Patisiran: Arthralgia

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SUMMARY

- In the APOLLO study, arthralgia occurred in 7% of patients in the patisiran arm and was not reported in the placebo arm during the 18-month treatment period.[1] Arthralgia was reported as a symptom of IRR in 3 out of 148 patients (2%) over the 18-month treatment period.[2]
- In the APOLLO-B study, arthralgia occurred in 14 out of 181 patients (8%) in the patisiran arm and 8 out of 178 patients (4%) in the placebo arm during the 12-month treatment period.[3]
- In the HELIOS-A study, arthralgia occurred in 4 out of 42 patients (9.5%) in the patisiran reference arm and 13 out of 122 (10.7%) in the vutrisiran arm during the 18-month treatment period.[4]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns involving arthralgia.[5]

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CLINICAL DATA

APOLLO

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]

Arthralgia occurred in 7% of patients in the patisiran arm. No cases of arthralgia were reported amongst patients in the placebo arm.[1]

Arthralgia was reported as a symptom of IRR in 3 out of 148 patients (2%) over the 18-month treatment period.[2]

To minimize the risk of IRRs, patients in the APOLLO study received the following premedications or equivalent at least 60 minutes before each study drug infusion[6,7]:

- IV dexamethasone (10 mg)
- Oral paracetamol/acetaminophen (500 mg)
- IV H1 blocker (e.g., diphenhydramine 50 mg)
- IV H2 blocker (e.g., ranitidine 50 mg, famotidine 20 mg)

Patients were started on the above premedication regimen. However, modifications to the premedication doses were allowed after consultation with the medical monitor either due to a patient's inability to tolerate one or more of the premedications or to the occurrence of IRRs unresponsive to a reduction in the infusion rate.[7]

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 OLE period.[3]

Arthralgia occurred in 14 out of 181 patients (8%) in the patisiran arm and 8 out of 178 patients (4%) in the placebo arm during the 12-month treatment period.[3]

To minimize the risk of IRRs, patients in the APOLLO-B study received premedications at least 60 minutes before each study drug infusion.[8]

HELIOS-A

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.[4]

Arthralgia occurred in 4 out of 42 patients (9.5%) in the patisiran reference arm and 13 out of 122 (10.7%) in the vutrisiran arm during the 18-month treatment period.[4]

To minimize the risk of IRRs, patients randomized to patisiran received premedications at least 60 minutes before each patisiran infusion. Patients randomized to vutrisiran did not require premedication.[4]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns involving arthralgia. The analysis of the available data does not change the understanding of the severity, frequency, or nature of IRR-related AEs, including arthralgia.[5]

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

The ADVERSE REACTIONS section provides the following information[1]:

> *Upper respiratory tract infections and infusion-related reactions were the most common adverse reactions. One patient (0.7%) discontinued ONPATTRO because of an infusion-related reaction.*
>
> *Table 1 lists the adverse reactions that occurred in at least 5% of patients in the ONPATTRO-treated group and that occurred at least 3% more frequently than in the placebo-treated group in the randomized controlled clinical trial.*

Table 1: Adverse Reactions from the Placebo-Controlled Trial that Occurred in at Least 5% of ONPATTRO-treated Patients and at Least 3% More Frequently than in Placebo-treated Patients

Adverse Reaction	***ONPATTRO N=148 %***	***Placebo N=77 %***
Upper respiratory tract infections[a]	*29*	*21*
Infusion-related reaction[b]	*19*	*9*
Dyspepsia	*8*	*4*
Dyspnea[c,d]	*8*	*0*
Muscle spasms[c]	*8*	*1*
Arthralgia[c]	*7*	*0*
Erythema[c]	*7*	*3*
Bronchitis[e]	*7*	*3*
Vertigo	*5*	*1*

[a]Includes nasopharyngitis, upper respiratory tract infection, respiratory tract infection, pharyngitis, rhinitis, sinusitis, viral upper respiratory tract infection, upper respiratory tract congestion.
[b]Infusion-related reaction symptoms include, but are not limited to: arthralgia or pain (including back, neck, or musculoskeletal pain), flushing (including erythema of face or skin warm), nausea, abdominal pain, dyspnea or cough, chest discomfort or chest pain, headache, rash, chills, dizziness, fatigue, increased heart rate or palpitations, hypotension, hypertension, facial edema.
[c]Not part of an infusion-related reaction.
[d]Includes dyspnea and exertional dyspnea.
[e]Includes bronchitis, bronchiolitis, bronchitis viral, lower respiratory tract infection, lung infection.

The WARNINGS AND PRECAUTIONS section provides the following information[1]:

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRRs. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. IRRs led to infusion interruption in 5% of patients.

Patients should receive premedications on the day of ONPATTRO infusion, at least 60 minutes prior to the start of infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the ONPATTRO infusion and instituting medical management (e.g., corticosteroids or other symptomatic treatment), as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of one or more of the premedications with subsequent infusions to reduce the risk of IRRs.

The DOSAGE AND ADMINISTRATION section provides the following information[1]:

Required Premedication

All patients should receive premedication prior to ONPATTRO administration to reduce the risk of infusion-related reactions (IRRs). Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion:

- *Intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent)*
- *Oral acetaminophen (500 mg)*
- *Intravenous H1 blocker (e.g., diphenhydramine 50 mg, or equivalent)*
- *Intravenous H2 blocker (e.g., ranitidine 50 mg, or equivalent)*

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions related to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent.

Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRRs.

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; OLE = open-label extension; wtATTR = wild-type transthyretin amyloidosis.

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