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Patisiran

Updated: January 6, 2023.

OVERVIEW

Introduction

Patisiran is a synthetic small interfering RNA (siRNA) molecule directed against the mRNA of transthyretin that is used to treat the rare genetic disease transthyretin-mediated amyloidosis. Patisiran has not been linked to serum aminotransferase elevations during therapy or to instances of clinically apparent liver injury with symptoms or jaundice.

Background

Patisiran (pa" ti sir' an) is a synthetic, double-stranded, small interfering RNA (siRNA) directed against the mRNA of transthyretin, a serum protein made in the liver whose major function is transport of vitamin A and thyroxine. Rare mutations in the transthyretin gene result in misfolding of the protein and accumulation of large amyloid deposits of transthyretin molecules most prominently in peripheral nerves and the heart. Patients with inherited transthyretin amyloidosis typically present with polyneuropathy or autonomic dysfunction followed by cardiomyopathy which, if untreated, is usually fatal within 5 to 12 years. Patisiran was developed to reduce production of transthyretin (both the wild type and mutant forms) and prevent accumulation of further amyloid deposits. Patisiran is administered intravenously, and uptake by the liver is facilitated by its packaging in lipid nanoparticles (which also protect against ribonuclease digestion). Once taken up by hepatocytes, the siRNA is cleaved into smaller fragments and separated into single strands that bind and silence the mRNA of transthyretin. In animal models, patisiran reduced transthyretin protein levels in blood and mRNA levels in liver. In trials of patisiran in patients with hereditary transthyretin amyloidosis with polyneuropathy, intravenous infusions resulted in rapid and sustained reductions in serum transthyretin levels (averaging ~78%) and significant improvements in neuropathy and quality of life scales compared to placebo therapy. Patisiran was approved for use in the United States in 2018 for adults with transthyretin amyloidosis and polyneuropathy. It is under evaluation for efficacy and safety in patients with cardiomyopathy due to transthyretin amyloidosis. Patisiran is available in a lipid complex solution in single dose vials of 10 mg in 5 mL (2 mg/mL) under the brand name Onpattro. The recommended dose regimen is 0.3 mg/kg (to a maximal dose 30 mg) administered intravenously every 3 weeks. Administration by a health care provider is required as is premedication with corticosteroids, acetaminophen, antihistamines and an H2 blocker. Patisiran is generally well tolerated the most common side effects being injection site reactions. Other potential adverse events include peripheral edema, fatigue, arthralgias, diarrhea and musculoskeletal pains. In preregistration studies, 3% of patisiran treated patients developed anti-drug antibodies, but their presence was not associated with decreased efficacy or safety. Because patisiran reduces serum transthyretin levels, it also reduces serum vitamin A levels and vitamin A supplementation is recommended using doses of the recommended daily allowance.

Hepatotoxicity

In preregistration trials, patisiran therapy was well tolerated except for infusion reactions. Patients with amyloidosis often have hepatomegaly and mild serum enzyme elevations. Serum aminotransferase elevations arose in approximately 20% of patisiran- vs 10% of placebo-recipients, but the elevations were usually mild (less than 5 times ULN), transient and without accompanying symptoms or jaundice. Since its approval, there have been no published reports of liver injury attributed to patisiran therapy. Thus, patisiran is an unlikely cause of clinically apparent liver injury, although it has had limited widescale clinical use.

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

Mechanism of Injury

The possible cause of hepatic injury from patisiran or other siRNA therapeutics is not known. Patisiran has been linked to mild-to-moderate, transient serum aminotransferase elevations that usually resolve spontaneously without dose modification. The cause of these abnormalities is unknown, but patients with amyloidosis can have hepatomegaly and minor serum enzyme elevations while on no therapy. Alternatively, the serum ALT and AST elevations may relate to the lipid complex used to improve hepatic update of the siRNA. Patisiran, like other RNA therapeutic agents, is metabolized intracellularly by nucleases and is not a substrate of cytochrome P450 enzymes or hepatic transporters.

