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Elective Preterm Birth for Earlier Spinal Muscular Atrophy Treatment

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Motor neuron degeneration starts in 3rd trimester

Gestation ▶ Birth ▶ Early Postnatal Life

In utero therapy

- Experimental
- Limited safety data

Birth at 39 gestational weeks

Day 2
Risdiplam

Planned Preterm Birth (35+4) → Immediate Postnatal Treatment

- Planned preterm birth
- Immediate postnatal treatment
- Pragmatic alternative

Day 2
Risdiplam

Month 2
Zolgensma

Term Birth

- Later treatment
- Neuron loss already ongoing

Term Birth → NBS → Delayed Treatment

- Later treatment
- Neuron loss already ongoing

Balancing timing, risk and feasibility

Elective Preterm Birth for Earlier Spinal Muscular Atrophy Treatment

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Short title: Elective Preterm Birth for Earlier SMA Treatment

Abstract

Spinal muscular atrophy is a severe neuromuscular disorder in which early treatment significantly improves outcomes. Prenatal diagnosis, particularly in fetuses with two *SMN2* copies, presents unique challenges. We report a late-preterm infant diagnosed in utero with homozygous *SMN1* deletion and two *SMN2* copies, whose older sibling developed motor deficits despite early postnatal treatment. Following multidisciplinary consultation, delivery was planned at 35+4 weeks to enable immediate therapy. The infant received oral risdiplam on day 2 of life, followed by intravenous onasemnogene abeparvovec on day 59. Neurofilament light chain levels were normal at birth and remained low, except for a transient rise after gene therapy. Initial motor development was normal until 2 months, when hypotonia appeared, followed by recovery and normalization by 5 months. This case suggests that planned preterm delivery with rapid postnatal treatment may be a pragmatic alternative to in utero therapy for high-risk spinal muscular atrophy, pending further longitudinal data.

Introduction

Spinal muscular atrophy (SMA) is a severe neuromuscular disorder where early treatment with risdiplam, nusinersen, or gene therapy can significantly improve outcomes.[1,2] While newborn screening enables early diagnosis, limited data are available to guide management when the diagnosis is made *in utero*, particularly in foetuses with two copies of *SMN2*, who are at high risk of early-onset disease. Evidence suggests that degeneration begins in the third trimester, with biomarkers indicating substantial motor neuron loss in full-term newborns within the first days of life.[3] Recently, a foetus with SMA and two copies of *SMN2* was successfully treated through the placenta, with the mother receiving oral risdiplam from 32 weeks 5 days' gestation.[4] Although promising, prenatal intervention raises complex medical, ethical, and logistical issues. To date, only this case has been reported, and the long-term safety of such interventions remains to be established.

Patient details and clinical findings

Here, we report a case of a female foetus identified with homozygous *SMN1* deletion and two copies of *SMN2*, following amniocentesis. Her older sibling, diagnosed via newborn screening and treated at day 18, exhibited motor deficit by age 20 months despite early intervention.

Following multidisciplinary meetings involving maternal-fetal medicine specialists, neonatologists, and neuropaediatricians, preterm delivery was planned at 35 weeks and 4 days to enable early postnatal initiation of therapy while avoiding the risks associated with in utero intervention, balancing them with those related to late prematurity.

The infant was delivered via C-section without complications (APGAR scores 7/8/9) and required non-invasive ventilation from birth until day 3 of life, which was attributed to late prematurity. She was discharged on day 17 after achieving feeding autonomy and thermal regulation. Oral risdiplam was initiated on day 2 (D2) of life after MLPA confirmation of the diagnosis. Intravenous onasemnogene abeparvovec was administered at day 59 (D59).

Importantly, light chain phosphorylated neurofilaments, a biomarker of neuronal destruction that is elevated in patients with two *SMN2* copies—even when presymptomatically diagnosed via newborn screening [5]—were within the normal range at birth and remained stable during the first weeks of life (<17pg/ml) *Figure 1*. The level increased during the switch from risdiplam to gene therapy (778pg/ml) and subsequently decreased but remained above normal values [6,7]. Although normative data for premature infants remain limited, additional samples are being collected from healthy late preterm neonates to contextualize these findings.

