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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Inclisiran. [Updated 2023 Jan 6].
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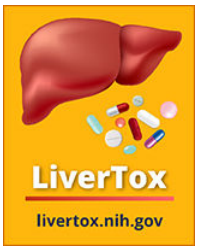

Inclisiran

Updated: January 6, 2023.

OVERVIEW

Introduction

Inclisiran is a synthetic small interfering RNA (siRNA) molecule directed against PCSK-9 that is used to treat hypercholesterolemia. Inclisiran has not been linked to ALT elevations during therapy or to instances of clinically apparent liver injury with symptoms or jaundice.

Background

Inclisiran (in clis' er an) is a synthetic, double-stranded, small interfering RNA (siRNA) directed against the mRNA of PCSK9 (proprotein convertase subtilisin/kexin type 9), a small polypeptide produced in the liver than binds to and causes degradation of the low density lipoprotein (LDL) cholesterol receptor. The binding of PCSK9 to the receptor leads to its internalization and lysosomal digestion, resulting in less uptake of LDL cholesterol from the serum and rise in cholesterol levels. Inhibition of this protein prevents the breakdown of the LDL cholesterol receptor, resulting in an increase in LDL cholesterol by the liver and a marked decrease in serum LDL cholesterol. The siRNA molecule is covalently linked to three N-acetylgalactosamine residues, which facilitate its uptake by hepatocytes. Once taken up by cells, the siRNA is cleaved into smaller fragments and separated into single strands that bind and silence the mRNA of PCSK9. In animal models, inclisiran reduced PCSK9 mRNA levels in liver and PCSK9 protein in serum, which was accompanied by an increase in hepatocyte LDL cholesterol receptors and decrease in serum LDL cholesterol. In placebo controlled trials of inclisiran in patients with hypercholesterolemia, single subcutaneous injections resulted in dose related reductions in serum cholesterol levels that persisted for several weeks. With 3 to 6 monthly injections of higher doses, serum LDL cholesterol levels fell by 50%. Inclisiran was approved for use in the United States in 2021 for patients with heterozygous familial hypercholesterolemia or patients with a history of cardiovascular disease with inadequate lowering of serum LDL cholesterol by statins due to resistance or intolerance of statin side effects. Inclisiran is available in solution in single dose prefilled syringes of 284 mg in 1.5 mL under the brand name Leqvio. The recommended dose regimen is 284 mg initially and again 3 months later, followed by every 6 months. Administration should be by a health care provider. Inclisiran is generally well tolerated, but side effects can include injection site reactions, fatigue, arthralgias, diarrhea and musculoskeletal pains. In preregistration studies, 5% to 13% of inclisiran treated patients developed anti-drug antibodies, but their presence was not associated with decreased efficacy or safety.

Hepatotoxicity

In multiple pivotal trials, inclisiran therapy was well tolerated and serum ALT elevations arose in less than 1% of patients that were invariably transient, mild-to-moderate in severity, and without accompanying symptoms or

jaundice. In controlled trials, rates of ALT and AST elevations during inclisiran therapy were similar to those with placebo or comparator agents. Since its approval and more widescale use, there have been no published reports of liver injury attributed to inclisiran therapy. Thus, inclisiran is an unlikely cause of clinically apparent liver injury, although it still has had limited clinical use.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The possible cause of hepatic injury from inclisiran or other siRNA therapeutics is not known. One possibility is that suppression of intracellular PCSK9 levels might cause or predispose to liver injury. Inclisiran, like other siRNA therapeutic agents, is metabolized intracellularly by nucleases and is not a substrate of cytochrome P450 enzymes or hepatic transporters.

Outcome and Management

Inclisiran has not been linked to ALT elevations or to clinically apparent liver injury and regular monitoring of routine liver tests is not recommended.

Drug Class: Genetic Disorder Agents, Antilipemic Agents

Other Therapeutic siRNA-based Agents: Eteplirsen, Givosiran, Golodirsen, Patisiran

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Inclisiran – Leqvio®

DRUG CLASS

Genetic Disorder Agents, Antilipemic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Inclisiran	1639324-58-5	C529-H707-F12-N176-O316-P43-S6	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 06 January 2023

Abbreviations: mRNA, messenger RNA; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA.

FDA. Inclisiran. Clinical Review. 2021. Available at:

Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214012Orig1s000MedR.pdf

(The FDA clinical review of inclisiran for efficacy and safety; reported ALT elevations above 5 times ULN arose in 6 of 2990 [0.2%] inclisiran treated patients, all of which were transient and asymptomatic and none were associated with jaundice).

Setten RL, Rossi JJ, Han SP. The current state and future directions of RNAi-based therapeutics. Nat Rev Drug Discov. 2019;18:421–46. PubMed PMID: 30846871.

