Patterns of Troponin I Elevations in Patients with SMA Treated with Onasemnogene Abeparvovec: Real-World Findings from the RESTORE Registry

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Introduction

- SMA is characterized by progressive loss of muscle strength and function, and the cardiovascular system may also be impacted[1–3]
- OA, a one-time, intravenous, AAV9 vector-based gene replacement therapy has demonstrated improved motor function and survival for patients with SMA in clinical trials[4–10]
- Elevations in troponin I, a biomarker that may indicate myocardial injury, were observed in some patients before and after OA treatment in clinical trials[11–13]
- While the clinical significance of troponin I elevations after treatment with OA is unknown, these elevations, coupled with consistent cardiac findings in preclinical studies,[11] led to the recommendation to monitor troponin I before and after OA[4]
- The RESTORE registry (NCT04174157) is a prospective, multicenter, multinational, non-interventional, treatment-neutral registry of patients with SMA designed to build on existing real-world data on treatment patterns and long-term outcomes for these patients[10,14]
- RESTORE provides an opportunity to evaluate the nature, incidence, and severity of cardiac AEs in OA-treated patients, and to explore potential correlation with troponin I elevations

Objective

- We sought to describe the magnitude and duration of troponin I elevations, cardiac AEs, and motor outcomes for patients with SMA treated with OA (alone or with other SMA treatments) who were enrolled in RESTORE

Methods

- RESTORE target enrollment was reached after a 5-year enrollment period and has a follow-up duration up to 15 years (**Figure 1**)[14]
- As of May 2023, 519 patients with SMA were enrolled in RESTORE
- All patients treated with OA were included in this subanalysis
  - Any potentially OA-related AEs reported in RESTORE were reviewed (up to May 23, 2023, data cutoff) to identify patients with troponin I elevations (≥0.04 ng/mL) at varying time points after OA treatment
  - Troponin I assays were performed at a variety of clinical laboratories per the treating physician (i.e., no central laboratory, with some inter-laboratory variability expected)
  - Outcomes assessed for patients with troponin I elevations included:
    - Baseline demographics and clinical characteristics
    - Troponin I concentrations at each visit, when known
    - Safety (cardiac AEs) for patients with or without troponin I elevations
      - Echocardiograms evaluated any potential of structural abnormalities or thrombosis
    - Motor outcomes
      - Motor milestone achievement measured by performance criteria from the WHO MGRS and the Bayley Scales of Infant and Toddler Development[15–17]
      - Motor function measured by CHOP INTEND

Figure 1. RESTORE study design

RESTORE Global SMA Registry

Patients	Prospective, multicenter, multinational, observational study
≥500 patients with genetically confirmed 5q SMA • With appropriate consent/assent to participate • Not enrolled in any interventional clinical trial involving an investigational medicinal product for SMA	Rolling enrollment over a 5-year period → Followed for up to 15 years or until early termination Patient care will follow usual SMA treatment practices in each country and participating clinical sites
Study objectives	**Enrollment sources**
• Primary objective is to assess the effectiveness of treatments for SMA, short- and long-term safety, and overall patient survival • Secondary objectives include the assessment of HCRU, caregiver burden, and changes in patient functional independence over time	• Individual *de novo* clinical sites • MAP: patients from the US MAP cohort and patients from the single-patient IND program are included in the registry. The US MAP provided onasemnogene abeparvovec access to eligible patients with a genetic diagnosis of SMA, which ended with US FDA approval of onasemnogene abeparvovec.

HCRU, health care resource utilization; IND, investigational new drug; MAP, managed access program; SMA, spinal muscular atrophy; US FDA, United States Food and Drug Administration.

Results

Patients

- Of 383 OA-treated patients from RESTORE, 21 patients (5.5%) had ≥1 post-OA troponin I elevation reported as an OA-related AE (**Table 1**)
- Of these, over half were male (11/21; 52.4%), and a majority were symptomatic at diagnosis (15/21, 71.4%), had SMA type 1 (non-sitters) (14/21, 66.7%), and had two *SMN2* gene copies (13/21; 61.9%)
- Mean (SD) ages at SMA diagnosis and at initial treatment were 5.00 (6.66) months and 6.43 (7.44) months, respectively; mean (SD) duration from diagnosis to initial treatment was 1.43 (2.96) months

Table 1. Demographics and clinical characteristics of patients with troponin I elevations

