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Original Article

A randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan (ODYSSEY KT)

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BACKGROUND: Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, has been shown to provide significant reductions in low-density lipoprotein cholesterol (LDL-C). Data about its efficacy and safety in patients from South Korea and Taiwan are limited.

OBJECTIVE: ODYSSEY KT assessed the efficacy and safety of alirocumab in patients from South Korea and Taiwan.

METHODS: Patients with hypercholesterolemia at high cardiovascular risk who were on maximally tolerated statin were randomized (1:1) to alirocumab (75 mg every 2 weeks, with dose increase to 150 mg every 2 weeks at week 12 if LDL-C ≥70 mg/dL at week 8) or placebo for 24 weeks. The primary efficacy endpoint was percentage change in LDL-C from baseline to week 24. Safety was assessed throughout.

RESULTS: At week 24, alirocumab changed LDL-C levels by −57.1% (placebo: +6.3%). In the alirocumab group, 9 patients (9.5%) received dose increase at week 12. At week 24, 85.8% of patients

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in the alirocumab group reached LDL-C <70 mg/dL (placebo: 14.2%; $P \leq .0001$ vs placebo). Alirocumab significantly improved non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B, total cholesterol, lipoprotein (a), and HDL-C vs placebo ($P \leq .05$). Two consecutive calculated LDL-C values <25 mg/dL were recorded in 27.8% of alirocumab-treated patients. Overall, 58.8% (alirocumab) and 61.8% (placebo) of patients experienced treatment-emergent adverse events; 2.1% and 1.0% discontinued treatment due to treatment-emergent adverse events, respectively.

CONCLUSION: Alirocumab significantly improved LDL-C, apolipoprotein B, non-HDL-C, lipoprotein (a), HDL-C, and total cholesterol in Asian patients. Alirocumab was generally well tolerated. These findings are consistent with ODYSSEY findings to date.

Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) levels correlate with an increased risk of coronary heart disease (CHD).[1] An increasing trend of cardiovascular (CV) mortality has been observed in Taiwan and South Korea.[2,3] Recent lipid guidelines have recommended LDL-C targets of <70 or <100 mg/dL in patients with very-high or high CV risk, respectively.[4,5] The CEPHEUS Pan-Asian survey showed that LDL-C goals were reached by 34.9% (LDL-C <70 mg/dL) and 55.4% (LDL-C <100 mg/dL) of patients with very-high and high CV risk, respectively.[6] Recent American College of Cardiology and European Society of Cardiology/European Atherosclerosis Society consensus statements recommend that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may be considered in patients with very-high or high CV risk who have high baseline LDL-C levels, despite maximally tolerated statin and ezetimibe therapies.[7,8] PCSK9 is a key regulator for cholesterol homeostasis, downregulating the low-density lipoprotein receptor protein and thus increasing LDL-C levels.[9]

Alirocumab, a fully human monoclonal antibody to PCSK9, with the dosing regimen 75 mg every 2 weeks (Q2W) (with possible dose increase to 150 mg Q2W) and 150 mg Q2W reduced LDL-C levels by up to 61% in addition to background statin therapy with or without other lipid-lowering therapies (LLTs) or as monotherapy in phase 3 ODYSSEY clinical studies.[10–16] Data regarding the efficacy and safety of alirocumab in patients from Asia are limited.[17,18] In phase 1 and 2 studies conducted in Japan, alirocumab treatment significantly reduced LDL-C levels and was well tolerated in healthy subjects or in patients with hypercholesterolemia.[18] In the phase 3 ODYSSEY Japan study, which enrolled Japanese patients with heterozygous familial hypercholesterolemia or high CV risk and hypercholesterolemia, the change in LDL-C levels from baseline to week 24 was −62.5% in the alirocumab 75/150 mg Q2W group (placebo: +1.6% increase).[17]

The phase 3 ODYSSEY KT study was a placebo-controlled study evaluating the efficacy and safety of alirocumab 75 mg Q2W (with possible dose increase to 150 mg Q2W) as add-on to statin therapy in patients with high CV risk and inadequately controlled hypercholesterolemia in South Korea and Taiwan. We also conducted a pooled safety analysis of alirocumab in a broader patient population from Asia, including an alirocumab phase 2 study from Japan and ODYSSEY phase 3 studies.

Methods

ODYSSEY KT was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in 27 active centers (which screened at least 1 patient) from 16 study centers in South Korea and 11 in Taiwan. The study was conducted in accordance with the ethical principles in the Declaration of Helsinki and applicable amendments, and the International Conference on Harmonization guidelines for Good Clinical Practice. The protocol was approved by the relevant institutional review boards or independent ethics committees. All participating patients provided written informed consent.

Patients

The study enrolled patients (aged ≥18 years) with high CV risk who had inadequately controlled hypercholesterolemia on maximally tolerated statin therapy at a stable dose for at least 4 weeks before screening. High CV risk was defined as history of CV disease (CVD), moderate chronic kidney disease, or diabetes with multiple risk factors. Inadequately controlled hypercholesterolemia was defined as LDL-C ≥70 mg/dL in patients with a history of documented CVD, or LDL-C ≥100 mg/dL in patients without such history. Maximally tolerated statin therapy was defined as atorvastatin 40 to 80 mg daily, rosuvastatin 20 mg daily, or simvastatin 40 mg daily. Patients were also eligible if they were receiving a daily dose of atorvastatin, rosuvastatin, or simvastatin considered appropriate by the investigator.

Background treatment with LLTs other than statins was allowed for all patients, provided that they had been on a stable dose for at least 4 weeks before the screening visit.