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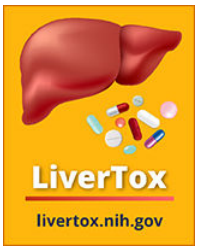

Golodirsen

Updated: February 27, 2020.

OVERVIEW

Introduction

Golodirsen is synthetic antisense oligonucleotide designed to cause skipping of abnormal exons in the synthesis of the dystrophin gene and that is used to treat Duchenne muscular dystrophy. Golodirsen has not been reported to cause ALT elevations during therapy and has not been linked to instances of acute liver injury with symptoms and jaundice.

Background

Golodirsen (go" loh dir' san) is a synthetic antisense oligonucleotide designed to cause exon 53 skipping during the processing of the mRNA of the dystrophin gene, which encodes an essential protein for muscle integrity. Patients with Duchenne muscular dystrophy typically have deletion mutations in exons [43 to 55], which disrupt the open-reading frame and the normal synthesis of dystrophin. The lack of functional dystrophin leads to damage to muscles during contraction that eventually results in replacement of normal muscle by fibrous tissue and fat. Duchenne muscle dystrophy is an X-linked disorder that presents clinically in boys by the age of 2 or 3 years and often results in loss of ambulation by age 10, ventilation dependency by age 20, and premature death within 5 to 20 years thereafter. In animal models of muscular dystrophy, golodirsen resulted in skipping of exon 53 and creation of a truncated but functional dystrophin gene. In small placebo controlled trials of golodirsen in patients with Duchenne muscular dystrophy with mutations in exon 53 amenable to correction by the drug, dystrophin protein levels increased in treated subjects and not in controls. The studies did not demonstrate convincing evidence of clinical improvement. Nevertheless, based solely upon changes in dystrophin levels, golodirsen was approved for use in the United States in 2019 with its indications limited to patients with Duchenne muscular dystrophy with a confirmed mutation that was correctable by exon 53 skipping. Golodirsen is available in solution in single dose vials of 100 mg in 2 mL. The recommended regimen is 30 mg per kg body weight once weekly by intravenous infusion. Side effects of golodirsen include headache, fever, falls, abdominal pain, cough and nausea. Injection site reactions and hypersensitivity reactions including rash, pruritus, urticaria and skin exfoliation have occurred. Renal toxicity, which was observed in preclinical studies in animals was not found in human trials. The weekly intravenous infusions of golodirsen generally require an indwelling venous access catheter, which may predispose to complications of infection and septicemia with long term use.

Hepatotoxicity

Duchenne muscular dystrophy is rare affecting ~1:5000 newborn boys, and those with deletion mutants in exon 53 that would be amenable to golodirsen therapy account for only 8% of patients with the disease. The pivotal trials of golodirsen were conducted in rather small numbers of patients, and the full spectrum of hepatotoxicity

may not be fully known. Nevertheless, serum aminotransferase elevations were not described in the registration trials of golodirsen and there were no discontinuations for liver adverse events and no episodes of clinically apparent liver injury. Thus, golodirsen has not been linked to instances of acute hepatitis or jaundice, but it has had limited clinical use.

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

Mechanism of Injury

The reasons why golodirsen or other RNA antisense therapeutics might cause of hepatic injury are unknown. One possibility is that exon skipping may cause disruption of translation of other genes in hepatocytes. Golodirsen is metabolized intracellularly by nucleases and has little effect on cytochrome P450 enzyme activities.

Outcome and Management

Golodirsen therapy has not been associated with liver injury, either in the form of minor serum enzyme elevations or clinically apparent liver injury. There is no reason to suspect cross reactivity of the hepatic injury with other antisense therapies or drugs used to treat Duchenne muscular dystrophy. Monitoring of liver tests during therapy is not recommended.

Drug Class: Genetic Disorder Agents

Other Therapeutic siRNA and Antisense Agents: Eteplirsen, Givosiran, Patisiran

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Golodirsen – Vyondys 53®

DRUG CLASS

Genetic Disorder Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Golodirsen	1422959-91-8	C305-H481-N138-O112-P25	

ANNOTATED BIBLIOGRAPHY

References updated: 27 February 2020

Abbreviations: siRNA, small interfering RNA.

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, no cases were attributed to RNAi or antisense therapies or medications for muscular dystrophy).

Chi X, Gatti P, Papoian T. Safety of antisense oligonucleotide and siRNA-based therapeutics. Drug Discov Today. 2017;22:823–33. PubMed PMID: 28159625.

(Oligonucleotide and siRNA based treatments are currently being evaluated in several diseases and have been found to have unexpected toxicities including antisense thrombocytopenia [mipomersen, drisapersen] and peripheral neuropathy [revusiran]; no discussion of hepatotoxicity).

Levin AA. Treating disease at the RNA level with oligonucleotides. N Engl J Med. 2019;380:57–70. PubMed PMID: 30601736.

(Review of the mechanism of action, current status and future promise of RNA based therapies that use synthetic oligonucleotides to modulate RNA function and have been applied to diseases ranging from hemophilia, amyloidosis, muscular dystrophy and hyperlipidemia).

Messina S, Vita GL. Clinical management of Duchenne muscular dystrophy: the state of the art. Neurol Sci. 2018;39:1837–45. PubMed PMID: 30218397.

(Review of current optimal clinical management of Duchenne muscular dystrophy focusing upon standard respiratory, cardiovascular, orthopedic and nutritional support as well as recent innovative approaches to therapy including exon and premature stop codon suppression).

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]).

Verhaart IEC, Aartsma-Rus A. Therapeutic developments for Duchenne muscular dystrophy. Nat Rev Neurol. 2019;15:373–86. PubMed PMID: 31147635.

(Review of mechanisms of action, challenges, and clinical efficacy of new molecular approaches to therapy of muscular dystrophy including gene therapy with viral vectors, exon skipping using antisense oligonucleotides [casimersen, eteplirsen, drisapersen, golodirsen], stop coding readthrough [ataluren], gene addition, CRISPR-Cas9 genome editing, and myoblast transplantation).

FDA Multi-Disciplinary Review and Evaluation. Golodirsen. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000MedR.pdf

(The FDA clinical review of golodirsen for efficacy and safety found minor increases in dystrophin levels in muscle biopsies but no improvement in clinical measures such as 6 minute walk test distances; therapy required intravenous infusions once weekly and insertion of a venous access port, but there were no serious

adverse events attributable to the medication and no hepatic related serious adverse events or discontinuations because of liver toxicity; no mention of changes in ALT levels during therapy).

Heo Y-A. Golodirsen: First approval. Drugs. 2020;80:329–33. PubMed PMID: 32026421.

(Review of the mechanism of action, history of development, clinical efficacy and safety of golodirsen shortly after its approval for use in Duchenne muscular dystrophy mentions that in the registration trial, all patients showed exon 53 skipping responses and the mean dystrophin levels from muscle biopsies increased from baseline, but that clinical improvement rates were not reported, while adverse events in treated vs control subjects included headache [41% vs 10%], fever [41% vs 14%], falls [29% vs 19%], abdominal pain [27% vs 10%], cough [27% vs 19%], and nausea [20% vs 10%], but does not mention ALT elevations or hepatotoxicity).

Aartsma-Rus A, Corey DR. The 10th oligonucleotide therapy approved: golodirsen for Duchenne muscular dystrophy. Nucleic Acid Ther. 2020 Feb 11. [Epub ahead of print].

(Review of the efficacy and safety of 10 oligonucleotide therapies approved in the US or Europe, including specific discussions of formvirsen, mipomersen, eteplirsen, nusinersen, patisiran, givosiran and golodirsen).