

Patisiran: Vitamin A Levels

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SUMMARY

- Treatment with patisiran reduces serum TTR levels, resulting in reduced levels of RBP and vitamin A in the serum.¹
- All patients in the APOLLO and APOLLO-B studies were required to take a daily supplement containing the dose of 2,500 IU of vitamin A, which is the approximate recommended daily allowance.^{2,3}
- In the patisiran arm of the APOLLO study, serum vitamin A levels decreased in parallel with decreasing serum TTR levels.⁴ At 18 months, the mean percent change in serum vitamin A was $-62.4 \pm 14.4\%$ (range: -9 to -84%) in the patisiran arm and $-0.1 \pm 15.7\%$ (range: 53 to -29%) in the placebo arm.¹
- Data regarding the change in serum vitamin A levels is not available for the APOLLO-B study.⁵
- In the patisiran reference arm of the HELIOS-A study, serum vitamin A levels decreased in parallel with decreasing serum TTR levels.⁶ At 18 months, the AE of vitamin A decreased was reported in 2 patients (4.8%) in the patisiran arm. This AE was considered by the Investigator to be related to patisiran treatment.⁷
- 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

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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. Consequentially, 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 during treatment with patisiran.¹

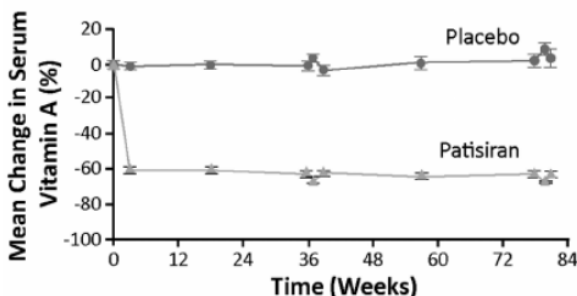
CLINICAL DATA

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. 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.⁸ 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.²

At baseline, mean ($\pm$ SD) serum vitamin A levels were 37.8 ± 13.7 μ g/dL (range: 11.0 to 70.0 μ g/dL) in the patisiran group and 37.0 ± 12.3 μ g/dL (range: 14.0 to 67.0 μ g/dL) in the placebo group. In the patisiran arm, serum vitamin A levels decreased in parallel with decreasing serum TTR levels.⁴ At 18 months, the mean percent change in serum vitamin A was $-62.4 \pm 14.4\%$ (range: -9 to -84%) in the patisiran arm and $-0.1 \pm 15.7\%$ (range: 53 to -29%) in the placebo arm (**Figure 1**).¹

Figure 1. Change in Vitamin A over 18 Months.⁴



Error bars represent SEM.
From Zhang et al.⁴

APOLLO-B

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.³

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.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.⁶

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.⁶ At 18 months, the AE of vitamin A

decreased was reported in 2 patients (4.8%) in the patisiran arm. This AE was considered by the Investigator to be related to patisiran treatment.⁷

GLOBAL SAFETY DATABASE

Vitamin A deficiency is a clinical syndrome resulting from low vitamin A levels. Typical signs and symptoms include night blindness, xerophthalmia, and keratomalacia.⁹ In patisiran clinical studies, vitamin A deficiency events were identified by using the following Preferred Terms: “Keratomalacia,” “Night blindness,” “Vitamin A decreased,” “Vitamin A deficiency,” “Vitamin A deficiency eye disorder,” “Vitamin A deficiency related conjunctival disorder,” “Vitamin A deficiency related corneal disorder,” and “Xerophthalmia.”¹

Patisiran has been associated with decreased vitamin A levels due to reductions in RBP. However, physiologic consequences of this reduction in vitamin A levels have not been observed despite extensive monitoring in clinical trials, including electroretinography. 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. No new and important safety information relevant to this risk was identified in any of the available sources.¹

ONPATTRO US PRESCRIBING INFORMATION – RELEVANT CONTENT

The WARNINGS AND PRECAUTIONS section of the ONPATTRO US Prescribing Information provides the following information¹⁰:

Reduced Serum Vitamin A Levels and Recommended Supplementation

ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking ONPATTRO. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

The ADVERSE REACTIONS section of the ONPATTRO US Prescribing Information provides the following information¹⁰:

Clinical Trials Experience

Patients were instructed to take the recommended daily allowance of vitamin A. Sixty-four percent of patients treated with ONPATTRO had normal vitamin A levels at baseline, and 99% of those with a normal baseline developed low vitamin A levels. In one case, the decreased vitamin A level was reported as an adverse reaction.

The USE IN SPECIFIC POPULATIONS section of the ONPATTRO US Prescribing Information provides the following information¹⁰:

Pregnancy

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.

The CLINICAL PHARMACOLOGY section of the ONPATTRO US Prescribing Information provides the following information¹⁰:

Pharmacodynamics

Serum TTR is a carrier of retinol binding protein, which is involved in the transport of vitamin A in the blood. Mean reductions in serum retinol binding protein of 45% and serum vitamin A of 62% were observed over 18 months.

ABBREVIATIONS

6-MWT = 6-minute walk test; AE = adverse event; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IU = international unit; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; PD = pharmacodynamic; PT = Preferred Term; RBP = retinol binding protein; SD = standard deviation; SEM = standard error of the mean; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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REFERENCES

1. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTR02-2300176.
2. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTR02-1800579.
3. 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. 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*. 2019;60(1):37-49. doi:10.1002/jcph.1480
5. Alnylam Pharmaceuticals, Inc. APOLLO-B: a study to evaluate patisiran in participants with transthyretin amyloidosis with cardiomyopathy (ATTR amyloidosis with cardiomyopathy). ClinicalTrials.gov website. Updated September 19, 2024. Accessed October 2, 2024. ClinicalTrials.gov Identifier: NCT03997383.
6. 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
7. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTRSC02-2200007.
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. Johnson LE. Vitamin A deficiency - nutritional disorders. Merck Manuals Professional Edition. November 2022. Accessed September 21, 2023. <https://www.merckmanuals.com/professional/nutritional-disorders/vitamin-deficiency,-dependency,-and-toxicity/vitamin-a-deficiency>.
10. ONPATTRO (patisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.