Patisiran: Vitamin A Levels

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

The full Prescribing Information for ONPATTRO® (patisiran) is provided here. Alnylam Pharmaceuticals does not recommend the use of its products in any manner that is inconsistent with the approved Prescribing Information. This resource may contain information that is not in the approved Prescribing Information.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- Treatment with patisiran reduces serum TTR levels, resulting in reduced levels of RBP and vitamin A in the serum. In the APOLLO study, serum vitamin A levels were reduced in parallel with reductions in serum TTR levels in patients treated with patisiran.[1,2]
- In the phase 3 APOLLO and APOLLO-B studies, patients were advised to take vitamin A supplementation at the recommended daily allowance. In the APOLLO study, patients were required to take an oral daily supplemental dose of 2,500 IU of vitamin A.[3,4]
- In a pooled analysis including data from phase 3 vutrisiran and patisiran clinical studies, no safety findings attributable to vitamin A deficiency were observed or led to study drug discontinuation. Patients were instructed to take daily vitamin A supplementation in these studies.[5]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any AEs definitively resulting from vitamin A deficiency in patients treated with patisiran.[1]
- Supplementation at the recommended daily allowance of vitamin A is advised for patients taking patisiran.[6] Alnylam is unable to provide patient specific recommendations on the dose or type of vitamin A supplement beyond the recommended daily dose.

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MECHANISM OF ACTION

Serum TTR is a carrier of RBP, facilitating transport of vitamin A in the blood. Treatment with patisiran reduces serum TTR levels, resulting in reduced levels of RBP and vitamin A in the serum. The mechanism of action attributes to the theoretical risk of vitamin A deficiency. However, the transport and tissue uptake of vitamin A can occur through alternative mechanisms in the absence of RBP. Patients receiving TTR-lowering RNAi therapeutics are advised to receive vitamin A supplementation at the recommended daily allowance, as a precautionary measure.[5,7–11]

Laboratory tests for serum vitamin A do not reflect the total amount of vitamin A in the body and should not be used to guide vitamin A supplementation beyond the recommended daily dose during treatment with patisiran.[5]

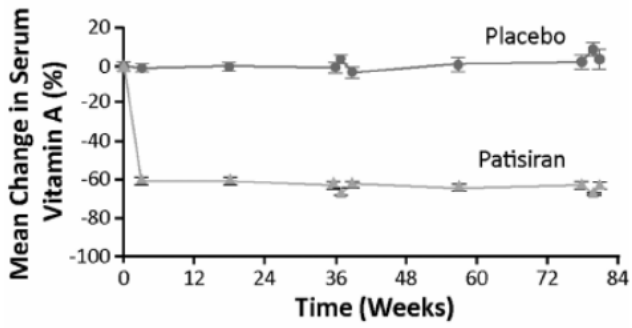
CLINICAL DATA

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. Vitamin A levels were measured as a PD assessment, and the percent reduction in vitamin A levels over time was included as an exploratory endpoint.[12] All patients in the study were required to take a daily supplement containing the dose of 2,500 IU of vitamin A, the approximate recommended daily allowance.[3]

At baseline, mean (±SD) serum vitamin A levels were 37.8±13.7 µg/dL (range: 11.0 to 70.0 µg/dL) in the patisiran group and 37.0±12.3 µg/dL (range: 14.0 to 67.0 µg/dL) in the placebo group. In the patisiran arm, serum vitamin A levels decreased in parallel with decreasing serum TTR levels.[2] At 18 months, the mean percent change in serum vitamin A was -62.4±14.4% (range: -9 to -84%) in the patisiran arm and -0.1±15.7% (range: 53 to -29%) in the placebo arm (**Figure 1**).[1]

Figure 1. Change in Vitamin A over 18 Months.[2,a]



Abbreviations: SEM = standard error of the mean.
[a]Error bars represent SEM.
From Zhang et al.[2]

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 open-label extension period.[4]

All patients were instructed to take the recommended daily allowance of vitamin A for the duration of their participation in the study. Data regarding change in serum vitamin A levels is not available as it was not evaluated as part of the APOLLO-B study design.[13]

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.[14]

Consistent with the expected PD effect from previous studies, serum vitamin A levels decreased in parallel with reductions in the TTR levels in the patisiran reference arm.[14]

Pooled Safety Analysis

An analysis of pooled data from patients with ATTR-CM or hATTR-PN who received at least 1 dose of vutrisiran, patisiran, or placebo from Phase 3 studies was conducted to evaluate the frequency and event rates of clinical and/or laboratory AEs related to vitamin A deficiency (**Table 1**).[5]

There were no reports of visual AEs directly attributed to vitamin A deficiency and therefore were no confirmed cases of clinical vitamin A deficiency. No events attributed to vitamin A deficiency led to study drug discontinuation.[5]

Table 1. Event Rates for PTs Related to Vitamin A Deficiency.[5]

PT, n events / EAER (per 100 PY)	Patisiran APOLLO, Patisiran OLE[a], APOLLO-B, HELIOS-A N=613; PY=1831.9	Vutrisiran HELIOS-A, HELIOS-B N=709; PY=1915.1	Placebo APOLLO, APOLLO-B, HELIOS-B N=583; PY 1098.5
PT[b], Clinical and/or Laboratory			
Dry eye	24 / 1.3	17 / 0.9	11 / 1.0
Keratomalacia	0	0	0
Retinopathy	0	0	0
Vitamin A deficiency-related eye disorder	0	0	0
Vitamin A deficiency-related conjunctival disorder	0	0	0
Vitamin A deficiency-related corneal disorder	0	0	0
Xerophthalmia	0	1 / 0.1	1 / 0.1
PT[b], Laboratory only			
Vitamin A decreased	2 / 0.1	11 / 0.6	NR[c]
Vitamin A deficiency	2/ 0.1	2 / 0.1	NR[c]

Abbreviations: AE = adverse event; EAER = exposure-adjusted event rate; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; NR = not reported; OLE = open-label extension; PT = preferred term; PY = patient-years.

[a]Includes patients with hATTR-PN from the APOLLO and patisiran Phase 2 OLE study.

[b]List of PTs has been previously established to monitor for AEs related to vitamin A deficiency in post-marketing aggregate safety reports.

[c]Laboratory vitamin A decrease or deficiency would not be reported for patients receiving placebo, as they were in the double-blind period of corresponding studies during which vitamin A measurements were prohibited due to risk of unblinding.

GLOBAL SAFETY DATABASE

Patisiran has been associated with decreased vitamin A levels due to reductions in RBP. Clinical consequences of this reduction in vitamin A levels have not been observed despite extensive

monitoring in clinical trials. A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any AEs definitively resulting from vitamin A deficiency in patients treated with patisiran.[1]

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following sections of the ONPATTRO Prescribing Information[6]:

- WARNINGS AND PRECAUTIONS Section 5.2 Reduced Serum Vitamin A Levels and Recommended Supplementation
- ADVERSE REACTIONS Section 6.1 Clinical Trials Experience
- USE IN SPECIFIC POPULATIONS Section 8.1 Pregnancy
- CLINICAL PHARMACOLOGY Section 12.2 Pharmacodynamics
- PATIENT COUNSELING INFORMATION Section 17

ABBREVIATIONS

6-MWT = 6-minute walk test; AE = adverse event; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; EAER = exposure-adjusted event rate; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IU = international unit; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; NR = not reported; OLE = open-label extension; PD = pharmacodynamic; PT = preferred term; PY = patient-years; RBP = retinol binding protein; RNAi = ribonucleic acid interference; SD = standard deviation; SEM = standard error of the mean; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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