Commentary

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PCSK9 Inhibitors or Ezetimibe as the Second Line Add-on to Statin Therapy

Aniruddha Singh*

Cardiologist, University of Kentucky, Bowling Green, USA

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***Corresponding author:** Aniruddha Singh

Aniruddha.Singh@uky.edu

Cardiologist, University of Kentucky, Bowling Green, USA.

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The Proprotein convertase subtilisin/kexin-9 inhibitors (PCSK9i): Evolocumab and Alirocumab, have shown promising results in clinical practice recently. These agents efficacious having shown to Lower Low-density Lipoprotein (LDL) by 50-65% [1,2]. Two large outcomes trials [3,4] have demonstrated that both Evolocumab and Alirocumab are effective in reducing major adverse cardiac events in high risk Atherosclerotic Cardiovascular Disease (ASCVD) conditions. Most recent multi-society guidelines are endorsing the use of PCSK9i in patients at very high cardiovascular risk [5]. A joint consensus statement from the European Society of Cardiology and European Atherosclerosis Society suggested that PCSK9i could be considered in patients with clinical ASCVD treated with maximal tolerated statin therapy and/or ezetimibe who have continued to have LDL-C >100 mg/dL [6]. Despite all the available data supporting its efficacy and clinical benefits, the cost-effectiveness and economic value of PCSK9 inhibitors has been reported to be 'low value' [5]. The guidelines have also felt that the economic value of PCSK9i could be improved by restricting its use to patients at high risk of ASCVD events [5]. In this regard the use of ezetimibe therapy as an add-on to statin treatment has been recommended first prior to initiating PCSK9i [6].

Mechanism of action of PCSK9i

PCSK9 inhibits LDL receptor recycling. The binding of PCSK9 to the LDL receptors leads to degradation of the LDL receptors by activating lysosomal degradation, in turn preventing LDL receptors from returning to the surface of the hepatocyte to bind to additional LDL particles.

Two antibodies against PCSK9 are currently available: Alirocumab and Evolocumab, which bind with a 1:1 ratio to circulating PCSK9. Once the antibody binds to PCSK9, PCSK9 is unable to attach to LDL receptors which in turn inhibit the receptors degradation. This leads to an increased expression of LDL receptors on hepatocytes, leading subsequently to rapid clearance of LDL particles [7].

Mechanism of action of Ezetimibe

Ezetimibe inhibits intestinal cholesterol absorption by selectively blocking the Niemann-Pick C1-like 1 protein in the jejunal brush border. This leads to lower uptake of intestinal lumen micelles into the enterocyte leading to less cholesterol absorption.

Available scientific evidence for PCSK9i

The FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) tested clinical outcomes when Evolocumab was added to maximum statin therapy in ASCVD patients [8]. A total of 27,564 patients were randomized to either Evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or placebo. Patients who were treated with Evolocumab had close to 60% LCL-C lowering. After a follow up period of 24 months, the combined endpoint of cardiovascular mortality, myocardial infarction, stroke, hospitalization related to angina, or revascularization was seen in 9.8% of patients in the Evolocumab group compared to 11.3% in the placebo group.

The Odyssey Outcomes trial (Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome during Treatment with Alirocumab) evaluated outcomes in patients treated with alirocumab after acute coronary syndrome who were already on maximally tolerated statins [9]. A total of 18,924 patients were randomized to either Alirocumab or placebo. The composite endpoint of CV death, nonfatal myocardial infarction, fatal and nonfatal stroke, or hospitalization due to angina occurred less the Alirocumab arm compared to placebo (9.5% Vs. 11.1%, p=0.003).

The GLAGOV (Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial was designed to study the effect of using PCSK9 inhibition on atherosclerotic plaque burden and regression [10]. Over a period of 18 months a total of 968 patients with ASCVD were treated with either Evolocumab or placebo. LDL-C levels were significantly lower in the Evolocumab group compared to the placebo group. Atheroma volume was assessed using intravascular ultrasound, which demonstrated larger reduction in the Evolocumab group compared to placebo.

Scientific evidence supporting Ezetimibe

In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial); 18, 144 patients after acute coronary syndrome were randomized to 40 mg ezetimibe/simvastatin or 40 mg placebo/simvastatin [11]. The primary composite end point was cardiovascular death, major coronary events, and stroke. The median time-weighted average LDL cholesterol level during the study was 53.7 mg per deciliter in the combination group, as compared with 69.5 mg per deciliter in the simvastatin-monotherapy group (P<0.001). The Kaplan-Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin–ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (Hazard Ratio, 0.936; 95% CI, 0.89 to 0.99; P=0.016).

The PRECISEIVUS (Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial was a multicenter, prospective, randomized, controlled study, which evaluated coronary plaque changes from atorvastatin/ezetimibe combination [12]. Serial intravascular ultrasound was performed at baseline and again at 9 to 12 months to assess the coronary plaque burden in 202 patients. The combination group had lower levels of LDL-C than atorvastatin monotherapy (63.2 mg/dl vs. 73.3 mg/dl; p<0.001). A significantly greater percentage of patients who received the combination showed coronary plaque regression (78% vs. 58%; p=0.004).

Appropriate use of PCSK9i

Based on the results from multiple large scale clinical outcome trials of PCSK9i, this class of LDL-C lowering agents, has been recommended as appropriate second line agents, or as an alternative therapy in cases of significant statin intolerance, for patients with established ASCVD and suboptimal LDL levels. As evidence supporting their efficacy and safety continues to mount, use of PCSK9i is likely to keep expanding in the current ASCVD population.

A study looked at electronic health record data to characterize use of PCSK9 inhibitors, in addition to standard therapies [13]. Data were obtained from 18 health systems within the National Patient-Centered Clinical Research Network using a common data model. Out of more than 17.5 million adults, 3.6 million met study criteria. Approximately half of patients had been prescribed lipid-lowering medication, but <1% were prescribed PCSK9 inhibitors. A trend towards increased PCSK9 inhibitor prescription over time was seen for patients with ASCVD but not for those with dyslipidemia. PCSK9i, which effectively lower LDL cholesterol, had low use during this surveillance period.

Multiple factors were thought to contribute to the low rates of PCSK9i use. High cost, prior authorization requirements, and lack of insurance approval were thought to be some of the reasons. High copays have been shown to lower access to PCSK9i, despite Medicare and other third-party payer coverage for PCSK9 inhibitors [14]. PCSK9i cost of treatment has been estimated to be $14000 a year which argues about its cost effectiveness [15]. Most cost-effectiveness studies have concluded that currently, PCSK9 inhibitors are not cost-effective with the accepted threshold of $100 000 per quality-adjusted life-year gained [16].

Discussion and Conclusion

PCSK9i have emerged as a breakthrough antihyperlipidemic therapy in the current era, where ASCVD is the leading cause for morbidity and mortality. PCSK9i are efficacious and safe. Current literature on their suboptimal use in real-world settings indicates that a large proportion of these patients could benefit from more aggressive treatment with this class of lipid lowering therapy. The cost-effectiveness of PCSK9i can be improved by restricting its use in patients with increased risk of ASCVD. Also, the most recent AHA/ACC multi-society guidelines on the management of hyperlipidemia gave a class 1 recommendation to adding ezetimibe to maximally tolerate statin therapy for secondary prevention prior to initiation of PCSK9 inhibitors. This would not only triage PCSK9i use in people who are highest risk but also improve its cost effectiveness.

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