety and efficacy of alirocumab, compared with ezetimibe, among patients (n = 720) with hypercholesterolemia who are at high cardiovascular risk and who had inadequate LDL-C control at baseline despite stable maximally tolerated statin therapy.

Inclusion criteria included either a history of CVD and LDL-C ≥ 1.81 mmol/L (≥ 70 mg/dL) or no history of CVD but with other risk factors and LDL-C ≥ 2.59 mmol/L (≥ 100 mg/dL) and receipt of a maximally tolerated daily statin dose (stable for > 4 weeks prior to screening). Exclusion criteria included receipt of other lipid-lowering therapies [Colhoun HM et al. *BMC Cardiovasc Disord*. 2014].

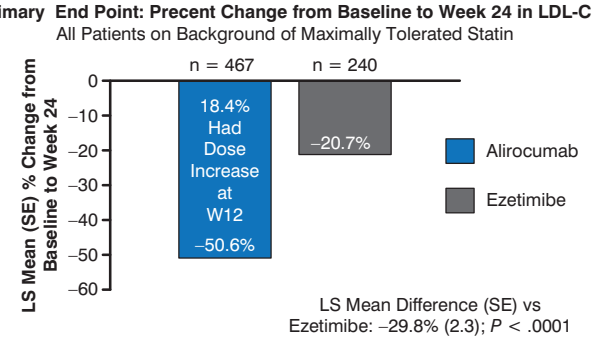
Patients were randomized 2:1 to either alirocumab (75 mg, subcutaneously, Q2W; n = 479) or ezetimibe (10 mg, daily; n = 241) in addition to statin therapy. After 12 weeks, the dose of alirocumab was increased to 150 mg, Q2W, if the week 8 LDL-C level was ≥ 1.81 mmol/L (70 mg/dL). The primary end point was the percentage change in LDL-C from baseline to week 24.

At week 24, alirocumab significantly reduced LDL-C levels as compared with ezetimibe (–50.6% vs –20.7%; $P < .0001$; Figure 1), with a least squares mean difference versus ezetimibe of –29.8% ($P < .0001$). This reduction was maintained to 52 weeks (–49.5% for alirocumab vs –18.3% for ezetimibe).

At week 24, the majority of patients in the alirocumab arm were able to achieve a prespecified LDL-C target of < 1.81 mmol/L (70 mg/dL), with 77.0% and 45.6% of alirocumab and ezetimibe patients, respectively, achieving this level ($P < .0001$). In a post hoc analysis of a lower LDL-C target of < 1.3 mmol/L (50 mg/dL), 60.3% of alirocumab versus 14.2% of ezetimibe patients, respectively, achieved this lower level.

In an analysis of all safety data collected until last the patient visit at week 52, alirocumab appeared to be well tolerated. Treatment-emergent adverse events (TEAEs) occurred in 71.2% patients in the alirocumab arm and 67.2% of those in the ezetimibe arm and led to discontinuation in 7.5% and 5.4% patients in each treatment arm, respectively. The most commonly reported TEAEs (occurring in ≥ 5% of patients in each treatment arm) were upper respiratory tract infection, accidental overdose, dizziness, and myalgia.

Figure 1. Effect of Alirocumab and Ezetimibe on LDL-C Levels at 24 Weeks



LDL-C, low-density lipoprotein cholesterol; LS, least squares (a statistical mean estimated from a linear model); SE, standard error.

Reproduced with permission from CP Cannon, MD.

Dr Cannon summarized that, in this population of patients with high CVD risk who were unable to achieve targets with maximal statin use, a treat-to-target approach with alirocumab (where ~80% of patients did not need to up-titrate the initial dose) allowed more than three-quarters of patients to achieve target LDL-C levels at week 24.

PARADIGM-HF: Novel Drug Reduced Outcomes, Improved Symptoms Better Than ACE Inhibition

Written by Mary Mosley

A greater reduction in cardiovascular (CV) death or heart failure (HF) hospitalization was achieved with an investigational drug, LCZ696, than with enalapril, an angiotensin-converting enzyme (ACE) inhibitor representing the gold standard treatment for HF that has been shown to reduce CV mortality in patients with HF with reduced ejection fraction (HFrEF) on top of optimal medical therapy in a large-scale, international, double-blind clinical trial. The trial was terminated early because of the improvement in CV death.

LCZ696 is an angiotensin receptor neprilysin inhibitor (ARNI), which combines a neprilysin inhibitor and the angiotensin receptor blocker (ARB) valsartan, to simultaneously counteract maladaptive mechanisms caused by degradation of vasoactive peptides by neprilysin and deficiencies in the endogenous adaptive elements in HF, stated Milton Packer, MD, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

The Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial [PARADIGM-HF; McMurray JJV et al. *N Engl J Med*. Published online August 30, 2014] randomized patients with clinically stable NYHA class II to IV HF, left ventricular ejection fractions (LVEFs) ≤40%, and modestly increased levels of brain natriuretic peptide (≥150 pg/mL) after a 2-week run-in phase to LCZ696 200 mg BID (n=4212) or enalapril 10 mg BID (n=4187). During the run-in, patients were switched from their current ACE inhibitor or ARB to enalapril 10 mg BID for 2 weeks, and then, to ensure tolerance of both drugs, LCZ696 was added at escalating doses (100 mg BID for 2 weeks, then 200 mg BID for 2 weeks).

The median follow-up period was 27 months, and the average daily doses at the last visit were LCZ696 375 mg and enalapril 18.9 mg. The patients were representative of patients with HF seen in the general community. They were aged 63.8 years, 22% were women, 60% had ischemic cardiomyopathy, and the LVEF was ~30%.

The results for the composite primary end point of CV death or HF hospitalization, for its components, and the secondary end point of all-cause mortality are detailed in Table 1. For all prespecified subgroups, LCZ696 was more effective than enalapril in reducing primary end point events and CV mortality.

Quality of life as measured by the Kansas City Cardiomyopathy Questionnaire at 8 months was significantly improved with LCZ696 versus enalapril ($P=.001$). There was no significant difference between the groups for new-onset atrial fibrillation (HR, 0.97; 95% CI, 0.72 to 1.31; $P=.84$) or protocol-defined decline in renal function (HR, 0.86; 95% CI, 0.65 to 1.13; $P=.28$).

Regarding safety, more patients in the enalapril group than the LCZ696 group discontinued treatment because of hypotension, hyperkalemia, or worsening renal function, and blinded, adjudicated angioedema was similar in the 2 groups (Table 2).

Dr Packer stated that LCZ696 was more effective than guideline-recommended doses of enalapril in patients with HFrEF to reduce all-cause mortality and CV death, the symptoms and physical limitations of HF, and the risk for HF hospitalization. LCZ696 was better tolerated and less likely to be discontinued because of an adverse event than enalapril. The rates of cough, hyperkalemia, and renal impairment were lower with LCZ696 than with enalapril, as was drug discontinuation for hypotension. The reduction in CV mortality with LCZ696 over enalapril was similar to that achieved when an ACE inhibitor is compared with placebo, indicating that LCZ696 doubles the effect of ACE inhibitors on CV death. These results provide robust support for using the novel drug instead of an ACE inhibitor or ARB, he stated.