Vutrisiran: Vitamin A Levels

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SUMMARY

- 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]
  - Vutrisiran has been associated with decreased serum vitamin A levels due to reductions in RBP, which facilitates transport of vitamin A in the blood.
  - Patients were advised to take vitamin A supplementation at the recommended daily allowance while in the study.
- Decreased vitamin A levels is a known ADR of vutrisiran. The available data from the global safety database do not suggest any new safety concerns relating to the potential risk of vitamin A deficiency in patients treated with vutrisiran.[2]

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RELEVANT INFORMATION

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.[2]

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 the polyneuropathy of hATTR. 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 (NCT01960348) 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.[1]

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.[3]

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.[3]

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.[4]

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.[5] In the phase 3 HELIOS-A study, 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, and Xerophthalmia, Dry eye, and Retinopathy, and high-level term Visual impairment and Blindness (excluding Color blindness).[2]

A cumulative post-marketing review of the global safety database did not identify any new safety concerns relating to 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.[2]

AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

The WARNINGS AND PRECAUTIONS section provides the following information[4]:

Reduced Serum Vitamin A Levels and Recommended Supplementation

AMVUTTRA treatment leads to a decrease in serum vitamin A levels.

Supplementation at the recommended daily allowance of vitamin A is advised for patients taking AMVUTTRA. 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 AMVUTTRA, 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 provides the following information[4]:

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- *Reduced Serum Vitamin A Levels and Recommended Supplementation [see Warnings and Precautions section of USPI].*

Clinical Trials Experience

In [the Phase 3 HELIOS-A study], a total of 122 patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) received AMVUTTRA. Of these, 118 patients received at least 18 months of treatment. The mean duration of treatment was 18.8 months (range: 1.7 to 19.4 months). The median patient age at baseline was 60 years and 65% of the patients were male. Seventy percent of AMVUTTRA-treated patients were Caucasian, 17% were Asian, 3% were Black, and

9% were reported as Other. Forty-four percent of patients had the Val30Met mutation in the transthyretin gene; the remaining patients had one of 21 other mutations. At baseline, 70% of patients were in Stage 1 of the disease and 30% were in Stage 2.

The most common adverse reactions (at least 5%) were pain in extremity, arthralgia, dyspnea, and vitamin A decreased (see Table 1).

In [the Phase 3 HELIOS-A study], patients were instructed to take the recommended daily allowance of vitamin A. Seventy-four percent of patients treated with AMVUTTRA had normal vitamin A levels at baseline, and 98% of those with a normal baseline developed low vitamin A levels. In some cases, the decreased vitamin A level was reported as an adverse reaction (see Table 1).

Table 1: Adverse Reactions Reported in at least 5% of Patients Treated with AMVUTTRA [HELIOS-A]

Adverse Reaction	***AMVUTTRA N=122 %***
*Pain in extremity**	*15*
*Arthralgia**	*11*
*Dyspnea**	*7*
Vitamin A decreased†*	*7*
**Comprised of several similar terms* †*Percentage only reflects those reported as an adverse reaction*	

The USE IN SPECIFIC POPULATIONS section provides the following information[4]:

Pregnancy

Risk Summary

There are no available data on AMVUTTRA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. AMVUTTRA treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking AMVUTTRA. Vitamin A is essential for normal embryo fetal 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 AMVUTTRA and of vitamin A supplementation are unknown.

The CLINICAL PHARMACOLOGY section provides the following information[4]:

Pharmacodynamics

In [the Phase 3 HELIOS-A study], following administration of the recommended AMVUTTRA dosage every 3 months to patients with hATTR amyloidosis, vutrisiran reduced mean serum TTR at steady state by 83%. Similar TTR reductions were observed regardless of Val30Met genotype status, weight, sex, age, or race.

Vutrisiran also reduced the mean steady state serum vitamin A by 62% over 9 months.

ABBREVIATIONS

ADR = adverse drug reaction; hATTR = hereditary transthyretin amyloidosis; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; PD = pharmacodynamic; PT = Preferred Term ; RBP = retinol binding protein; TTR = transthyretin.

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