(Extensive review of gene silencing using RNA interference pathways and the potential of RNAi therapeutics, which have promise in many genetic and acquired diseases including transthyretin amyloidosis [transthyretin], HIV infection [CCR5], HBV [HBV mRNA], alpha-1-antitrypsin deficiency [zz A1AT], hypercholesterolemia [PCSK9]).

Fitzgerald K, Frank-Kamenetsky M, Shulga-Morskaya S, Liebow A, Bettencourt BR, Sutherland JE, Hutabarat RM, et al. Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial. Lancet. 2014;383(9911):60–68. PubMed PMID: 24094767.

(In a phase 1, dose-finding and safety study of single injections of inclisiran or placebo in 32 patients not receiving medications for hypercholesterolemia, inclisiran led to a rapid 50% decline in PCSK9 levels and marked decline in LDL cholesterol levels at the highest doses that was sustained for several weeks, and there were no drug related serious adverse events).

Fitzgerald K, White S, Borodovsky A, Bettencourt BR, Strahs A, Clausen V, Wijngaard P, et al. A highly durable RNAi therapeutic inhibitor of PCSK9. N Engl J Med. 2017;376:41–51. PubMed PMID: 27959715.

(In a phase 1 dose findings of single or multiple doses of inclisiran, maximum reduction in LDL cholesterol was achieved with 300 mg doses, which were sustained for 6 months while adverse events were mild-to-moderate in severity and self-limited in course, one patient on inclisiran developing ALT levels above 2 times ULN improved on stopping atorvastatin and had recurrence on restarting it).

Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M, Hall T, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med. 2017;376:1430–1440. PubMed PMID: 28306389.

(In a phase 2 trial of multiple ascending doses of one or two doses of inclisiran vs placebo, the 2 dose regimen of 300 mg of inclisiran yielded the greatest reduction in LDL cholesterol, and adverse event rates were similar between two groups with ALT levels above 3 times ULN in 2 of 370 [0.5%] on inclisiran vs none of 127 on placebo).

Page MM, Watts GF. PCSK9 in context: A contemporary review of an important biological target for the prevention and treatment of atherosclerotic cardiovascular disease. Diabetes Obes Metab. 2018;20:270–282. PubMed PMID: 28736830.

(Review of the role of PCSK9 in cholesterol metabolism and the efficacy and safety of monoclonal antibody inhibitors of circulating levels [evolocumab and alirocumab] and siRNA inhibitors of its synthesis [inclisiran].

Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, Bisch JA, et al; ORION-10 and ORION-11 Investigators. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382:1507–1519. PubMed PMID: 32187462.

(Among 3178 patients with atherosclerotic cardiovascular disease [or at high risk for it] and high LDL cholesterol levels despite statin therapy in 2 placebo controlled trials of inclisiran [300 mg at 0, 90, 270and 450 days], LDL cholesterol levels decreased by 50-52% with inclisiran and adverse event rates were similar to placebo except for injection site reactions [4.7% vs 0.5%]; ALT levels rising above 3 times ULN in 0.4% of both groups).

Raal FJ, Kallend D, Ray KK, Turner T, Koenig W, Wright RS, Wijngaard PLJ, et al. ORION-9 Investigators. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med. 2020;382:1520–1530. PubMed PMID: 32197277.

(Among 482 adults with heterozygous familial hypercholesterolemia treated with inclisiran [300 mg] or placebo on days 0, 90, 270 and 450, LDL cholesterol levels decreased by 40% on inclisiran but increased by 8% on placebo, while adverse event rates were similar in the two groups except for injection site reactions [17% vs 1.7%], ALT levels above 3 times ULN occurring in 1.2% [3 of 241 inclisiran-] vs 0.4% [1 of 240 placebo recipients]).

Inclisiran (Leqvio) for LDL-cholesterol lowering. Med Lett Drugs Ther. 2022;64(1646):43–45. PubMed PMID: 35294427.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of inclisiran shortly after its approval for use in the United States, mentions side effects of injection site reactions [8%], arthralgia, urinary tract infections, diarrhea, bronchitis, extremity pain and dyspnea; no mention of ALT elevations or hepatotoxicity.

Lipid-lowering drugs. Med Lett Drugs Ther. 2022;64(1659):145–152. PubMed PMID: 36094548.

(Concise summary of efficacy, safety and costs of lipid-lowering drugs approved for use in the US mentions that inclisiran lowers LDL cholesterol levels by about 50% when added to maximally tolerated statin therapy, but includes no mention of serious adverse events, ALT elevations or hepatotoxicity).

Ranasinghe P, Addison ML, Dear JW, Webb DJ. Small interfering RNA: Discovery, pharmacology and clinical development–An introductory review. Br J Pharmacol. 2022 Oct 17. Epub ahead of print.

(Review of the history of development, mechanism of action, methods of delivery, clinical efficacy and safety of RNA silencing drugs including lumasiran, givosiran, inclisiran, patisiran and vutrisiran, discusses adverse events from inclisiran of injection site reactions, but does not mention hepatotoxicity or ALT elevations).