Transcript Details

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Reshaping LDL-C Management in Primary Hyperlipidemia with First-in-Class siRNA Therapy

Announcer

Welcome to ReachMD. This medical industry feature, titled "*LEQVIO (inclisiran) MOA: Reshaping LDL-C Management in Primary Hyperlipidemia*", is sponsored by Novartis Pharmaceuticals Corporation and is intended for US health care professionals.

The speakers have been compensated by Novartis Pharmaceuticals Corporation to conduct this presentation.

We are excited to have Dr Stephanie Saucier, a noninvasive cardiologist from Hartford, Connecticut and Dr Richard Wright, a clinical cardiologist and cardiovascular pharmacologist from Santa Monica, California with us today.

Before we begin, let's go over the indication for LEQVIO.

INDICATION: LEQVIO (inclisiran) injection is indicated as an adjunct to diet and statin therapy for the treatment of adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce low-density lipoprotein cholesterol (LDL-C).[1]

Dr. Saucier can you please get us started here?

Dr Saucier

We're going to be talking about some of the key features that make LEQVIO unique. It's a first-in-class siRNA lipid-lowering therapy that targets the liver. It's been proven to lower LDL-C, and LEQVIO is given in just 2 doses a year after the first 2 doses.

Dr Wright, can you share with us a reason why you choose LEQVIO for your patients?

Dr Wright

It's the first-in-class of this biologic agent that we call small interfering RNA.[2] This lowers LDL cholesterol in patients with atherosclerotic cardiovascular disease who have not responded appropriately enough to reach the thresholds that you're seeking to lower their LDL to goal.[1] LEQVIO is designed to selectively target the liver.[1] This particular PCSK9 protein that we're targeting can be made in other tissues, but it's predominantly in the liver, so that's where LEQVIO targets.[1,3] It reaches undetectable levels in the circulation within 48 hours of administration.[1]

It's a subcutaneous injection, it's absorbed in the first few hours from the skin, it hones in on the liver, it goes into the cytoplasm of the hepatocytes, and after two days, you can't detect any in the bloodstream any longer. Once it's within the liver cell, it uses the natural RNA interference mechanism, which is found in all cells and even in plants, they have this —as a means of regulating the production of proteins.[1,2]

In this particular case, this small interfering RNA, inclisiran, or LEQVIO, inhibits the translation of the messenger RNA, such that the PCSK9 protein will not be produced in the quantity it otherwise would be. And what this then leads to is an increased LDL receptor length-of-stay, if you will. The LDL receptor is not destroyed in the hepatocyte. It makes its way back to the surface of the hepatocyte, and therefore it can suck more LDL particles out of the bloodstream.[1]

This RNA interference is a natural biologic process. It was first discovered 25 years ago by individuals who won the Nobel Prize 6 years later.[2,4] And it has revolutionized the way we're really beginning to treat medical problems. RNA interference harnesses a natural biologic process. This is a way that the body auto-regulates at the source, which is production of the protein, and if the cell so seeks, it can lower the amount of protein produced.[2] So we're harnessing this mechanism using RNA that is produced and then given to the

patient in a subcutaneous manner.[1]

After its uptake by the liver cell, it's slowly released by endosomes. So it's actually stored within the liver cell, and this is why the injections only need to be given after the initial dose, and 3 months later, you can give it every 6 months because that's the resident time within the endosome, within the liver cell.[1,2,5] And once it's there, it can be partitioned into the cytoplasm, which is where proteins are manufactured. It binds to a complex called the RISC – R-I-S-C, not *K* – and this RISC will destroy messenger RNA that is meant to produce the protein PCSK9.[2] And it can do so over many, many months. Each of the RNA molecules will persist for a long time, which explains the long half-life of the process that you're affecting using inclisiran.[2,6]

This process occurs in the cytoplasm, as I mentioned, and that's important because it means that LEQVIO does not get into the nucleus and hence does nothing to interfere with the patient's DNA.[2]

Inhibition of PCSK9 synthesis increases and can fairly rapidly, and readily increase the number of LDL receptors at the liver cell surface. And this therefore enables the liver to uptake more LDL particles that are circulating in the blood, and this explains how this drug lowers LDL.[1]

Announcer

Thank you for joining us during this discussion on the mechanism of action for LEQVIO.

Important Safety Information: LEQVIO is contraindicated in patients with a prior serious hypersensitivity reaction to inclisiran or any of the excipients in LEQVIO. Serious hypersensitivity reactions have included angioedema. Adverse reactions in clinical trials (≥3% of patients treated with LEQVIO and more frequently than placebo) were injection site reaction, arthralgia, and bronchitis.[1]

Please see LEQVIO full Prescribing Information on this site or at LEQVIOHCP.com.

Important Safety Information for LEQVIO is available underneath the player of this audio presentation.

This program was sponsored by Novartis Pharmaceuticals Corporation. If you missed any part of this discussion, visit ReachMD.com/Industry Feature. This is ReachMD. Be Part of the Knowledge.

References:

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