Research Article

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Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors: Ready to Target Atherosclerotic Cardiovascular Disease beyond Statins.

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ABSTRACT

Fifty percent of atherogenic cardiovascular events (CVEs) are caused by dyslipidemia. Statins reduce LDL-C, or low-density lipoprotein cholesterol, by an average of 1 mmol, which results in a 20–25% reduction in CVE. Fully humanized monoclonal antibodies (MoAbs) against PCSK9 (proprotein convertase subtilisin/kexin type 9) reduce LDL-C by an additional 1 to 1½ mmol in addition to statins, which results in a 20% reduction in CVE.

Thus, the time has arrived when we can significantly reduce the atherogenic risk associated with dyslipidemia.

Every year, 12 to 26 injections are needed for the PCSK9 MoAbs. It has been demonstrated that inclisiran, a small interfering ribonucleic acid (siRNA), can consistently lower LDL-C for six months following a single injection. As a result, it is starting to pose a serious threat to PCSK9.

Keywords : Alirocumab, Proprotein convertase subtilisin/kexin type 9 inhibitors evolocumab, Small interfering ribonucleic acid.

INTRODUCTION

Fifty percent of atherogenic cardiovascular events (CVEs) are caused by dyslipidemia. Statins reduce LDL-C (low-density lipoprotein cholesterol) by an average of 1 mmol, which results in a 20–25% decrease in CVE. Fully humanized monoclonal antibodies (MoAbs) against PCSK9 (proprotein convertase subtilisin/kexin type 9) reduce LDL-C by an additional 1 to 1½ mmol in addition to statins, which results in a 20% reduction in CVE.

Thus, the time has arrived when we can significantly reduce the atherogenic risk associated with dyslipidemia.

Every year, 12 to 26 injections are needed for the PCSK9 MoAbs. It has been demonstrated that inclisiran, a small interfering ribonucleic acid (siRNA), can consistently lower LDL-C for six months following a single injection. As a result, it is starting to pose a serious threat to PCSK9. Although apolipoprotein B (ApoB) is also a target, it is typically not used because there are no capabilities for measuring it; instead, non-HDL-C is used to estimate its amount.

There is no evidence-based aim for HDL-C elevation over statins, and all trials that have attempted to raise it have failed. HDL-C is actually a fallen angel.

For the very high risk group, an LDL-C goal of less than 70 has been advised for a number of years. The American Association of Clinical Endocrinologists (AACE) guidelines 20172 reduced this objective to <55 mL/dL, while the Lipid Association of India reduced it to <501 (Tables 1 and 2). Thirty mg/dL more is the target for non-HDL-C than for LDL-C.

TRIGLYCERIDES

Although there hasn't been enough research done in India, TGs may be a significant factor in dyslipidemia in that country. Angiopoietin-like protein 4 (ANGPTL4)4 and low TG levels associated with loss of function mutation ApoC3)3 and TGs are linked to a lower risk of coronary heart disease; consequently, elevated TG levels are linked to a higher risk of cardiovascular and all-cause death. However, there isn't a single randomized controlled study that demonstrates the advantages of TG lowering in addition to statins. The efficacy of fibrates in addition to statins in diabetic individuals was examined in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial5, which did not show demonstrate any advantage. The problem with this data is that, while subgroup analysis of the ACCORD trial in patients with raised TG >204 mg/dL and low HDL-C <34 mg/dL did show a benefit, subgroup analysis is only hypothesis generating, and the finding needs to be confirmed in a large randomized trial, which is nonexistent at the present time. This is why diabetologists frequently use fibrates.

A number of additional medications are used to treat dyslipidemia in addition to statins. Table 3 lists the medications used to modify dyslipidemia. The first-line treatment for dyslipiemia is the use of statins. According to data from

the Cholesterol Treatment Trialists (CTT) Metaanalysis Collaboration, high-intensity statins reduce LDL-C by an average of 1 mmol. This reduction is observed across the whole range of LDL-C, and it translates into an approximate 20–25% reduction in CVE, regardless of baseline LDL-C.

NONSTATIN DRUGS

Nonstatin use may be taken into consideration in certain high-risk individuals, such as those with familial hypercholesterolemia (FH) who are not meeting LDL targets or those with pre-existing ASCVD, if maximally tolerated statin therapy has not demonstrated a >50% reduction in LDL-C from baseline. In the majority of these patient situations, ezetimibe is the first nonstatin drug that should be taken into account due to its safety, tolerability, and modest efficacy when combined with moderate-dose statins, as demonstrated by the IMPROVE IT Trial.When ezetimibe is not tolerated by a patient, biebene acid sequestrants (BASs) may be thought of as a second-line treatment option; however, individuals with TGs greater than 300 mg/dL should not use BASs.

Familial Hypercholesterolemia

It is challenging for patients with homozygous hypercholesterolemia to meet the objectives. Both statins and nonstatin medications, including as ezetimibe and BASs, are used.

