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Original Article

Alirocumab in high-risk patients: Observations from the open-label expanded use program

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LDL-C;
Statin intolerance;
ODYSSEY

BACKGROUND: The alirocumab expanded use program provided open-label access to alirocumab before its commercial availability to patients with severe hypercholesterolemia not controlled with maximally tolerated doses of standard-of-care lipid-lowering therapy.

OBJECTIVE: To describe the safety and lipid-lowering efficacy of alirocumab in high-risk patients who were likely to be early users of proprotein convertase subtilisin/kexin type 9 inhibitors after approval.

METHODS: Patients with heterozygous familial hypercholesterolemia (HeFH) and/or coronary heart disease (CHD) and baseline low-density lipoprotein cholesterol (LDL-C) of ≥160 mg/dL on maximally tolerated lipid-lowering therapy were enrolled and received alirocumab 150 mg every 2 weeks for 24 weeks. Patients were permitted use of all available statins; those not taking any dose of statin could also be enrolled.

RESULTS: Of 100 enrolled patients, 93 were white, 62 were women, and overall mean age was 58 years; 61 had HeFH, 3 had unknown type of familial hypercholesterolemia, 66 had CHD, and 30 had both familial hypercholesterolemia and CHD. Sixty-four patients were identified by their providers to have some level of statin intolerance; of these, 47 were not on statin. Alirocumab reduced LDL-C on average from 221 mg/dL at baseline to 102 mg/dL by week 24 (−55%). Treatment-emergent adverse events were experienced in 61% of patients and treatment-emergent adverse events leading to permanent treatment discontinuation in 3% of patients; no deaths occurred.

CONCLUSIONS: Safety and efficacy observations from the open-label alirocumab expanded use program of very high-risk patients with HeFH and/or CHD and baseline LDL-C of ≥160 mg/dL uncontrolled by maximally tolerated lipid-lowering therapy were consistent with those in the placebo/ezetimibe-controlled ODYSSEY trials.

Introduction

Patients with severely elevated low-density lipoprotein cholesterol (LDL-C) levels have increased risk of cardiovascular disease and may require additional

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LDL-C-lowering treatment in addition to statin and other nonstatin therapies.[1–3] The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab has been shown in the ODYSSEY phase 3 clinical trial program to be generally well tolerated and produce significant reductions in LDL-C and other lipid levels in patients with heterozygous familial hypercholesterolemia (HeFH),[4–7] statin intolerance,[8] and high cardiovascular risk.[7,9,10] The results of the ODYSSEY phase 3 trials supported the approval of alirocumab in July 2015 as adjunct therapy to diet and maximally tolerated statin therapy in patients with HeFH or clinical atherosclerotic cardiovascular disease who need additional LDL-C reduction.[11]

Before its approval in the US, based on numerous requests for access to alirocumab by health care providers, Sanofi and Regeneron Pharmaceuticals, Inc., implemented an expanded use program for alirocumab in high-risk patients who met stringent eligibility criteria. Based on clinical data from the ODYSSEY phase 3 trials, and in accordance with the US Food and Drug Administration regulations,[12] this program was restricted to patients with HeFH or coronary heart disease (CHD) with severe hypercholesterolemia not controlled with maximally tolerated standard-of-care lipid-lowering therapy.

Safety and lipid-lowering efficacy of alirocumab (150 mg every 2 weeks [Q2W] for 24 weeks) were assessed in very high-risk patients with severe hypercholesterolemia who were likely to be early users of PCSK9 inhibitors after approval. Observations from this program provide insight into early clinical use of alirocumab in high-risk patients that are complementary to the clinical findings from the ODYSSEY program.

Methods

The alirocumab expanded use program was a prospective, multicenter, single arm, open-label, expanded-access program in the US. The program included patients with HeFH and/or CHD and baseline LDL-C of ≥160 mg/dL (≥4.14 mmol/L) on standard-of-care maximally tolerated lipid-lowering therapy in addition to diet for at least 3 months. Unlike most of the ODYSSEY development studies, which required all patients to be taking maximally tolerated doses of simvastatin, atorvastatin, or rosuvastatin, the expanded use program permitted use of all available statins (which were to be at maximal tolerated doses); high-dose statin was defined as the highest dose of each statin. Patients who were documented as being unable to tolerate any dose of statin were included in the program. Diagnosis of HeFH was required to be made either by genotyping or by clinical criteria based on either the Simon Broome criteria (with a diagnosis of "definite familial hypercholesterolemia [FH]")[13,14] or the World Health Organization/Dutch Lipid Network criteria (score > 8 points).[14] CHD was defined as one or more of the following: acute myocardial infarction, silent myocardial infarction, unstable angina, coronary revascularization procedure (eg, percutaneous coronary intervention or coronary artery bypass graft

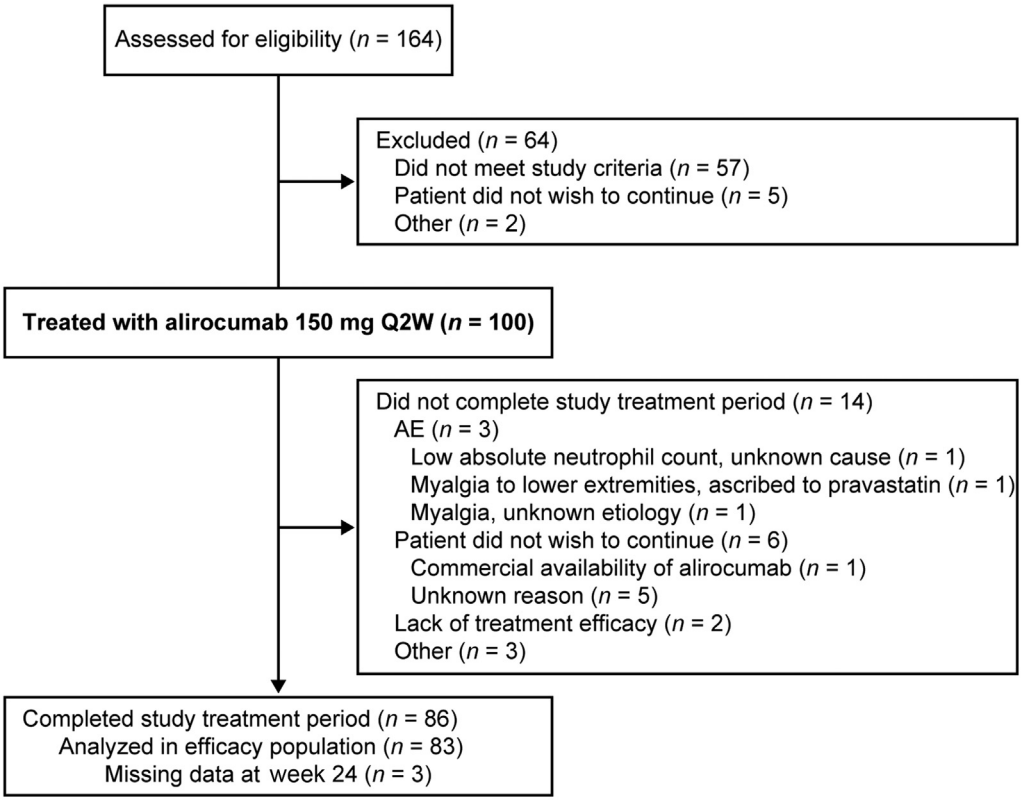

Figure 1 Patient flow through the alirocumab expanded use program. AE, adverse event; Q2W, every 2 weeks.