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Lack of Cross-Reactivity Allergy Following a Switch from Alirocumab to Evolocumab

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Abstract
The proprotein convertase subtilisin/kexin type 9 (PCSK9) gene and gain-of-function mutations were first described in 2003. The gain-of-function mutations observed were associated with low-density lipoprotein-cholesterol (LDL-C) levels in the 400's, in addition to premature cardiovascular disease. Subsequent loss-of-function experiments conducted in mice demonstrated marked reductions in plasma cholesterol levels in the absence of PCSK9. Physiologically, PCSK9 serves as a chaperone protein and functions to reduce low-density lipoprotein (LDL) receptor recycling; consequently, less LDL-C is removed from circulation and serum lipid concentrations become elevated. Inhibition of PCSK9 prevents LDL receptor degradation and preserves receptor recycling to the hepatocyte surface; this in turn results in reduced LDL-C levels. We report a lack of cross-sensitivity following the administration of evolocumab after an allergic reaction to alirocumab.

Keywords
PCSK9, alirocumab, evolocumab, allergy

Lack of Cross-Reactivity Allergy Following a Switch from Alirocumab to Evolocumab

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Abstract

The proprotein convertase subtilisin/kexin type 9 (PCSK9) gene and gain-of-function mutations were first described in 2003. The gain-of-function mutations observed were associated with low-density lipoprotein-cholesterol (LDL-C) levels in the 400's, in addition to premature cardiovascular disease. Subsequent loss-of-function experiments conducted in mice demonstrated marked reductions in plasma cholesterol levels in the absence of PCSK9. Physiologically, PCSK9 serves as a chaperone protein and functions to reduce low-density lipoprotein (LDL) receptor recycling; consequently, less LDL-C is removed from circulation and serum lipid concentrations become elevated. Inhibition of PCSK9 delays LDL receptor degradation and preserves receptor recycling to the hepatocyte surface; this in turn results in reduced LDL-C levels. Clinical studies have demonstrated consistent reductions in LDL-C of 50% to 60%. We report a lack of cross-reactivity following the administration of evolocumab after an allergic reaction to alirocumab.

Introduction

Two PCSK9 inhibitors, alirocumab and evolocumab, have been commercially available in the United States since the summer of 2015 and each has demonstrated appreciable and consistent reductions in LDL-C levels. Both agents are indicated as an adjunct to diet for patients on maximally tolerated statin therapy with clinical atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia who require additional LDL-C lowering.[1,2] In addition, evolocumab is indicated for homozygous familial hypercholesterolemia.[2] Although prospective cardiovascular outcome studies are currently ongoing, a recent meta-analysis reported a significant decrease in all-cause mortality (odds ratio [OR] 0.45; 95% confidence interval [95% CI] 0.23 to 0.86; p = 0.015) and a non-significant decrease in cardiovascular mortality (OR 0.50; 95% CI 0.23 to 1.10; p = 0.084).[3] The most common reported adverse reactions for alirocumab include: nasopharyngitis, injection site reactions and influenza.[1] In addition to the adverse reactions associated with alirocumab, influenza, upper respiratory tract infections and back pain are cited as common adverse reactions for evolocumab.[2]

Case Report

We report a case of a 63-year-old female who was initiated on alirocumab 75 mg, the recommended starting dose,[1] once every 2 weeks for the management of her dyslipidemia. Her past medical history is remarkable for coronary calcifications, peripheral vascular disease, including carotid plaque, likely heterozygous familial hypercholesterolemia, hypertension, dyslipidemia, anemia, obesity, status-post Roux-en-Y gastric bypass surgery, ischemic colitis, which was associated with a gastrointestinal bleed, osteopenia and drop attacks causing a fractured shoulder. She also has a significant family history for premature heart disease as her brother died from a myocardial infarction (MI) at 50 years of age, her father died from an MI at age 46 and her mother experienced an MI and stroke at age 60. At the time of referral, the patient was receiving moderate-intensity statin therapy, rosuvastatin 5 mg once daily, with an LDL-C level of 135 mg/dL. Additional medications the patient was taking concurrently, which remained unchanged for over a year, included: hydrochlorothiazide 25 mg once daily, lisinopril 20 mg twice daily, omeprazole delayed release 40 mg twice daily, sucralfate 1 g / 10 mL two teaspoonfuls four times daily, CoQ10 once daily and a multivitamin once daily.

