Patisiran: Infusion-Related Reactions

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SUMMARY

- IRRs have been observed in patients treated with patisiran. In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines to reduce the risk of IRRs.[1]
- In the APOLLO study, IRRs were observed in 28 patients (18.9%) in the patisiran arm and 7 patients (9.1%) in the placebo arm. All IRRs were reported as mild or moderate in severity. The frequency of IRRs decreased over time.[2]
- The pattern of IRRs was evaluated in a pooled safety population, which included data from 636 patients who received patisiran in clinical studies for up to 88.6 months. IRRs were reported in 20.4% of patients and were mostly mild (14.0%) in severity, with 39 patients (6.1%) reporting moderate IRRs and 2 patients (0.3%) reporting severe IRRs. As with the APOLLO study, the number of patients experiencing IRRs and the number of IRRs decreased over time.[3]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns involving IRRs.[4]

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CLINICAL DATA

Phase 2 OLE Study

The Phase 2 OLE study (N=27) was a multicenter, international study in patients with hATTR-PN. Patients who previously received and tolerated patisiran in the Phase 2 study were eligible to enroll in the Phase 2 OLE study. Patients received IV patisiran 0.3 mg/kg every 3 weeks for approximately 2 years.[5]

During the study, 6 patients (22%) experienced IRRs. All IRRs were mild in severity, and the incidence and number of IRRs decreased over time. All patients received a complete dose of patisiran, but

2 patients had temporary infusion interruptions due to IRRs. In 1 patient, the infusion rate was slowed with no subsequent IRRs. The other patient had mild local IV site irritation.[5]

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.[6]

During the study, 148 patients received a cumulative total of 3740 infusions of patisiran, and 77 patients received a cumulative total of 1637 infusions of placebo. IRRs were observed in 28 patients (18.9%) in the patisiran arm and 7 patients (9.1%) in the placebo arm. Severity of an IRR was categorized as mild, moderate, or severe depending on the actions taken to manage the IRR (**Table 1**).[2]

Table 1. APOLLO: Categorization of Infusion-Related Reactions.[2]

Categorization	Description
Mild	Infusion may be continued; if intervention is indicated, it is minimal, and additional treatment (other than paracetamol for delayed reactions) is not required.
Moderate	Requires treatment including more intensive therapy (e.g., IV fluids, NSAIDs) in addition to infusion interruption but responds promptly to medication. Treatment is indicated for ≤24 hours.
Severe	Not rapidly responsive to medication or to interruption of infusion; and/or prolonged treatment (indicated for >24 hours); recurrence of severe symptoms following initial improvement.

Abbreviations: IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs.

In the patisiran arm, all IRRs were either mild (95.2%) or moderate (4.8%) in severity, and most IRRs were managed without additional medications (**Table 2**). Signs and symptoms of IRRs reported in ≥2% of patients in the patisiran arm were back pain (6.1%), flushing (4.1%), nausea (3.4%), headache (2.7%), arthralgia and dyspnea (2.0% each). Flushing was reported in 7.8% of patients in the placebo arm, suggesting this adverse event may be due to the premedication regimen (given in both the patisiran and placebo arms) or causes other than patisiran.[2]

Table 2. Severity of Infusion-Related Reactions in the APOLLO Study.[2]

Number of patients with at least 1 IRR / Number of IRRs, n (%)	Placebo (n=77)		Patisiran (n=148)	
	Patients	IRRs	Patients	IRRs
At least 1 Mild IRR	7 (9.1)	78 (98.7)	25 (16.9)	138 (95.2)
Medication received	1 (1.3)	18 (22.8)	5 (3.4)	10 (6.9)
No medication received	7 (9.1)	60 (75.9)	23 (15.5)	128 (88.3)
At least 1 Moderate IRR	1 (1.3)	1 (1.3)	6 (4.1)	7 (4.8)
Medication received	1 (1.3)	1 (1.3)	3 (2.0)	3 (2.1)
No medication received	0	0	3 (2.0)	4 (2.8)
At least 1 Severe IRR	0	0	0	0

Abbreviations: IRR = infusion-related reaction.

IRRs were managed, depending on the severity, by slowing or temporarily stopping the infusion. In the patisiran arm, 8 patients (5%) had a total of 17 infusion interruptions due to IRRs. In 15 of the 17 infusion

interruptions, the patients resumed and completed their infusion of patisiran. The majority (approximately 80%) of the IRRs requiring interruptions occurred within 30 minutes of the start of the infusion. Of the 8 patients with infusion interruptions, all had their first IRR within the first 2 infusions of patisiran and their first interruption of an infusion within the first 4 infusions of patisiran[2]:

- 5 patients resumed the infusion with no change in the rate of the infusion.
- 2 patients resumed the infusion at a slower rate and received subsequent infusions at a slower rate.
- 1 patient discontinued treatment and withdrew from the study due to flushing of the face (moderate in severity) that began at the start of the infusion; the patient received a partial infusion.

