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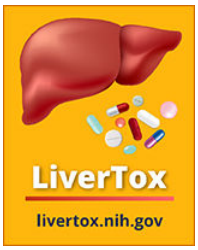


Givosiran

Updated: February 27, 2020.

OVERVIEW

Introduction

Givosiran is synthetic small interfering RNA (siRNA) molecule directed against 5-aminolevulinic acid synthase that is used to treat acute hepatic porphyria. Givosiran has been linked to mild-to-moderate ALT elevations during therapy, but has not been linked to instances of idiosyncratic acute liver injury with symptoms and jaundice.

Background

Givosiran (giv" oh sir' an) is a synthetic double stranded, small interfering RNA (siRNA) directed against 5-aminolevulinic acid synthase 1, which results in decreases in serum delta aminolevulinic acid (ALA) and porphobilinogen (PBG), intermediates in porphyrin metabolism which accumulate in patients with acute hepatic porphyrias and are believed to cause the neurologic and visceral symptoms of acute attacks. The siRNA molecule is covalently linked to three N-acetylgalactosamine residues which directs it to specific receptors found largely on hepatocytes. Once taken up by the hepatocyte, the siRNA is cleaved into smaller fragments and separated into single strands that bind and silence the mRNA of ALA synthase. In animal models, givosiran reduced ALA synthase mRNA levels in liver that was accompanied by a corresponding decline in urine and plasma ALA and PBG. In placebo controlled trials of givosiran in patients with recurring acute attacks, single infusions of givosiran resulted in dose related reductions in urinary ALA and PBG levels and, with monthly injections, annualized rates of attacks were reduced by 75% to 90%. Givosiran was approved for use in the United States for adults with acute hepatic porphyria in 2019. Current indications are limited to adults. Givosiran is available in solution in single dose vials of 189 mg/mL under the brand name Givlaari. The recommended regimen is 2.5 mg per kg body weight once monthly by subcutaneous injection. Givosiran is generally well tolerated but side effects can include nausea, injection site reactions, rash, fatigue and creatinine and serum aminotransferase elevations. Less common, but more severe side effects include severe injection reactions, anaphylaxis and recall reactions. In registration studies, immunogenicity was uncommon; only 1% of givosiran treated patients developed anti-drug antibodies.

Hepatotoxicity

The acute hepatic porphyrias are rare, and the pivotal trials of givosiran were conducted in rather small numbers of patients, so the full spectrum of hepatotoxicity may not be fully known. Nevertheless, in the registration controlled trials, serum aminotransferase elevations arose in 13% of givosiran- versus 2% of placebo-recipients, but rose to levels above 5 times the upper limit of normal only rarely. One patient was reported as discontinuing givosiran therapy because of aminotransferase elevations, but no patient developed concurrent elevations in

serum bilirubin or symptoms suggestive of hepatitis. Thus, givosiran has not been linked to instances of acute hepatitis or jaundice, but it has had limited clinical use.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

The cause of hepatic injury from the givosiran and other siRNA therapeutics is unknown. One possibility is that suppression of 5-aminolevulinic acid synthase may cause cell damage in some hepatocytes. The mRNA suppression appears to lower but not completely eliminate enzyme activity, but individual hepatocytes may vary in the sensitivity to the enzyme inhibition and effects of its loss. Givosiran is metabolized intracellularly by nucleases and is not a substrate of cytochrome P450 enzymes. On the other hand, the chronic inhibition of ALA synthase can result in decreases in CYP 1A2 and 2D6 synthesis and lead to supra-therapeutic or toxic levels of drugs that are metabolized by these enzymes.

Outcome and Management

The liver injury associated with givosiran therapy has invariably been mild, not associated with jaundice and rapidly resolving often without discontinuation or even dose adjustment. In prelicensure clinical trials, subjects received hemin therapy for acute attacks without evidence of liver injury, and there is no reason to suspect cross reactivity of hepatic injury with other therapies of acute porphyria. Monitoring of liver tests during therapy is recommended during givosiran therapy as well as interruption or discontinuation for significant elevations in serum aminotransferases.

Drug Class: Genetic Disorder Agents

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Givosiran – Givlaari®

DRUG CLASS

Genetic Disorder Agents

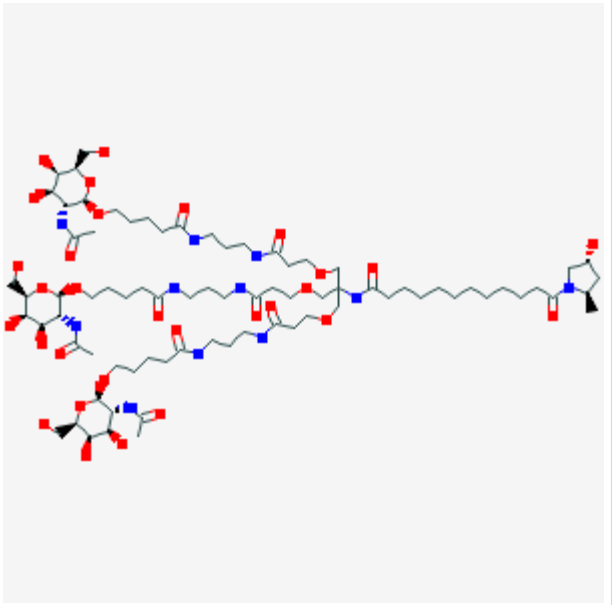
COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE

Table continued from previous page.