Characteristics	Patients with elevated troponin I N=21
Sex, n (%)	
Male	11 (52.4)
Female	10 (47.6)
Number of *SMN2* gene copies, n (%)	
One copy	0
Two copies	13 (61.9)
Three copies	6 (28.6)
Four copies	1 (4.8)
More than four copies	1 (4.8)
Country, n (%)	
United States	9 (42.9)
Japan	11 (52.4)
Russia	1 (4.8)
Treatment, n (%)[a]	
OA monotherapy	8 (38.1)
Add-on to OA	4 (19.1)
Switch to OA from another DMT	2 (9.5)
Combination	2 (9.5)
Bridging to nusinersen	2 (9.5)
Bridging to risdiplam	3 (14.3)
NBS, n (%)	7 (33.3)
Symptomatic at diagnosis, n (%)	15 (71.4)
SMA type, n (%)	
Type 1	14 (66.7)
Type 2	1 (4.8)
Type 3	1 (4.8)
Missing/not assigned	5 (23.8)
Age at SMA diagnosis, months	
Median (min, max)	2 (0, 23)
IQR	1–7
Mean (SD)	5.00 (6.66)
Age at symptom onset, months[b]	
Median (min, max)	1 (0, 18)
IQR	0–4.5
Mean (SD)	3.38 (5.33)
Age at initial SMA treatment, months	
Median (min, max)	4 (0, 24)
IQR	1–8
Mean (SD)	6.43 (7.44)
Duration from diagnosis to treatment, months	
Median (min, max)	1 (0, 14)
IQR	0–1
Mean (SD)	1.43 (2.96)
Duration of follow-up after OA infusion, months	
Median (min, max)	23.03 (5.29, 38.57)
IQR	14.98–25.07
Mean (SD)	20.76 (8.61)

DMT, disease-modifying treatment; IQR, interquartile range; NBS, newborn screening; OA, onasemnogene abeparvovec; SD, standard deviation; SMA, spinal muscular atrophy *SMN2*, *survival motor neuron 2*.
[a]OA monotherapy: received only OA infusion; Switch to OA from another DMT: longer-duration treatment >3 months with nusinersen or risdiplam, which was then discontinued prior to receiving OA; Add-on to OA: any *SMN*-targeting DMT administered after infusion with OA; Bridging: short-duration treatment with nusinersen or risdiplam (loading doses only or ≤3 months, respectively) serving as a bridge to gene therapy with OA; Combination: initial treatment with nusinersen and/or risdiplam with ongoing or added treatment after infusion with OA; Transient add-on to OA: add-on treatment to OA that is discontinued.[18]
[b]n=16.

Troponin I

- Four of 13 (30.8%) patients with pre-OA infusion measurements had elevated troponin I (Patients 14, 15, 17, and 18) (**Table 2**)

Table 2. Demographics and clinical characteristics for patients with pre-OA elevated troponin I

Characteristics	Patient 14	Patient 15	Patient 17	Patient 18
Sex	Male	Male	Female	Female
Number of *SMN2* gene copies	Three	Three	Three	Three
Country	US	Japan	US	US
Treatment	OA	OA	Nusinersen to OA	OA to risdiplam
NBS	Yes	Yes	No	No
Symptomatic at diagnosis	No	No	Yes	Yes
SMA type	NA	NA	1	3
Age at SMA diagnosis, months	2	5	8	21
Age at symptom onset, months	NA	NA	4	14
Age at initial SMA treatment, months	2	5	14	21
Duration from diagnosis to treatment, months	0	0	6	0
Duration of follow-up after OA infusion, months	6	16	22	26

NA, not available; NBS, newborn screening; OA, onasemnogene abeparvovec; SMA, spinal muscular atrophy *SMN2*, *survival motor neuron 2*.

- Post-infusion troponin I elevations ranged as high as ~13× ULN and elevations ≥2× ULN were recorded for nine of 21 patients (42.9%)
- The median (min, max) troponin I was 0.04 (0, 0.53) ng/mL, with a mean (SD) of 0.05 (0.07) ng/mL
- Troponin I elevations resolved in all cases; recovery to normal levels was observed by the second assessment after initial elevation in over half of cases (**Table 3**)

