AIM-LO: PCSK9 inhibition (mAbs and siRNA) - Mechanisms of Action
Presented by Dr. Michael Heffernan

Introduction

Hi, I'm Dr. Michael Heffernan, cardiologist at the Oakville Trafalgar Hospital and research director of Halton Healthcare. In this video, I'll be discussing the role of PCSK9 in ASCVD and two different approaches to PCSK9 inhibition: monoclonal antibodies and small interfering RNA.

Role of PCSK9 in ASCVD

PCSK9 proteins play a crucial role in the pathogenesis of atherosclerotic cardiovascular disease (ASCVD). They regulate the expression of LDL receptors on hepatocytes, which are responsible for removing LDL cholesterol from circulation.

In individuals with high levels of PCSK9, the degradation of LDL receptors is enhanced, leading to reduced LDL clearance and elevated LDL cholesterol levels. This dysregulation contributes to the development and progression of atherosclerosis, as increased LDL cholesterol promotes the formation of lipid-rich plaques in arterial walls.

Furthermore, PCSK9 has been implicated in promoting inflammation, endothelial dysfunction, and oxidative stress, all of which are key mechanisms underlying ASCVD.

By targeting PCSK9, either through monoclonal antibodies or small interfering RNA therapy, we can effectively modulate LDL receptor expression, lower LDL cholesterol levels, and ultimately reduce the risk of ASCVD events in our patients.

We now have two distinct approaches to PCSK9 inhibition that have revolutionized the management of hypercholesterolemia: monoclonal antibodies and small interfering RNA (siRNA). While both methods aim to reduce LDL cholesterol levels, they employ different mechanisms to achieve this goal.

PCSK9 inhibition with mAbs

Monoclonal antibodies selectively bind to PCSK9 in the blood, preventing its interaction with LDL receptors on hepatocytes. By blocking this interaction, monoclonal antibodies enhance the recycling of LDL receptors, leading to increased LDL clearance from the circulation.

This approach, exemplified by drugs like evolocumab and alirocumab, is highly effective, however, it requires regular subcutaneous injections and access in Canada can be challenging.

I invite you to watch the video by my colleague Dr. Sandeep Aggarwal, who is sharing some key tips to maximize therapeutic access for your patients. This may help you navigate some of these challenges.

PCSK9 inhibition with siRNA therapy

The second approach to PSCK9 inhibition employs small interfering RNA. Small interfering RNA is a class of double-stranded RNA molecules that play a crucial role in the regulation of gene expression.

By harnessing the natural RNA interference pathway, small interfering RNA can be used to selectively inhibit the expression of specific genes.

Inclisiran: Mechanism of action

Inclisiran is the only small interfering RNA therapy used for the treatment of hypercholesterolemia. It specifically targets and inhibits the production of PCSK9 in the liver. Inclisiran has a unique delivery system which involves the conjugation of the small interfering RNA to a sugar molecule known as GalNAc.

There are GalNAc receptors on hepatocytes and as a result, upon administration by subcutaneous injection, inclisiran-GalNAc conjugates circulate in the bloodstream and are recognized by the receptors on hepatocytes.

The complex is endocytosed into the hepatocyte and, while inside the endosome, the inclisiran-GalNAc conjugate is released. Inclisiran is then able to interact with the RNA-induced silencing complex (referred to as RISC) in the cytoplasm of the hepatocyte. This initiates the RNA interference pathway, leading to the specific inhibition of PCSK9 production.

The GalNAc conjugation enhances the uptake of inclisiran by hepatocytes, increasing the concentration of inclisiran within the target cells. This targeted delivery system allows for efficient and selective delivery of inclisiran to hepatocytes, maximizing its therapeutic effect while minimizing off-target effects in other tissues.

An important component of inclisiran's safety is the GalNAc conjugation as its binding to asialoglycoprotein receptors confers liver specificity and as such, inclisiran is undetectable from the plasma within 48 hours of injection.

With decreased PCSK9 levels, the recycling and expression of low-density lipoprotein (LDL) receptors on hepatocyte surfaces are enhanced. These receptors play a vital role in removing LDL cholesterol from the bloodstream. As a result, the enhanced recycling and expression of LDL receptors lead to increased LDL clearance, resulting in reduced LDL cholesterol levels.

Inclisiran: Summary

The unique feature of inclisiran is its long duration of action. Its prolonged and sustained PCSK9 suppression enables inclisiran to be administered in relatively infrequent dosing intervals, every six months, except for the first year of treatment, when a second injection is required 3 months after the first.

Conclusion

So, in summary, while both inclisiran and monoclonal antibodies aim to reduce PCSK9 activity and LDL cholesterol levels, they do so through different mechanisms: inclisiran targets the production of PCSK9 proteins within hepatocytes, while monoclonal antibodies interfere with the interaction of PCSK9 with LDL particles in the bloodstream.