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Case Report

Case reports of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition nonresponse

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Abstract: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, a novel class of monoclonal antibodies, reduces low-density lipoprotein cholesterol levels and improves cardiovascular outcomes. Given the short time frame, these agents have been available for use; reports of nonresponse to the PCSK9 inhibitor therapy are scarce in literature. We describe 2 cases with substantially lesser than expected low-density lipoprotein cholesterol lowering on PCSK9 therapy. Nonresponse to PCSK9 inhibition was attributed to autosomal recessive hypercholesterolemia (secondary to low-density lipoprotein receptor adaptor protein 1 mutation) and plasmapheresis after PCSK9 inhibitor drug injections. Additional PCSK9 inhibitor nonresponders are likely to emerge as the use of these agents increases overtime.
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Proprotein convertase subtilisin/kexin type 9 (PCSK9), a serine protease enzyme, facilitates the endocytosis and breakdown of the low-density lipoprotein receptor (LDL-R) in the liver. This limits the LDL-R recycling to the hepatocyte surface for LDL clearance and therefore leads to increased LDL cholesterol (LDL-C) levels in the plasma. Gain-of-function mutations in the PCSK9 gene have been associated with familial hypercholesterolemia (FH). Cholesterol-lowering statin therapy has also been shown to increase circulating PCSK9 levels.[1]

In 2015, 2 PCSK9 inhibitor (PCSK9i) monoclonal antibodies, alirocumab, and evolocumab, were approved by the United States Food and Drug Association, as an adjunct to diet and maximally tolerated statin therapy, for further LDL-C lowering in patients with FH or those with clinical atherosclerotic cardiovascular disease (ASCVD). These monoclonal antibodies bind free plasma PCSK9 and inhibit its function. Therefore, lower levels of free PCSK9 bind LDL-R, thereby increasing recycling LDL-

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Rs back to the surface of the hepatocyte and consequently, increasing LDL clearance.[2]

The PCSK9i drugs can lower LDL-C levels by 50%–60% when added to background statin therapy. A recent outcomes study has shown evolocumab further reduces recurrent events in patients with ASCVD[3] without serious side effects compared with placebo.[4] The production of antidrug antibodies (ADA) against the PCSK9i leads to the discontinuation of bococizumab; however, the currently available agents have had no reported issues with antidrug antibody and overall their discontinuation rate due to side effects has been low.[3,4]

Given the short time this class of therapy has been available, reports of less-than-expected response in LDL-C lowering to PCSK9i, although present,[5] are limited in number. In our lipid clinic, we have, to date treated 37 patients with PCSK9 inhibitors of which 2 have shown a nonresponse to PCSK9i.

Here we describe the 2 nonresponders to PCSK9i therapy.

Case 1

A 30-year-old South Asian man with the past medical history significant for FH and premature coronary artery disease (status after coronary artery bypass grafting) first presented to our clinic for secondary prevention at age 28 years. At age 26 years, he was diagnosed with phenotypic FH with an untreated total cholesterol (TC) of 450 mg/dL (11.6 mmol/L) and an LDL-C of 380 mg/dL (9.8 mmol/L). He had tried several statin therapies and attained the best lipid reduction with rosuvastatin 40 mg daily, ezetimibe 10 mg daily, colesevelam 3.75 gm daily, and niacin 1 gm daily: TC 182 mg/dL (4.7 mmol/L); LDL-C of 143 mg/dL (3.7 mmol/L) (62% reduction from baseline untreated levels of LDL-C). Family history was significant for 2 brothers with TC levels between 450 and 500 mg/dL (10.3–12.9 mmol/L) and tendon xanthomas. The patient's parents, who had a consanguineous marriage, reported normal lipid levels.

After establishing care in our clinic, the patient's lowest LDL-C, with a 4-drug medication regimen (as aforementioned) as well as optimal lifestyle adjustment, was 134 mg/dL (3.47 mmol/L) (total reduction in LDL-C of approximately 66%). The patient was enrolled in the SPIRE 1 (Evaluation of PCSK9 inhibitor Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects) trial in October 2014. As per protocol, he completed the blinded study in January 2015 without the knowledge about treatment assignment. During the trial, he had 3 flagged alerts for LDL-C being at least 30 points over 70 mg/dL. Before beginning of the trial, his LDL-C was 134 mg/dL (3.47 mmol/L), and after completing the trial, LDL-C was noted to be higher (180 mg/dL [4.65 mmol/L] to 200 mg/dL [5.17 mmol/L]). At the completion of the trial, treatment assignment revealed that he was in the placebo arm. To be noted, the patient later admitted that during the course of the trial, he stopped taking his niacin medication intermittently due to severe "flushing", which resolved after discontinuation of the medicine.

We started him on subcutaneous injections of evolocumab 140 mg/dL every 2 weeks in addition to rosuvastatin 40 mg daily, ezetimibe 10 mg daily, and colesevalam 3.75 gm daily. Laboratory results before evolocumab initiation were TC 302 mg/dL (7.81 mmol/L); triglycerides (TGs) 118 mg/dL (1.32 mmol/L); LDL-C 250 mg/dL (6.47 mmol/L); and high-density lipoprotein cholesterol (HDL-C) 32 mg/dL (0.82 mmol/L). The first lipid panel after 3 doses of evolocumab 140 mg every 2 weeks showed that the TC was 249 mg/dL (6.44 mmol/L); LDL-C was 204 mg/dL (5.28 mmol/L) (18% reduction), HDL-C was 33 mg/dL (0.85 mmol/L), and TGs was 89 mg/dL (1.00 mmol/L).

Owing to this poor response to the current regimen for over 6 months (LDL-C change approximate $\leq$18%), the patient was switched to alirocumab 150 mg/dL injections every 2 weeks along with same oral lipid drug combination. After the first 3 doses of alirocumab, his lipid levels were TC 423 mg/dL (10.94 mmol/L), LDL-C 376 mg/dL (9.74 mmol/L), HDL-C 36 mg/dL (0.93 mmol/L), TGs 154 mg/dL (1.74 mmol/L). Medication compliance was discussed at every visit. Appropriate injection technique and adherence was assessed by observation of PCSK9i injections by the patient in our clinic with expert staff.

We proceeded with genetic testing for FH and ADA with the patient's agreement. He tested negative for ADA against evolocumab. Furthermore, unblinded treatment assignment from the SPIRE trial revealed that the patient was assigned to the placebo arm of the trial; hence, no ADA against bococizumab were tested.

Genetic testing for FH importantly showed that he was positive for homozygous low-density lipoprotein receptor adaptor protein-1 (LDLRAP1) mutation consistent with autosomal recessive hypercholesterolemia (ARH). The patient's homozygous genetic variant is caused by a frameshift mutation located in a string of 7 guanine residues in exon 1 (deletion of guanine at nucleotide 71) on the LDLRAP1 gene.

Currently, our patient has been started on LDL apheresis every 2 weeks with LDL-C levels of $<$100 mg/dL after therapy. PCSK9i therapy was stopped and the use of microsomal transfer protein inhibitor, lomitapide, was discussed with the patient; however, given the increased risk of fatty liver disease and patient's personal preference, this was not started.

Case 2

A 71-year-old man with a past medical history of mixed hyperlipidemia with FH range LDL-C levels since early 30s and peripheral demyelinating neuropathy (status after therapeutic plasma exchange [TPE]) was referred to us for dyslipidemia management.

He was initially started on statins in his 40s, which he took for approximately 17 years with alternating regimens