Vutrisiran: Vitamin A Levels

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SUMMARY

- Treatment with vutrisiran reduces serum TTR levels, resulting in reduced levels of RBP and vitamin A in the serum. In the HELIOS-A study, serum vitamin A levels were reduced in parallel with reductions in serum TTR levels in the vutrisiran treatment arm.[1,2]
- In the phase 3 HELIOS-A and HELIOS-B studies, patients were advised to take vitamin A supplementation at the recommended daily allowance.[2,3] In the HELIOS-A study, patients were supplemented with a dose of 2500 to 3000 IU of vitamin A.[4]
- Decreased vitamin A levels is a known ADR of vutrisiran. A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns regarding the potential risk of vitamin A deficiency in patients treated with vutrisiran.[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 vutrisiran 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 vutrisiran.[1]

CLINICAL DATA

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.[2]

Vitamin A levels were measured as part of a PD assessment, and the percent reduction in vitamin A levels over time was included as an exploratory endpoint. As the vitamin A content of the diet may vary between different individuals, all patients were instructed to take the recommended daily allowance of vitamin A while in the study.[5] Patients were supplemented with a dose of 2500 to 3000 IU of vitamin A.[4]

Nonclinical and clinical data with vutrisiran have shown that the lowering of circulating vitamin A associated with the reduction in TTR (a carrier of retinol) does not result in severe vitamin A deficiency.[5]

In the HELIOS-A study, consistent with the expected PD effect, serum vitamin A levels were reduced in parallel with reductions in serum TTR levels in vutrisiran arm; vutrisiran reduced the mean steady state serum vitamin A by 62% over 9 months.[2,6]

HELIOS-B Study

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months. The primary endpoint was the composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind treatment period, all eligible patients remaining on the study were allowed to receive vutrisiran in an OLE.[7]

As the vitamin A content of the diet may vary between different individuals, all patients were instructed to take the recommended daily allowance of vitamin A while in the study. Vitamin A levels were measured as part of a PD assessment.[3]

In the HELIOS-B study, vutrisiran reduced the mean steady state serum vitamin A by 65% over 36 months.[6]

GLOBAL SAFETY DATABASE

Vitamin A deficiency is a clinical syndrome resulting from low vitamin A levels. Typical signs and symptoms include night blindness, xeropthalmia, and keratomalacia.[8] In vutrisiran clinical studies, vitamin A deficiency events were reported using the following PTs: Keratomalacia, Vitamin A decreased, Vitamin A deficiency, Vitamin A deficiency eye disorder, Vitamin A deficiency related conjunctival disorder, Vitamin A deficiency related corneal disorder, Xerophthalmia, Dry eye, and Retinopathy, and high-level term Visual impairment and Blindness (excluding Color blindness).[1]

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns regarding the potential risk of vitamin A deficiency in patients treated with vutrisiran. As a known ADR of vutrisiran, decreased vitamin A levels will continue to be closely monitored through routine pharmacovigilance activities.[1]

AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

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

- WARNINGS AND PRECAUTIONS Section 5.1 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

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ABBREVIATIONS

ADR = adverse drug reaction; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PD = pharmacodynamic; PT = Preferred Term; RBP = retinol binding protein; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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