Outcome and Management

Patisiran has not been linked to clinically significant liver test abnormalities or to clinically apparent liver injury and regular monitoring of routine liver tests is not recommended. The requirements for intravenous administration and premedication makes management of therapy challenging.

Drug Class: Genetic Disorder Agents, siRNA and Antisense Agents

Other Therapeutic siRNA-based Agents: Givosiran, Inclisiran, Lumasiran, Vutrisiran

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Patisiran – Onpattro®

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
Patisiran	1420706-45-1	C412-H480-N148-Na40-O290-P40	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 03 January 2023

Abbreviations: mRNA, messenger RNA; siRNA, small interfering RNA.

FDA. Patisiran. Clinical Review. 2018. Available at:

Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210922Orig1s000MultiR.pdf

(The FDA clinical review of patisiran for efficacy and safety reported that ALT elevations arose in 20% of patisiran- vs 10% of placebo-recipients in preregistration controlled trials, but that all elevations were transient, less than 5 times the ULN, and were not associated with jaundice or symptoms; in addition, there were no hepatic serious adverse events or deaths).

Suhr OB, Coelho T, Buades J, Pouget J, Conceicao I, Berk J, Schmidt H, et al. Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: a phase II multi-dose study. Orphanet J Rare Dis. 2015;10:109. PubMed PMID: 26338094.

(Among 29 patients with hereditary transthyretin amyloidosis with polyneuropathy treated with varying doses regimens of patisiran, there was a rapid marked decline in serum transthyretin levels [averaging -85%] and adverse events were mild-to-moderate, mostly infusion reactions, not requiring discontinuation, and "no clinically significant changes in liver function tests…were recorded").

Butler JS, Chan A, Costelha S, Fishman S, Willoughby JL, Borland TD, Milstein S, et al. Preclinical evaluation of RNAi as a treatment for transthyretin-mediated amyloidosis. Amyloid. 2016;23:109–18. PubMed PMID: 27033334.

(In a murine model of hereditary transthyretin-mediated amyloidosis, patisiran resulted in knock down of transthyretin and dose related regression of amyloid deposits).

Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379:11–21. PubMed PMID: 29972753.

(Among 245 patients with hereditary transthyretin amyloidosis treated with patisiran [0.3 mg/kg] or placebo intravenously every 3 weeks for up to 6 months, neuropathy and quality of life scores improved with patisiran therapy and usually worsened with placebo, while adverse event rates were similar in the two groups except for infusion reactions [19% vs 9%] and peripheral edema [30% vs 22%], and there were no "clinically relevant changes in laboratory values" including indicators of liver function).

Hoy SM. Patisiran: first global approval. Drugs. 2018 Oct;78(15):1625–1631. PubMed PMID: 30251172.

(Review of the mechanism of action, structure, history of development, clinical efficacy and safety of patisiran shortly after its approval for use in hereditary transthyretin amyloidosis with polyneuropathy, mentions that there were no treatment related serious adverse events; no mention of ALT elevations or hepatotoxicity).

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]).

Zhang X, Goel V, Attarwala H, Sweetser MT, Clausen VA, Robbie GJ. Patisiran pharmacokinetics, pharmacodynamics, and exposure-response analyses in the phase 3 APOLLO Trial in patients with hereditary transthyretin-mediated (hATTR) amyloidosis. J Clin Pharmacol. 2020;60:37–49. PubMed PMID: 31322739.

(Pharmacokinetic studies conducted on 145 patients with hereditary transthyretin amyloidosis treated with patisiran for 18 months demonstrated stable drug levels and only 5 subjects developed anti-drug antibodies [3.4%] that had no appreciable effects on drug levels, efficacy or safety).

Coelho T, Adams D, Conceição I, Waddington-Cruz M, Schmidt HH, Buades J, Campistol J, et al. A phase II, open-label, extension study of long-term patisiran treatment in patients with hereditary transthyretin-mediated (hATTR) amyloidosis. Orphanet J Rare Dis. 2020;15:179. PubMed PMID: 32641071.