The proportion of patients with IRRs and the number of IRRs decreased over time in the APOLLO study. Among patients with IRRs, the median number (range) of IRRs was 2.5 (1–24) in the patisiran arm and 11.0 (1–15) in the placebo arm. Of the patients in the patisiran arm who experienced IRRs, 78.6% had their first IRR within the first 2 infusions. Symptoms were more common earlier in the course of treatment and did not increase in frequency or severity with repeated patisiran infusions.[2]

Global Open-Label Extension Study

The Global OLE study (N=211) was a multicenter, international study designed to evaluate the long-term safety and efficacy of IV patisiran in patients with hATTR-PN. Patients with hATTR-PN who completed the patisiran Phase 2 OLE study or phase 3 APOLLO study and met eligibility criteria were able to start or continue IV patisiran 0.3 mg/kg every 3 weeks for up to 5 years. The study enrolled 25 patients from the patisiran Phase 2 OLE study (Phase 2 OLE-patisiran group), 137 patients from the APOLLO-patisiran arm (APOLLO-patisiran group), and 49 patients from the APOLLO-placebo arm (APOLLO-placebo group).[7]

Over the 5-year period of the Global OLE, the most common treatment-related AE was IRR, which occurred in 13 patients (26.5%) in the APOLLO-placebo group, 17 patients (12.4%) in the APOLLO-patisiran group, and 4 patients (16%) in the Phase 2 OLE-patisiran group. The types of AEs reported were similar to those observed in APOLLO.[7]

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.[8]

During the 12-month double-blind treatment period of the study, 22 patients (12%) in the patisiran arm and 16 patients (9%) in the placebo arm experienced IRRs. One patient in the patisiran arm discontinued the trial regimen due to a mild IRR.[8]

In the 24-month analysis of the APOLLO-B OLE, the most common treatment-related AE was IRR, which occurred in 15% of patients.[9]

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.[10]

In the patisiran arm of the HELIOS-A study, 10 patients (23.8%) experienced IRRs.[10]

Phase 3b Post-OLT Study

A phase 3b, open-label study was conducted to evaluate the safety, efficacy, and pharmacokinetics of patisiran in patients with hATTR-PN progression post-OLT. Patients in the study (N=23) received IV patisiran 0.3 mg/kg every 3 weeks for 12 months.[11]

During the study, 6 patients (26.1%) experienced IRRs. Signs and symptoms of IRRs were all mild to moderate, which included back pain that occurred in 4 patients (17.4%). Four patients had an infusion interruption due to an IRR, but the entire dose was completed in each case. One patient reported an IRR that was considered a SAE of dizziness related to patisiran. This event occurred after the first patisiran infusion, resolved by the following day without intervention, and did not recur at subsequent infusions.[11]

Pooled Safety Population

The pattern of IRRs was evaluated in a pooled safety population, which included data from 636 patients who received patisiran in clinical studies for up to 88.6 months. Clinical safety data was collected from the Phase 2 OLE, APOLLO, Global OLE, APOLLO-B, HELIOS-A, and Phase 3b post-OLT studies. IRRs were reported in 20.4% of patients and were mostly mild (14.0%) in severity, with 39 patients (6.1%) reporting moderate IRRs and 2 patients (0.3%) reporting severe IRRs. Among a total of 32,009 doses given to 636 patients, 94 infusions were interrupted due to IRRs for 35 patients. Most infusions (92.6%) that were interrupted were completed, and the full dose was administered. Four patients (0.6%) discontinued treatment due to an IRR that was either mild or moderate in severity. As with the APOLLO study, the number of patients experiencing IRRs and the number of IRRs decreased over time.[3]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns involving IRRs. An analysis of the available data did not change the understanding of the severity, frequency, or nature of IRR-related AEs observed with patisiran.[4]

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following sections of the ONPATTRO Prescribing Information[1]:

- WARNINGS AND PRECAUTIONS Section 5.1 Infusion-Related Reactions
- PATIENT COUNSELING INFORMATION Section 17 Infusion-Related Reactions

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; IRR = infusion-related reaction; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; NSAIDs = nonsteroidal

anti-inflammatory drugs; OLE = open-label extension; OLT = orthotopic liver transplantation; SAE = serious adverse event; wtATTR = wild-type transthyretin amyloidosis.

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