Table 3. Troponin I measurements for patients with elevated troponin I

Characteristics	Patients with elevated troponin I N=21
Troponin I serum concentration, ng/mL	
Median (min, max)	0.04 (0, 0.53)
IQR	0.02–0.06
Mean (SD)	0.05 (0.07)
Number of troponin I measurements per patient	
Median (min, max)	8 (4, 23)
IQR	5–10
Mean (SD)	8.62 (4.53)
Number of patients with troponin I <0.04 ng/mL by number of assessment(s) after OA infusion, n (%)	
1	8 (38.1)
2	3 (14.3)
3	3 (14.3)
4	4 (19.0)
5	1 (4.8)
6	2 (9.5)
Number of troponin I measurements required to reach <0.04 ng/mL	
Median (min, max)	2 (1, 6)
IQR	1–4
Mean (SD)	2.67 (1.71)
Duration from first post-OA troponin I elevation to <0.04 ng/mL, days	
Median (min, max)	36 (4, 148)
IQR	14–64
Mean (SD)	41.76 (37.57)
Duration from first post-OA troponin I elevation to any AE, days	
Median (min, max)	9 (1, 380)
IQR	2–40
Mean (SD)	54.24 (100.07)

AE, adverse event; IQR, interquartile range; OA, onasemnogene abeparvovec; SD, standard deviation.

Cardiac AEs

- There were no clinical cardiac manifestations in the 21 OA-treated patients with elevated troponin I concentrations
- There were 20 OA-treated patients (5.2%) with normal troponin I with cardiac AEs, most commonly bradycardia (n=6) and dyspnea (n=5) (**Table 4**)

Table 4. Cardiac AEs for patients without elevated troponin I

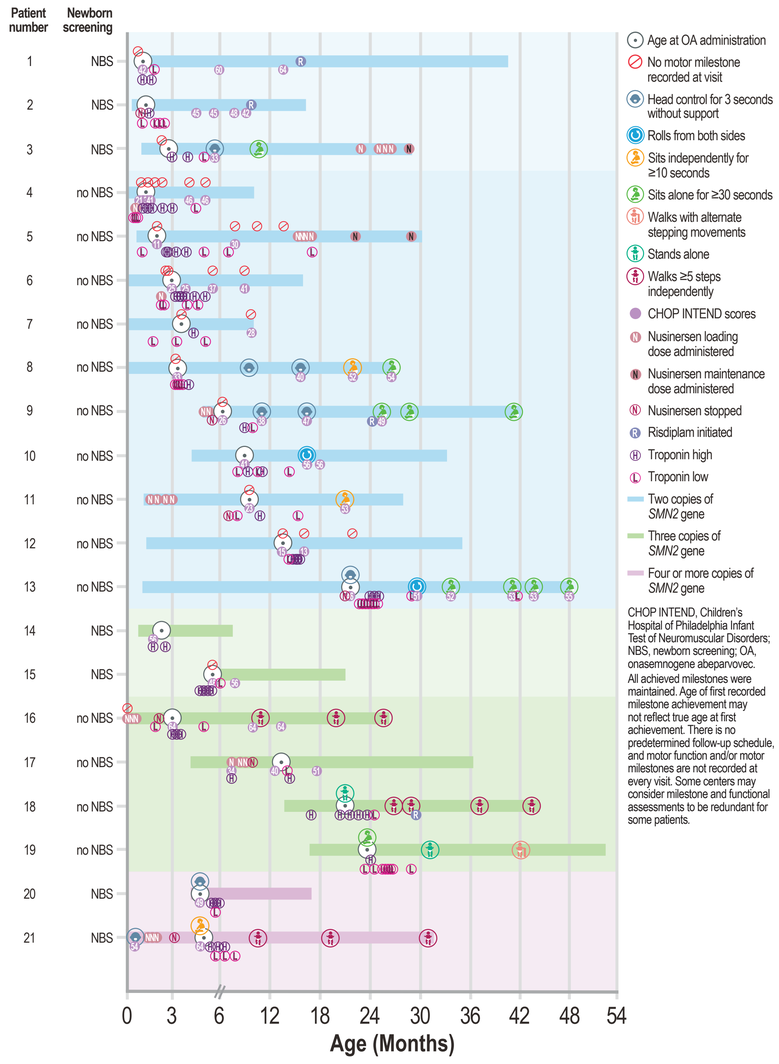
Cardiac AE	Patients without elevated troponin I and with cardiac AEs n=20
Bradycardia	6
Dyspnea	5
Tachycardia	4
Cardiac arrest	3
Elevated CPK-MB	2
Congestion (pulmonary edema)	2
N-terminal prohormone brain natriuretic peptide increased	1
Cardiopulmonary arrest	1
Ventricular hypertrophy	1

AE, adverse event; CPK-MB, creatine phosphokinase-MB.
Four patients had more than one cardiac AE reported.

