Patisiran: Pregnancy and Lactation

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SUMMARY

- Patisiran has undergone comprehensive toxicology testing, demonstrating no mutagenic, clastogenic, or aneugenic effects. In reproductive studies, patisiran did not affect fertility or embryofetal development in rats. Maternal toxicity was observed only at high doses in rabbits, and no adverse effects on offspring growth or development were noted at doses up to 1.5 mg/kg.[1]
- In the APOLLO, APOLLO-B, and HELIOS-A studies, pregnant or breastfeeding women were excluded from participation.[2,3,4] Women of childbearing potential were required to provide a negative pregnancy test, confirm they were not breastfeeding, and use highly effective contraception.[2,4,5]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new risks associated with exposure to patisiran during pregnancy.[6]
- A case report from published medical literature describes exposure to patisiran treatment in a patient during early pregnancy.[7]

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PRECLINICAL DATA

A comprehensive program of toxicology studies has been performed with patisiran, which includes single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity.[1]

Genotoxicity

Patisiran was not determined to be mutagenic in the bacterial reverse mutation assay. It was also found that patisiran was not clastogenic or aneugenic in the mammalian chromosome aberration assay in human blood peripheral lymphocytes. Single IV doses of patisiran at ≤ 30 mg/kg (maximum tolerated dose) did not lead to micronucleus formation in the bone marrow of male and female CD-1 mice. Patisiran was not found to be genotoxic in either the in vitro or in vivo assays conducted.[1]

Reproductive Toxicity

Since patisiran is not pharmacologically active in rats and rabbits, the rat-specific surrogate formulation was used in the reproductive and developmental toxicity studies in the following animal models to evaluate the potential on-target pharmacological effects of patisiran on reproduction and development.[1]

Fertility and Embryofetal Development

Despite reductions in serum TTR (-90%), vitamin A (-79%) and thyroxine (-68%), patisiran did not exhibit pharmacological effects on male or female reproductive parameters in a combined fertility and embryofetal development study in rats.[1]

In the patisiran dose-range finding rabbit embryofetal development study, several adverse manifestations, such as reduced maternal body weight gain and appetite, were observed at 0.6 mg/kg. Based on this finding, the maternal NOAEL for patisiran was 0.3 mg/kg. At 0.3 mg/kg, the fetal concentrations of patisiran and its excipient (PEG_{2000}-C-DMG) were below detection limits.[1]

Prenatal and Postnatal Development, Including Maternal Function

The NOAEL for maternal toxicity and for viability and growth in the offspring and the highest dose tested for patisiran and the rat-specific surrogate formulation were 1.5 mg/kg. After two hours post-administration of a 1.5 mg/kg dose, patisiran was undetectable in milk, and the milk concentrations of the two excipients (DLin-MC3-DMA and PEG_{2000}-C-DMG) were around 5% of their respective maternal plasma concentrations. There were no patisiran-related effects on serum TTR, vitamin A, or thyroid hormones reported in the filial 1 generation.[1]

CLINICAL DATA

APOLLO Study

APOLLO was a multicenter, international, randomized (2:1), double-blind, placebo-controlled, phase 3 study designed to assess the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=148) versus placebo (n=77) in patients with hATTR-PN. The primary endpoint was the change from baseline in the mNIS+7 at 18 months.[8]

Pregnant or breastfeeding women were excluded from participating in the clinical study. Women of child-bearing potential were required to provide a negative pregnancy test, not be breastfeeding, and utilize 2 highly effective methods of contraception before screening, throughout study participation, and for 75 days after the last administration of study drug.[2] There were no reported pregnancies during the course of this study.[1]

APOLLO-B Study

APOLLO-B was a multicenter, randomized (1:1), double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=181) versus placebo (n=179) in patients with ATTR-CM, including both hATTR and wtATTR. The primary endpoint was the change from baseline in the 6-MWT at 12 months. After the 12-month double-blind treatment period, all patients received patisiran in an OLE period.[9]

Pregnant or breastfeeding women were excluded from participating in the clinical study.[3] Women of child-bearing potential were required to provide a negative pregnancy test, not be breastfeeding, and utilize a highly effective method of contraception from 14 days before the first dose, throughout study participation, and for 12 weeks after the last administration of study drug.[5]

HELIOS-A Study

HELIOS-A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[10]

Pregnant or breastfeeding women were excluded from participating in the clinical study. Women of child-bearing potential randomized to patisiran required to provide a negative pregnancy test, not be breastfeeding, and utilize a highly effective method of contraception prior to dosing and for 12 weeks after the last dose of patisiran if they did not switch and continue treatment with vutrisiran starting at Day 337 (Week 48).

Pharmacodynamics: Vitamin A and Retinol Binding Protein

A reduction in vitamin A and RBP concentrations were observed during the clinical development program for patisiran, which aligns with expectations, as serum TTR is a carrier of RBP. Vitamin A levels that are too high or too low can potentially result in teratogenic effects for the fetus. In case of unplanned or planned pregnancy, monitoring of vitamin A level throughout the pregnancy period was recommended.[1]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new risks associated with exposure to patisiran during pregnancy. The use of patisiran in pregnancy and lactation remains missing information and will be closely monitored through routine and additional pharmacovigilance activities.[6]

CASE REPORTS

The following information provides an overview of published case reports regarding the use of patisiran in patients during pregnancy. It is not intended to be an all-inclusive list or summary of relevant publications, abstracts, and manuscripts.

