Does Early Administration of Disease Modifying Therapy Prevent Early Onset Scoliosis in Young Children with Spinal Muscular Atrophy

Hiroko Matsumoto[1,2], Yuri Ota[1], Thomas Coleman[3], Lennert Plasschaert[1,2], Joyce Huang[1], Amy Pasternak[1], Jason Anari[3,4], Elena Losina[2,5], Robert Graham[1,2], Basil Darras[1,2], Patrick Cahill[3,4], Brian Snyder[1,2]
[1]Boston Children's Hospital, Boston, MA, [2]Harvard Medical School, Boston, MA, [3]Children's Hospital of Philadelphia, Philadelphia, PA, [4]University of Pennsylvania Perelman School of Medicine, Philadelphia PA, [5]Brigham and Women's Hospital, Boston MA
Email: Hiroko.Matsumoto@childrens.harvard.edu

Disclosures: H. Matsumoto: None. Y. Ota: None. T. Coleman: None. L. Plasschaert: None. J. Huang: None. A. Pasternak: 2; Biogen, Scholar Rock. 3B; Biogen, Scholar Rock. J. Anari: None. E. Losina: None. R. Graham: 3B; Astellas Pharmaceuticals. B. Darras: None. P. Cahill: 5; Setting Scoliosis Straight Foundation, Pediatric Spine Foundation. 8; Journal of Bone and Joint Surgery-American. 9; Pediatric Orthopaedic Society of North America, Scoliosis Research Society. B. Snyder: 9; CureSMA.

INTRODUCTION: Spinal muscular atrophy (SMA) is an inherited autosomal recessive neuromuscular disorder characterized by profound weakness due to insufficient production of survival motor neuron (SMN) protein because of deletion or mutation of the *SMN1* gene (exon 7 or 8) on chromosome 5q that results in degeneration of α-motor neurons in the anterior horn of the developing spinal cord. The extent of clinical involvement is determined by the number of *SMN2* "rescue" gene copies that produce a less functional form of the SMN protein: <3 *SMN2* gene copies is associated with profound motor weakness, debilitating medical co-morbidities and excess mortality, while ≥3 *SMN2* gene copies is associated with less morbidity and mortality. Approved in 2016, disease-modifying therapies (DMTs) such as Nusinersin - an intrathecal oligonucleotide and Risdiplam- an oral small-molecule splicing modifier, enable production of functional SMN protein from *SMN2* gene copies; Onasemnogene Abeparvovec uses an intravenous AAV9 virus vector to deliver *SMN1* DNA to transfected cells to enable continuous SMN protein production. Clinical trials demonstrate that DMTs improve survival and motor function depending on the age at administration (≤6 weeks of life)[1-4], *SMN2* gene copy number, and presence or absence of symptoms at birth. However early onset scoliosis (EOS), a skeletal deformity associated with SMA that independently contributes to physical disability, cardiopulmonary compromise, reduced health-related quality of life, and early mortality is little mitigated by DMTs, suggesting that spine pathoanatomy is part of the SMA skeletal phenotype previously unrecognized because of historically high childhood mortality. Thus, there is urgent need to elucidate the determinants of spine pathoanatomy in the expanding population of SMA survivors to develop preventative strategies for EOS in young children with SMA. The purpose of this study was to evaluate the effect of age at DMT initiation, *SMN2* gene copy numbers, symptom status and motor function at birth on the subsequent development of EOS.

METHODS: This IRB-approved multicenter retrospective (2017 – 2025) study included consecutive SMA infants receiving DMT within the first year of life. EOS was diagnosed on spinal X-rays as a Cobb angle ≥10°. Timing of DMT initiation was categorized as early (age ≤6 weeks) vs late (>6 weeks). Associations between DMT timing and age at EOS diagnosis were evaluated using Cox regression models, stratified by *SMN2* copy number (<3 vs. ≥3), symptom status at birth, and pre-DMT motor function assessed by Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders **(**CHOP-INTEND).

