Patisiran: Liver Function Tests

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SUMMARY

- In patisiran clinical studies, participants with AST or ALT levels >2.5×ULN or TBILI >ULN were excluded (a higher level allowed for individuals with Gilbert's syndrome).[1]
  - Over the 18-month duration of the APOLLO study, the mean change from baseline in the patisiran group ranged from 1.8 to 3.8 U/L for ALT and from 2.3 to 4.1 U/L for AST. The majority of patients had ALT and AST values below the ULN, and the majority of ALT or AST elevations were ≤3×ULN.[1]
  - In a pooled population of patisiran-treated patients (N=636) across multiple studies (including the phase 2 study, APOLLO, APOLLO-B, and OLE study), most of the hepatic events were mild or moderate in severity and considered not related to patisiran.[1]
  - At baseline in the pooled population, 71 (11.2%) had mild, 14 (2.2%) had moderate, and 1 (0.2%) had severe hepatic impairment. Therefore, data on patisiran exposure in patients with moderate or severe hepatic impairment are limited.[1]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns involving liver function tests or hepatic events related to patisiran.[2]

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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.[3]

Over the 18-month duration of the APOLLO study, the mean change from baseline in the patisiran group ranged from 1.8 to 3.8 U/L for ALT and from 2.3 to 4.1 U/L for AST. The majority of patients had ALT and AST values below the ULN. Overall, 12 (15.6%) patients in the placebo group and 47 (31.8%) patients in the patisiran group had at least 1 ALT or AST value above the ULN. All of the elevations were ≤3×ULN, except for 1 (0.7%) patient in the patisiran group who had a transient elevation of ALT of 4.2×ULN on Day 84 without changes in AST, ALP, or TBILI.[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.[4]

Pooled Patisiran Population

In a pooled population of patients (N=636; which included patisiran exposure data from the phase 2 study, APOLLO, APOLLO-B, and OLE study populations), 66 (10.4%) patients experienced events of drug-related hepatic disorders, 7 of which were serious events. Most of the hepatic events were mild or moderate in severity and considered not related to patisiran. The most frequent hepatic events were laboratory elevations, which occurred in 6.1% of patients. Hepatic events that occurred in ≥1% of patients were: transaminases increased (1.7%), blood ALP increased (1.4%), ALT increased (1.3%), hepatic enzyme increased (1.3%), ascites (1.3%), and blood AST increased (1.1%). No clinically significant changes in liver function tests were observed.[1]

At baseline in the pooled population, 71 (11.2%) had mild, 14 (2.2%) had moderate, and 1 (0.2%) had severe hepatic impairment. Therefore, data on patisiran exposure in patients with moderate or severe hepatic impairment are limited. There have been no Hy's law cases (ALT or AST >3×ULN concurrent with TBILI >2×ULN) in clinical studies of patisiran.[1]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns involving liver function tests or hepatic events related to patisiran.[2]

ONPATTRO US PRESCRIBING INFORMATION – RELEVANT CONTENT

The USE IN SPECIFIC POPULATIONS section provides the following information[5]:

No dose adjustment is necessary in patients with mild hepatic impairment (bilirubin ≤1 x ULN and AST >1 x ULN, or bilirubin >1.0 to 1.5 x ULN). ONPATTRO has not been studied in patients with moderate or severe hepatic impairment.

ABBREVIATIONS

6-MWT = 6-minute walk test; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; TBILI = total bilirubin; ULN = upper limit of normal; wtATTR = wild-type transthyretin amyloidosis.

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