Hyperlipidemia Management in Proprotein Convertase Subtilisin-
Kexin Type 9 (PCSK 9) Inhibitors Era

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Abstract

Significant improvement in control of cardiovascular risk factors has been driven by performance measurement that focused on attainment of specific risk factor thresholds for blood glucose, lipids and blood pressure. Diet, statin and ezetimibe have reasonably controlled hyperlipidemia. However the discovery of proprotein convertase subtilisin-kexin type 9 inhibitors has given new hope of reaching the target lipid profile especially in the high-risk group and familial hypercholesterolemia. Here with we reviewed the current data and explore the cardiovascular prevention effect of this group.

Keywords
Proprotein convertase subtilisin-kexin type 9 inhibitors, Evolocumab, Alirocumab, Hyperlipidemia, Familial hypercholesterolemia

Hyperlipidemia is an important risk factor for atherosclerotic cardiovascular disease. In a nationwide study of more than 900,000 patients with diabetes from 130 VA primary care centers, only 68% of eligible patients were on statins, half of them were on the need to be on moderate- to high-intensity statins.

A meta-analysis of randomized controlled trials showed consistent clinical benefit from decreasing LDL even further in patients with baseline LDL as low as 63 mg/dL and for each 38.7 mg/dL LDL reduction, there was a 21% reduction in relative risk for major vascular events. There was also a linear relationship between lowering serum LDL levels and improving outcomes in cardiovascular disease [1,2].

On the other hand, in spite of this overwhelming data, it was challenged by failure to reach the target with current lipid-lowering drugs.

Another challenge was statin intolerance, whether complete, defined as in tolerance to any statin at any dose or partial, defined as in tolerance to some statin at certain dosage [3].

The target is even more difficult to achieve in Familial Hypercholesterolemia (FH). In PLANET registry, a non-interventional, retrospective, cross-sectional, multicenter disease registry for adult patients with heterozygous FH in the Czech Republic and Slovakia, 1755 patients were enrolled; only 15.4% of patients attained the target LDL value. Fourteen percent (14.0%) had cardiovascular events in patients attaining the LDL goal, against 86.0% in the non-target group [4]. Similar data were published in South Africa. The mean untreated and best achieved LDL values during follow up were 8.1 ± 2.1 and 4.0 ± 1.5 mmol/l, respectively [5].

Scientists continued to explore this field till 2003 when proprotein convertase subtilisin-kexin type 9 (PCSK9) was discovered. PCSK9 is a protein mainly secreted by the liver, but a small amount is also secreted from the kidneys and small intestine.

PCSK9 promotes hypercholesterolemia by binding to LDL receptors on the surface of hepatocytes and is transported to lysosomes for degradation. The subsequent reduction in the number of LDL receptors resulted in reduced clearance of LDL from the blood. A less identified mechanism was via the Golgi-lysosomal intracellular route [6].

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The gene located on chromosome 1p32.3 encodes PCSK9. Genetic mutations with gain and loss kept LDLR regulation in a counter balance.

The gene theory was of real interest to researchers. Up to 32 million variants for association with lipid levels were tested and 118 novel genome-wide significant loci were identified after meta-analysis with data from the Global Lipids Genetics Consortium. Through a focus on mutations predicted to result in a loss of gene function and a phenomena-wide association study, a novel indications for pharmaceutical inhibitors targeting PCSK9 linked to abdominal aortic aneurysm), ANGPTL4 linked to type 2 diabetes and PDE3B linked to triglycerides and coronary disease were suggested [7].

Monoclonal antibodies inhibiting PCSK9 constitute a new class of lipid-lowering drugs. The theoretical advantage became a practical solution with two large placebo-controlled trials evaluating clinical outcomes in patients with LDL 1.8 mmol/L or greater on maximally tolerated statins and having associated CVD. In the first, evolocumab versus placebo in 27,564 patients over 2.2 years showed a significant reduction in new CVD events (9.8%, against 11.3%). The number needed to treat was 67 but there was no difference in death by any cause [8].

In the second study alirocumab was started in 18,924 patients after ACS and followed, up to 2.8 years demonstrating a statistically significant reduction in new CVD events (9.5% versus 11.1%). The number needed to treat was 63. and death by any cause was 3.5% against 4.1% [9].

Both drugs showed similar LDL reduction 55% vs. 53% and raised HDL 7.6% vs. 8% respectively [10].

Significantly more plaque volume reduction was seen with PCSK9. Tolerability was quite high in both studies, with low rates of discontinuation in up to 2.8 years. Adverse events were primarily injection site reactions. Developing neutralizing antibodies was rare and usually clinically insignificant.

However since data of the long-term effects are still lacking and the drug is a costly one, a step-wise approach is necessary. Dietary interventions remain the golden primary advice. Moderate to high dose statin should been tried. The statin group had a complex approach before being declared a failure or having caused intolerance. Ezetimibe had proved an effective drug with and without statin in preventing cardiovascular event.

If the LDL target is still lacking after a maximal tolerated dose of statin and ezetimibe treatment, then PCSK9 inhibitor would be a safe and effective alternative treatment with good intermediate follow up data [11]. Such a planned approach might change if the current price of the drug be reduced by half.

2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk drew up a map for Decision Pathways.

It focused on the very high-risk group, at risk of developing CV diseases and divided them into uncontrolled ASVCD risk factors vs. controlled and those aged 40 to 79 years vs. those aged 18 to 39 years. The target LDL was set at 70 mg/dl vs. 100 mg/dl. Familial hypercholesterolemia was considered the highest risk group. Non-HDL was the alternative treatment target.

In Conclusion

PCSK 9 inhibitor is an alternative LDL lowering drug that can either be added or replace statin/ezetimibe to obtain recommended LDL goals in patients with high risk of cardiac event. It has a large safety profile but is not currently cost-effective except in high risk patients.

References