RESULTS: Of 129 children, 84 (65%) developed EOS at a mean age of 2.2 ± 1.5 yrs. (range 0.2–7.1), with a mean major spine deformity coronal magnitude of 33±23° on sitting X-ray or 29±14° on supine X-ray. EOS occurred in 68% of males and 62% of females (p=0.455). *SMN2* copy number was predictive of EOS (p=0.001): developing in 100% of infants with 1 copy (n=4/4), 71% with 2 copies (n=71/100), 43% with 3 copies (n=9/21), and 0% with 4 copies (n=0/4). Using a binary cutoff, EOS developed in 72% of infants with <3 *SMN2* copies compared to 36% with ≥3 (p<0.001). EOS was observed in 77% of symptomatic and 67% of pre-symptomatic infants (p=0.546). Baseline CHOP-INTEND was significantly lower (p=0.004) in infants developing EOS (45±10) compared to those that did not develop EOS (54±13). The type of DMT initially administered appeared to affect EOS onset (p=0.010), developing in 74% of infants treated with nusinersen, 61% of infants treated with onasemnogene abeparvovec, and 31% of infants treated with risdiplam, however, when adjusted for age of administration, DMT type was not associated with EOS risk (hazard ratio (HR)=1.15, p=0.500). Age at DMT initiation significantly influenced risk (p<0.001): EOS occurred in 31% of infants treated by age 6 weeks vs. 82% treated later. Among infants treated after age 6 weeks, subsequent DMT initiation did not lessen EOS risk regardless of timing. Stratified analyses demonstrated that the development of EOS varied by *SMN2* copy number, timing of DMT and symptom status (Fig. 1). Among infants with <3 *SMN2* copies, EOS occurred in 46% of those receiving early-DMT vs. 82% receiving late-DMT (p<0.001), while infants with ≥3 *SMN2* copies, no EOS occurred in those receiving early-DMT vs. 82% of those receiving late-DMT (p<0.001). For pre-symptomatic infants, in those with <3 *SMN2* copies, early-DMT reduced EOS risk by 54% (HR=0.46, p=0.033), but in those with ≥3 *SMN2* copies, early DMT eliminated risk (HR≈0). No significant associations were observed among symptomatic infants, regardless of *SMN2* copy number.

DISCUSSION: For SMA, the efficacy of DMT mitigating EOS is influenced by the age of administration (age ≤ 6 weeks), *SMN2* copy number, and symptom status at birth. Among infants with <3 *SMN2* copies, most developed EOS by age 4, but risk was partially (~30%) moderated if DMT was initiated by age 6 weeks. These results underscore the need for universal neonatal SMA screening and routine bi-annual radiographic surveillance in high-risk (<3 *SMN2* copies and/or DMT after 6 weeks) children.

SIGNIFICANCE/CLINICAL RELEVANCE: This study reveals that *SMN2* gene copy number, symptom status at birth, and timing of DMT initiation impact the risk of developing EOS in SMA. Since the age of DMT administration is the only modifiable variable that can reduce EOS in certain genotypes, these findings provide a strong scientific premise for early diagnosis of SMA via universal neonatal screening and the need for early DMT intervention by age 6 weeks to diminish EOS risk. This study also establishes the need for routine surveillance of spinal deformity in high-risk children to initiate EOS treatment strategies in a timely fashion before the deformity becomes severe.

REFERENCES: 1. De Vivo DC et al. Neuromuscul Disord. 2019. PMID: 31704158. 2. Vill K et al. Neuromuscul Dis. 2019. PMID: 31594245. 3. Strauss KA. Nat Med.2022. PMID: 35715567. 4. Strauss KA. Nat Med. 2022. PMID: 35715566.

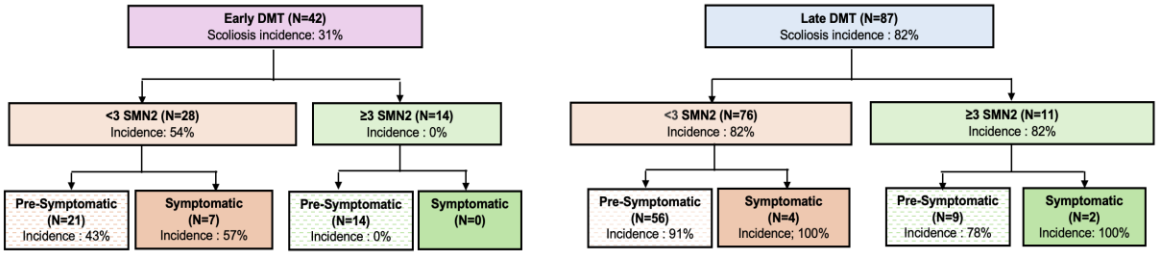

Figure 1. Incidence of EOS diagnosis in patients who administered DMT within the first year of their lives