Motor outcomes

- Of 14 OA-treated patients with troponin I elevations and ≥2 motor milestone assessments, nine (64.2%) attained new motor milestones (**Figure 2**)
- Of 15 OA-treated patients with troponin I elevations who had ≥2 assessments for CHOP INTEND, 13 (86.7%) achieved substantial improvements (≥3 points) between assessments

Figure 2. Motor milestone achievements by age for patients with elevated troponin I



CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NBS, newborn screening; OA, onasemnogene abeparvovec.
All achieved milestones were maintained. Age of first recorded milestone achievement may not reflect true age at first achievement. There is no predetermined follow-up schedule, and motor function and/or motor milestones are not recorded at every visit. Some centers may consider milestone and functional assessments to be redundant for some patients.

Limitations

- The patient population was limited to patients enrolled in the RESTORE registry, and almost half of patients in this cohort were from Japan
- RESTORE is an observational study; therefore, there may be variability in data collection due to clinical site differences
- Some patients had missing pre- and/or post-OA troponin I measurements, limiting interpretation of troponin I patterns

Conclusions

- Troponin I elevations in OA-treated RESTORE patients were transient and self-limiting, returning to normal levels in all patients
- Troponin I elevations were not associated with cardiac AEs, similar to clinical study findings
- Although cardiac events may occur in patients with SMA because of the underlying disease process, these real-world findings in this cohort do not suggest an immediate cardiotoxicity of OA
- In this cohort, there was no evidence of association between troponin I elevation and reduced motor response

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Abbreviations

AAV9, adeno-associated virus 9; AE, adverse event; AESI, adverse event of special interest; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; DMT, disease-modifying treatment; IQR, interquartile range; NBS, newborn screening; OA, onasemnogene abeparvovec; SD, standard deviation; SMA, spinal muscular atrophy; *SMN*, *survival motor neuron*; *SMN2*, *survival motor neuron 2*; ULN, upper limit of normal; WHO MGRS, World Health Organization Multicentre Growth Reference Study.

Acknowledgments and Disclosures

This analysis was funded by Novartis Gene Therapies, Inc.

Medical writing and editorial support was provided by Caryne Craige, PhD, Kay Square Scientific, Newtown Square, PA. This support was funded by Novartis Gene Therapies, Inc.

The authors wish to thank the RESTORE investigators and site coordinators and, most importantly, all of the patients, families, and caregivers for their willingness to participate in this registry, which is sponsored by Novartis Gene Therapies, Inc.

Disclosures: MH received personal compensation from Sarepta Therapeutics, Pfizer, Novartis, and Biogen for advisory board or consulting activities; he is a consultant for Encoded Therapeutics. **LS** received personal compensation as an advisory committee board member/consultant from Novartis Gene Therapies, Inc., Biogen, Biophytis, Cytokinetics, Dynacure, Roche, Santhera, and Sarepta Therapeutics; and has received research support from Novartis Gene Therapies, Inc., Biogen, Dynacure, and Roche. **NB** has received personal compensation from Biogen for advisory board or consulting activities. **PBS** received personal compensation from Novartis Gene Therapies, Inc., Alexion, argenx, Biogen, Catalyst, Grifols, CSL Behring, Genentech, Pfizer, PTC Therapeutics, Sanofi, Sarepta Therapeutics, and UCB; research funding from Abcuro, AMO Pharma, Astellas Gene Therapies, Avidity, Biogen, Dyne, Edgewise Therapeutics, Fulcrum, NMD Pharma, Pfizer, PTC, ReveraGen, Sanofi-Genzyme, Sarepta, and Solid Biosciences. **NLG** received personal compensation from Sarepta Therapeutics for consulting activities. **MAW** received personal compensation from Novartis Gene Therapies, Inc., for advisory board activities and personal compensation from Sarepta Therapeutics for consulting activities. **DR**, **IA**, **FK**, **KB**, and **SPR** are employees of Novartis and hold stock/other equities. **RSF** received personal compensation for advisory board/data safety monitoring board participation from Novartis Gene Therapies, Inc., Biogen, Catabasis, Capricor, ReveraGen, Roche, and Scholar Rock; editorial fees from Elsevier for co-editing a neurology textbook; license fees from the Children's Hospital of Philadelphia; research funding from Novartis Gene Therapies, Inc., Biogen, Capricor, Catabasis, ReveraGen, Roche, and Scholar Rock; and received personal compensation for serving as a speaker for a workshop with the National Academy of Sciences

Presented at the 2024 Muscular Dystrophy Association (MDA) Clinical & Scientific Conference, March 3–6, 2024, Orlando, FL, USA.