Loser V, et al. Patisiran exposure in early pregnancy: a case report. *Ther Adv Neurol Disord*. 2024;17:17562864241239755. doi: 10.1177/17562864241239755. PMID: 38532802.[7]

- A case report detailed a 36-year-old female with symptomatic hATTR, on patisiran and vitamin A substitution since 2019, who was exposed to patisiran during an unplanned pregnancy in 2022.
- The patient received her last dose of patisiran during the third week of amenorrhea, after which the patient informed the authors of the pregnancy and patisiran treatment was discontinued. The patient was closely monitored by a maternofetal medicine specialist, which included monthly serum vitamin A and prealbumin levels, as well as fetal ultrasounds.
- Vitamin A was increased at the beginning of pregnancy from 4,000 IU 3 times per week to 4,000 IU per day due to low serum levels, then was discontinued at 3 months of gestation when levels normalized.
- There were no major complications during pregnancy and delivery, except for a postpartum hemorrhage due to uterine atony. There was no sign of minor or major congenital abnormalities of the baby.
- During pregnancy, the patient experienced mild worsening of a preexisting loss of sensitivity in the lower limbs and an increase and in the frequency of orthostatic dizziness without syncope. Three months after delivery, patisiran was resumed.

ONPATTRO US PRESCRIBING INFORMATION – RELEVANT CONTENT

The USE IN SPECIFIC POPULATIONS section provides the following information[11]:

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ONPATTRO during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant

women may register themselves in the program by calling 1-877-256-9526 or by contacting alnylampregnancyprogram@iqvia.com.

Risk Summary

There are no available data on ONPATTRO use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. ONPATTRO treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking ONPATTRO. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by ONPATTRO and of vitamin A supplementation are unknown.

In animal studies, intravenous administration of patisiran lipid complex (patisiran-LC) to pregnant rabbits resulted in developmental toxicity (embryofetal mortality and reduced fetal body weight) at doses that were also associated with maternal toxicity. No adverse developmental effects were observed when patisiran-LC or a rodent-specific (pharmacologically active) surrogate were administered to pregnant rats.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Intravenous administration of patisiran LC (0, 0.15, 0.50, or 1.5 mg/kg) or a rodent-specific (pharmacologically active) surrogate (1.5 mg/kg) to female rats every week for two weeks prior to mating and continuing throughout organogenesis resulted in no adverse effects on fertility or embryofetal development.

Intravenous administration of patisiran-LC (0, 0.1, 0.3, or 0.6 mg/kg) to pregnant rabbits every week during the period of organogenesis produced no adverse effects on embryofetal development. In a separate study, patisiran-LC (0, 0.3, 1, or 2 mg/kg), administered to pregnant rabbits every week during the period of organogenesis, resulted in embryofetal mortality and reduced fetal body weight at the mid and high doses, which were associated with maternal toxicity.

Intravenous administration of patisiran-LC (0, 0.15, 0.50, or 1.5 mg/kg) or a rodent-specific surrogate (1.5 mg/kg) to pregnant rats every week throughout pregnancy and lactation resulted in no adverse developmental effects on the offspring.

Lactation

Risk Summary

There is no information regarding the presence of ONPATTRO in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ONPATTRO and any potential adverse effects on the breastfed infant from ONPATTRO or from the underlying maternal condition.

In lactating rats, patisiran was not detected in milk; however, the lipid components (DLin-MC3-DMA and PEG2000-C-DMG) were present in milk.

The PATIENT COUNSELING INFORMATION section provides the following information[11]:

Instruct patients that if they are pregnant or plan to become pregnant while taking ONPATTRO they should inform their healthcare provider. Advise female patients of childbearing potential of the potential

risk to the fetus. Encourage patients to enroll in the ONPATTRO pregnancy exposure registry if they become pregnant while taking ONPATTRO.

ABBREVIATIONS

6-MWT = 6-minute walk test; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CD-1 = cluster of differentiation 1; DLin-MC3-DMA= dilinoleyl-methyl-4-dimethylaminobutyrate; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IU = international unit; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; NOAEL = no observed adverse effect level; OLE = open-label extension; PEG = polyethylene glycol; RBP = retinol binding protein; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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REFERENCES

1. Onpattro : EPAR – Public assessment report. European Medicines Agency. Published October 30, 2018. Accessed November 25, 2024. https://www.ema.europa.eu/documents/assessment-report/onpattro-epar-public-assessment-report_.pdf.
2. Protocol for: Adams D, González-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153.
3. Supplement to: Maurer MS, Kale P, Fontana M, et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med*. 2023;389(17):1553-1565. doi:10.1056/NEJMoa2300757
4. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTRSC02-2300015.
5. Protocol for: Maurer MS, Kale P, Fontana M, et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med*. 2023;389(17):1553-1565. doi:10.1056/NEJMoa2300757
6. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTR02-2400049.
7. Loser V, Baumgartner T, Legardeur H, Panchaud A, Théaudin M. Patisiran exposure in early pregnancy: a case report. *Ther Adv Neurol Disord*. 2024;17:17562864241239755. doi:10.1177/17562864241239755.
8. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153
9. Maurer MS, Kale P, Fontana M, et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. *N Engl J Med*. 2023;389(17):1553-1565. doi:10.1056/NEJMoa2300757
10. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30(1):18-26. doi:10.1080/13506129.2022.2091985
11. ONPATTRO (patisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.