Background

PCSK9 inhibitors (PCSK9is) are monoclonal antibodies that bind to serum PCSK9 and delay LDL receptor degradation. Two PCSK9is are commercially available: evolocumab and alirocumab. FDA approved indications include LDL cholesterol (LDL-C) lowering on maximally tolerated statin therapy in patients with ASCVD and Familial Hypercholesterolemia (FH). Among patients with LDL-C receptor mutations, those with partial loss of function typically respond well to PCSK9 inhibition, while those with homozygous receptor-negative mutations, i.e. the null-null genotype, have minimal to no response.

Objective

To describe PCSK9I non-response in a patient with preserved LDL receptor function.

Methods

A 67 year old female with lifelong off-treatment LDL-C in the range of 250-280 mg/dL and statin intolerance presented to our clinic. The family history was limited by premature non-cardiac death of both parents. Two of her children have normal lipid panels; the third was not evaluated. The physical exam was unremarkable. The initial off-treatment lipid panel showed a total cholesterol of 366 mg/dL and an LDL-C of 283 mg/dL, with normal triglycerides and HDL-C. Her LDL levels were strongly suggestive of heterozygous FH, and she was treated accordingly. The patient was re-challenged with pitavastatin 2 mg. On maximally tolerated dose frequency of 5 times/week she experienced a LDL reduction of 31.1%, suggestive of preserved LDL receptor function. Subsequent adverse effects led to discontinuation of pitavastatin. Monotherapy with alirocumab was initiated at 75 mg subcutaneously every 2 weeks and up-titrated after 8 weeks to 150 mg. Subsequently she was given a trial of evolocumab 140 mg. Injection technique training and direct observation of periodic injections were used to support adherence.

Results

LDL-C levels after three and seven weeks of therapy with alirocumab 75 mg were 235 mg/dL and 239 mg/dL respectively. Three and seven weeks after up-titration, LDL-C was 249 mg/dL and 292 mg/dL, respectively. Total duration of alirocumab therapy was 16 weeks. LDL-C was 253 mg/dL after 3 weeks of therapy with evolocumab, at which time PCSK9 inhibitor therapy was discontinued due to lack of clinical response. The response to statin therapy was 16 weeks. LDL-C was 249 mg/dL and 292 mg/dL, respectively. Total duration of alirocumab therapy was 249 mg/dL and 292 mg/dL, respectively. Three weeks after up-titration, LDL-C was 235 mg/dL and 239 mg/dL, respectively. 

Conclusions

Absence of LDL receptor activity is not the only mechanism of PCSK9I inhibitor non-response. An alteration in the PCSK9 binding site for alirocumab and evolocumab is proposed as a hypothetical mechanism for non-response in this patient. Other alternatives include immunogenicity, noncompliance, or faulty injection technique.