If required, the new medications mipomersen9 and lomitapide8 are administered. For heterozygous FH, low-density lipoprotein apheresis is authorized. When maximally tolerated statin and ezetimibe therapy has failed to meet the goals of FH, PCSK9 inhibitors such as evolocumab and alirocumab may be investigated. Patients with clinical ASCVD who are at high risk are also treated with PCSK9 inhibitors.

What is PCSK9?

A protein called proprotein convertase subtilisin/kexin type 9 controls blood levels of low-density lipoprotein receptors (LDL-R), which in turn controls blood levels of LDL-C. It is released by the liver, enters the bloodstream, returns to the liver, and attaches itself to LDL-R to increase their degradation. This lowers the pace at which LDL-C is eliminated from circulation, raising blood levels of LDL-C. PCSK9 is a key regulator of LDL metabolism as a result. Additionally impacted by genetic mutation is PCSK9. Two categories of mutation exist: Gain of function mutation11 produces FH and predisposes to ASCVD; loss of function mutation lowers LDL-C and offers atheroprotection.

Ezetimibe12 and statins both raise PCSK9 secretion, which may lessen their effectiveness by lowering the quantity of cholesterol removed from the bloodstream. This clarifies the limitations of statin medication and could be the most appropriate explanation for the well-known rule of six that is seen in conjunction with statin therapy. This guideline states that there is only a 6% complementary drop in LDL-C levels for every time the statin dosage is doubled.

Consequently, combining PCSK9 inhibition with a statin would be a prudent and rational course of action that will result in a significant drop in LDL-C levels.

Evolocumab

This is available commercially as a 1 mL pen containing 140 mg and has already received approval for usage in clinical settings. Subcutaneous injections of 140 mg every two weeks or 420 mg every month are administered. It was examined in 14 trials involving about 30,000 patients as part of the Program to Reduce LDL-C and Cardiovascular Outcomes (PROFICIO) Global Program.

The majority of the trials are over, and the FOURIER results were released in 2017. The majority of these trials have demonstrated a 40–60% substantial reduction in LDL–C in addition to statins. Other lipoproteins are likewise consistently and significantly reduced. A quarter or so of the lipoprotein Lp(a), TG, and non-HDL-C are also reduced. There is an increase in Apo-A1 and HDL-C. The medication is taken as directed.

Alirocumab

This comes in a 1 mL pen that contains 75 or 150 mg and is commercially available. It is approved for clinical use in the United States. It is administered subcutaneously in doses of 150 mg or 75 mg every two weeks. It was assessed as part of the ODYSSEY Global Program, which involved about 22,000 patients and 11 trials. With the exception of the ODYSSEY outcome trial in post-ACS patients, the most of the trials have been completed, and the findings are eagerly awaited.

Bococizumab

Due to the existence of neutralizing antibodies in 29% and antidrug antibodies in 48% of patients receiving bococizumab, the SPIRE 1 and 2 trials were prematurely stopped. This is due to the fact that bococizumab, in contrast to evolocumab and alirocumab, which are fully humanized MoAbs, is a partially murine MoAb. Table 5 lists the prevalence of neutralizing and antidrug antibodies to different PCSK9 MoAbs. Despite the early termination of the SPIRE I and SPIRE II studies, the SPIRE II trial, which included LDL-C > 100 mg/dL, demonstrated a 21% decrease in CVEs after 12 months, suggesting that the treatment may also be helpful for main.

CONCLUSION

One important modifiable risk factor for ASCVD is dyslipidemia. LDL-C has been validated by statin studies; the lower the

better, and they reduce lipid-related CVEs by 20 to 25%. As seen in the FOURIER trial, further decreasing LDL-C to as low as 25 mg/dL yields incremental benefit with exceptional safety, a finding confirmed by the novel medication PCSK9 MoAbs. Therefore, it appears that LDL-C's objective will be further reduced in the future.

REFERENCES

1. Iyengar SS, Puri R, Narasingan SM, Wangnoo SK, Mohan V, Mohan JC, Misra A, Sriram U, Dalal JJ, Gupta R, et al. LAI Expert Consensus Statement on Management of Dyslipidemia in Indians 2016. JAPI 2016 Mar;64:7-52.

2. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, DeFronzo RA, Einhorn D, Fonseca VA, et al. Consensus statement by the American association of clinical endocrinologists and American college of endocrinology of the comprehensive type 2 diabetes management algorithm – 2017 executive summary. Endocr Pract 2017 Feb;23(2):207-227.

3. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute; Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitziel NO, Lange LA, Lu Y, Tang ZZ, Zhang H, et al. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med

4. 2014 Jul;371(1):22-31. Folsom AR, Peacock JM, Demerath E, Boerwinkle E. Variation in ANGPTL4 and risk of coronary heart disease: the atherosclerosis risk in communities study. Metabolism 2008 Nov;57(11):1591-1596.