Givosiran	1639325-43-1	C78-H139-N11-O30	

ANNOTATED BIBLIOGRAPHY

References updated: 27 February 2020

Abbreviations: ALA, aminolevulinic acid; ALAS, aminolevulinic acid synthetase; PBG, porphobilinogen; siRNA, small interfering RNA.

Yasuda M, Gan L, Chen B, Kadirvel S, Yu C, Phillips JD, New MI, et al. RNAi-mediated silencing of hepatic Alas1 effectively prevents and treats the induced acute attacks in acute intermittent porphyria mice. Proc Natl Acad Sci U S A. 2014;111:7777–82. PubMed PMID: 24821812.

(Screening of multiple small interfering RNAs [siRNA] for activity in suppressing aminolevulinic acid synthetase [ALAS] in cell culture identified several with potent activity which were formulated into lipid nanoparticles and shown to lower ALAS activity and decrease serum levels of aminolevulinic acid (ALA) and porphobilinogen (PBG) in mice and to protect against acute attacks of porphyria in mouse models of the disease).

Bonkovsky HL, Maddukuri VC, Yazici C, Anderson KE, Bissell DM, Bloomer JR, Phillips JD, et al. Acute porphyrias in the USA: features of 108 subjects from porphyrias consortium. Am J Med. 2014;127:1233–41. PubMed PMID: 25016127.

(Among 108 subjects with acute porphyria enrolled in a U.S. prospective clinical cohort study, 90 had acute intermittent porphyria, 9 hereditary coproporphyria and 9 variegate porphyria; most were women [81%], non-Hispanic and white, and delay in diagnosis after onset of symptoms was common [mean delay=15 years]).

Bissell DM, Lai JC, Meister RK, Blanc PD. Role of delta-aminolevulinic acid in the symptoms of acute porphyria. Am J Med. 2015;128:313–7. PubMed PMID: 25446301.

(32 year old woman using several Ayurvedic medications developed recurrent abdominal pain and had elevations in serum ALA but not PBG, subsequent testing demonstrating lead poisoning and symptoms improving with hemin infusions but ultimately resolving after chelation of excess lead; these results suggest that ALA rather than PBG is the cause of neurologic and visceral symptoms in acute hepatic porphyria).

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: 1340-52e7.

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

Sardh E, Harper P, Balwani M, Stein P, Rees D, Bissell DM, Desnick R, et al. Phase 1 Trial of an RNA interference therapy for acute intermittent porphyria. N Engl J Med. 2019;380:549–58. PubMed PMID: 30726693.

(A phase 1 trial of ascending, single doses of givosiran followed by studies of the two optimal doses vs placebo either once monthly or quarterly in 40 patients with acute intermittent porphyria demonstrated rapid and marked declines in urinary ALA and PBG levels and decreases in annualized acute attack rates of 75-90%; there were no liver related severe adverse events and "no clinically significant changes in laboratory measures").

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]).

Chen B, Whatley S, Badminton M, Aarsand AK, Anderson KE, Bissell DM, Bonkovsky HL, et al; International Porphyria Molecular Diagnostic Collaborative. an evidence-based database of verified pathogenic and benign variants for the porphyrias. Genet Med. 2019;21:2605–13. PubMed PMID: 31073229.

(Announcement of a collaborative international effort to define phenotypes and genotypes of the 4 acute hepatic porphyrias, 3 being autosomal dominant [acute intermittent porphyria, hereditary coproporphyria and variegate porphyria] and 1 autosomal recessive, the genetic variation and clinical expression of each being highly variable).

Gouya L, Ventura P, Balwani M, Bissell DM, Rees DC, Stölzel U, Phillips JD, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. Hepatology. 2019 Sep 12. [Epub ahead of print].

(Among 112 patients with acute hepatic porphyria and recurrent attacks followed for at least 6 months, 98 [88%] had a total of 483 attacks, 371 [77%] requiring hemin therapy and, compared to baseline, urinary levels of ALA, PBG and ALAS mRNA increased during acute attacks).

Naik H, Overbey JR, Montgomery GH, Winkel G, Balwani M, Anderson KE, Bissell DM, et al. Evaluating the patient-reported outcomes measurement information system scales in acute intermittent porphyria. Genet Med. 2020;22:590–7. PubMed PMID: 31690837.

(Analysis of symptom scores in a cohort of 259 patients [75% with symptoms] with acute intermittent porphyria).

Scott LJ. Givosiran: first approval. Drugs. 2020;80:335–9. PubMed PMID: 32034693.

(Review of the mechanism of action, history of development, clinical efficacy and safety of givosiran shortly after its approval for use in acute hepatic porphyria in the US and Europe mentions that in the registration trial, the median composite annualized attack rate at 6 months was decreased by 90% and adverse events in treated vs control subjects included nausea [27% vs 11%], injection site reactions [25% vs 0%], rash [17% vs 4%], creatinine increase [15% vs 4%], aminotransferase elevations [13% vs 2%] and fatigue [10% vs 4%]).

FDA. Givosiran. Multi-Disciplinary Review and Evaluation. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212194Orig1s000MultidisciplineR.pdf

(The FDA clinical review of givosiran for efficacy and safety reported ALT elevations above 3 times ULN arose in 6 of 48 [13%] givosiran treated vs 1 of 46 [2%] controls, one patient discontinuing therapy because of enzyme elevations after 3 doses [ALT 172 U/L, AST 95 U/L] which reportedly resolved rapidly upon stopping).