(Among 27 patients with transthyretin amyloidosis participating in a phase 2 trial of patisiran which was then continued for 24 months, improvements in neuropathy and quality of life were sustained and adverse events were generally mild, with no discontinuations for adverse events and no significant changes in liver biochemical test results).

Adams D, Polydefkis M, González-Duarte A, Wixner J, Kristen AV, Schmidt HH, Berk JL, et al. patisiran Global OLE study group. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. Lancet Neurol. 2021;20:49–59. PubMed PMID: 33212063.

(Among 211 patients with hereditary transthyretin amyloidosis and polyneuropathy enrolled in an open label extension study after phase 2 and 3 controlled trials of patisiran, improvements in neuropathy and quality of life scores arose in placebo groups when crossed over to active therapy and were sustained in active treatment groups, and there were "no clinically relevant safety concerns…related to hepatic events").

Luigetti M, Servidei S. Patisiran in hereditary transthyretin-mediated amyloidosis. Lancet Neurol. 2021;20:21–23. PubMed PMID: 33212064.

(Editorial in response to Adams [2021] summarizing results on the efficacy of patisiran in hereditary transthyretin amyloidosis and discussing the uncertainty related to long term therapy and treatment of advanced disease and cardiomyopathy).

Suzuki Y, Ishihara H. Difference in the lipid nanoparticle technology employed in three approved siRNA (Patisiran) and mRNA (COVID-19 vaccine) drugs. Drug Metab Pharmacokinet. 2021;41:100424. PubMed PMID: 34757287.

(Description of the lipid components used to create nanoparticles for administration of patisiran, the lipids protecting the RNA against nuclease digestion and allowing uptake by hepatocytes [via the LDL receptor] and release of the siRNA with acidification of the endosomes containing the incorporated patisiran).

Schmidt HH, Wixner J, Planté-Bordeneuve V, Muñoz-Beamud F, Lladó L, Gillmore JD, Mazzeo A, et al; Patisiran Post-LT Study Group. Patisiran treatment in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy after liver transplantation. Am J Transplant. 2022;22:1646–1657. PubMed PMID: 35213769.

(Among 12 patients with hereditary transthyretin amyloidosis with polyneuropathy who had undergone liver transplant but continued to have neuropathy were treated with patisiran for at least 12 months, neuropathy and autonomic syndrome scores improved while disability and nutrition status were stable; 11 [48%] patients developed ALT elevations that were usually transient and mild, one developed acute rejection and one cholangitis, but all abnormalities resolved despite continued patisiran therapy without dose modification).

Aimo A, Castiglione V, Rapezzi C, Franzini M, Panichella G, Vergaro G, Gillmore J, et al. RNA-targeting and gene editing therapies for transthyretin amyloidosis. Nat Rev Cardiol. 2022;19(10):655–667. PubMed PMID: 35322226.

(Extensive review of the molecular basis of hereditary transthyretin amyloidosis and the small molecule and RNA based therapies in current use and in experimental clinical trials, mentions the efficacy and relative safety of patisiran which has not been linked to instances of liver dysfunction).

Di Stefano V, Fava A, Gentile L, Guaraldi P, Leonardi L, Poli L, Tagliapietra M, et al. Italian real-life experience of patients with hereditary transthyretin amyloidosis treated with patisiran. Pharmgenomics Pers Med. 2022;15:499–514. PubMed PMID: 35592550.

(Case histories of 9 patients with transthyretin amyloidosis with polyneuropathy who were treated long term with patisiran in "Italian real-life" with clinical improvement and excellent tolerance; no mention of ALT elevations or hepatotoxicity).

Maurer MS. Overview of current and emerging therapies for amyloid transthyretin cardiomyopathy. Am J Cardiol. 2022;185 Suppl 1:S23–S34. PubMed PMID: 36371281.

(Review of the molecular basis of therapies for the cardiomyopathy of hereditary transthyretin-mediated amyloidosis including RNA silencing approaches such as patisiran and vutrisiran).

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 patisiran of injection site reactions, but does not mention hepatotoxicity or ALT elevations).