Following the administration of the first dose of alirocumab, the patient described a low-grade rash that spread from her torso to her arms, which resolved after 1 week. Two weeks later she self-administered her second dose of alirocumab and a more severe rash developed on her torso. Since this patient is at high risk for cardiovascular events, a mutual and informed decision was made to switch her to evolocumab. To the best of our knowledge, there are currently no published case reports describing an allergic reaction to one PCSK9 inhibitor and a subsequent challenge with the alternative agent.

Sixteen days after her last dose of alirocumab, the patient self-administered her first dose of evolocumab 140 mg, a recommended starting dose,[2] at our outpatient practice. In the abundance of caution, the patient received diphenhydramine prophylactically and remained under close supervision for thirty minutes with epinephrine nearby. After 10 months of biweekly evolocumab injections, this patient has not received any additional prophylactic diphenhydramine nor has she manifested any symptoms of an allergic reaction. Her cholesterol continues to remain significantly improved from baseline. The patient's history of lipid results is presented in **Tables 1** and **2**.

Dates	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Non-HDL-C (mg/dL)	TG (mg/dL)
Baseline					
9/18/2015	243	135	81	162	134
Alirocumab [Initiated: 9/21/2015, last dose received 10/05/2015]					
10/20/2015	160	34	104	56	114
Switch to Evolocumab [Initiated: 10/21/2015]					
11/17/2015	129	28	86	43	75

Abbreviations: HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; non-HDL-C – non-high-density lipoprotein cholesterol; TC – total cholesterol; TG – triglycerides

Table 1: Baseline and follow-up lipid laboratory information after the initiation of both PCSK9 inhibitors.

One reason that may explain the lack of immunogenicity observed following a challenge with the second PCSK9 inhibitor is the difference in the inactive ingredients of each product. The inactive ingredients in alirocumab include: histidine, polysorbate 20, sucrose and water for injection,[1] while the inactive ingredients for evolocumab include acetate, polysorbate 80, proline, water for injection and sodium hydroxide[2]. According to the prescribing information, hypersensitivity reactions, including serious events (e.g., hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization) have been reported with alirocumab; allergic reactions

were reported in 8.6% of patients receiving alirocumab and 7.8% of patients receiving placebo, with 0.6% and 0.2%, respectively, discontinuing treatment because of an allergic reaction.[1] Allergic reactions occurred in 5.1% of patients receiving evolocumab compared to 4.7% of patients receiving placebo.[2] Although it is not listed in the prescribing information, a personal communication with the manufacturer of evolocumab described one patient who reported a hypersensitivity reaction and subsequently discontinued evolocumab therapy.

Certain drug information resources (e.g., Lexicomp®) discourage the use of an alternative PCSK9 inhibitor when an allergic reaction occurs, because of similarities in structures.[4] However, this is not an absolute contraindication, nor is it stated in the package insert for either agent.[1,2]

This case reports the successful use of an alternative PCSK9 inhibitor in a patient with a documented allergic reaction to initial PCSK9 inhibitor therapy.

PCSK9 Inhibitor	Percent Reduction in Lipid Values from Baseline				
	TC	LDL-C	HDL-C	Non-HDL-C	TG
Alirocumab Compared to Baseline (%)	-34.2	-74.8	+28.4	-65.4	-14.9
Evolocumab Compared to Baseline (%)	-46.9	-79.3	+6.2	-73.5	-44.0
Evolocumab Compared to Alirocumab (%)	-19.4	-17.6	-17.3	-23.2	-34.2

Abbreviations: HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; non-HDL-C – non-high-density lipoprotein cholesterol; PCSK9 - proprotein convertase subtilisin/kexin type 9; TC – total cholesterol; TG – triglycerides

Table 2: Percent change in lipids compared to baseline for each PCSK9 inhibitor and the percent change in lipids following the switch to evolocumab compared to alirocumab.

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