At 2 months of age, the infant showed no clinical signs of SMA. A CHOP INTEND was performed at that time, with a score of 47/64, which is normal for age. Between 2 and 4 months, axial hypotonia and loss of head control emerged, but neurological improvement was observed from 4 months, with normalization of tone and function by 5 months. Follow-up at 10 months remained positive, with the infant babbling and achieving age-appropriate gross motor milestones, including crawling, weight-bearing on the lower limbs, and supported standing. No CMAPs or additional electrophysiological testing were performed. Clinical and biological follow-up is ongoing.

Discussion

Compared to *in utero* administration—which remains challenging from a regulatory (off-label use), ethical, and financial (as most payers would not reimburse risdiplam in this indication) standpoint—

planned preterm delivery followed by immediate postnatal treatment offers a pragmatic and potentially safer alternative when prenatal diagnosis is established.

While prenatal therapy remains an exciting avenue, evidence is still limited. Beyond the single published case of antenatal risdiplam administration—in which the child presented with an unexplained cerebral malformation not accounted for by genetic analysis—eight additional cases have recently been reported as a late-breaking news during the World Muscle Society 2025[8]. In these cases, clinical evolution was favourable in infants with two *SMN2* copies, whereas the infant with a single *SMN2* copy required tracheostomy and gastrostomy. Although these preliminary observations are encouraging, they remain insufficient to establish safety and generalizability. Moreover, prenatal treatment raises important unresolved questions regarding foetal pharmacokinetics, placental transfer efficiency, and long-term safety, which must be addressed before broader implementation can be considered.

Elective preterm delivery, while enabling earlier treatment, introduces its own risks. Late prematurity may be associated with respiratory distress, feeding difficulties, and thermoregulation challenges. In our case, these complications were transient and manageable, but they must be considered when evaluating the overall benefit-risk profile.

Standard postnatal treatment, although effective in many cases, may be initiated too late to prevent irreversible motor neuron loss, particularly in infants with only two SMN2 copies. Biomarker data suggest that degeneration begins in the third trimester, underscoring the need for timely intervention.

A recent report of premature dizygotic twins diagnosed with SMA and treated with onasemnogene abeparvovec at a corrected gestational age of 33 weeks and 5 days demonstrated favorable short-term outcomes and normal neurodevelopment at 24 months, [9] further supporting the feasibility of this strategy.

Our patient was treated with oral risdiplam on day 2 of life as a bridging therapy until intravenous gene therapy could be administered at day 59. This sequential approach may help minimize early motor neuron loss in high-risk infants allowing enabling treatment 4-5 weeks earlier than term, and

represents a practical compromise between the urgency of early treatment and the technical limitations of gene therapy in the immediate neonatal period.

A limitation of this report is the relatively short follow-up period (10 months at the time of writing). Longer-term outcomes, including achievement of motor milestones and sustained neurodevelopment, are essential to determine the true impact of this strategy.

Nonetheless, enthusiasm for preterm therapeutic strategies must be tempered by the current paucity of data. We advocate for systematic data collection and longitudinal follow-up across the SMA research community to better understand the burden and benefit of each approach—whether prenatal, preterm postnatal, or standard postnatal therapy.

Multicenter registries and collaborative studies will be key to establishing evidence-based guidelines and ensuring safe, equitable access to early treatment strategies.

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Declaration of interests

Tamara Dangouloff has given lectures sponsored by Biogen and Roche. LS has given consultancy/part of the board for Biogen, Novartis, Roche, Scholar Rock, NMD Biopharma, BioHaven, Biomarin, Dyne, Wave, Avidity, Entrada, Pfizer, RegenexBio, Italfarmaco, and Santhera. Other authors declare no conflict of interest.

Author contributions

Tamara Dangouloff: conceptualization, formal analysis, methodology, project administration, writing – original draft. Frédéric Chantraine: resources, validation. Nadège Hennuy: resources, data collection, validation. Vincent Rigo: resources, data collection, validation. Sophie Tribolet: resources, data collection, validation. Laura Vanden Brande: resources, data collection, validation. Laurent Servais: conceptualization, formal analysis, methodology, project administration, supervision, writing– review & editing.

Keywords

Spinal muscular atrophy, newborn screening, prenatal diagnosis, risdiplam, gene therapy, preterm delivery

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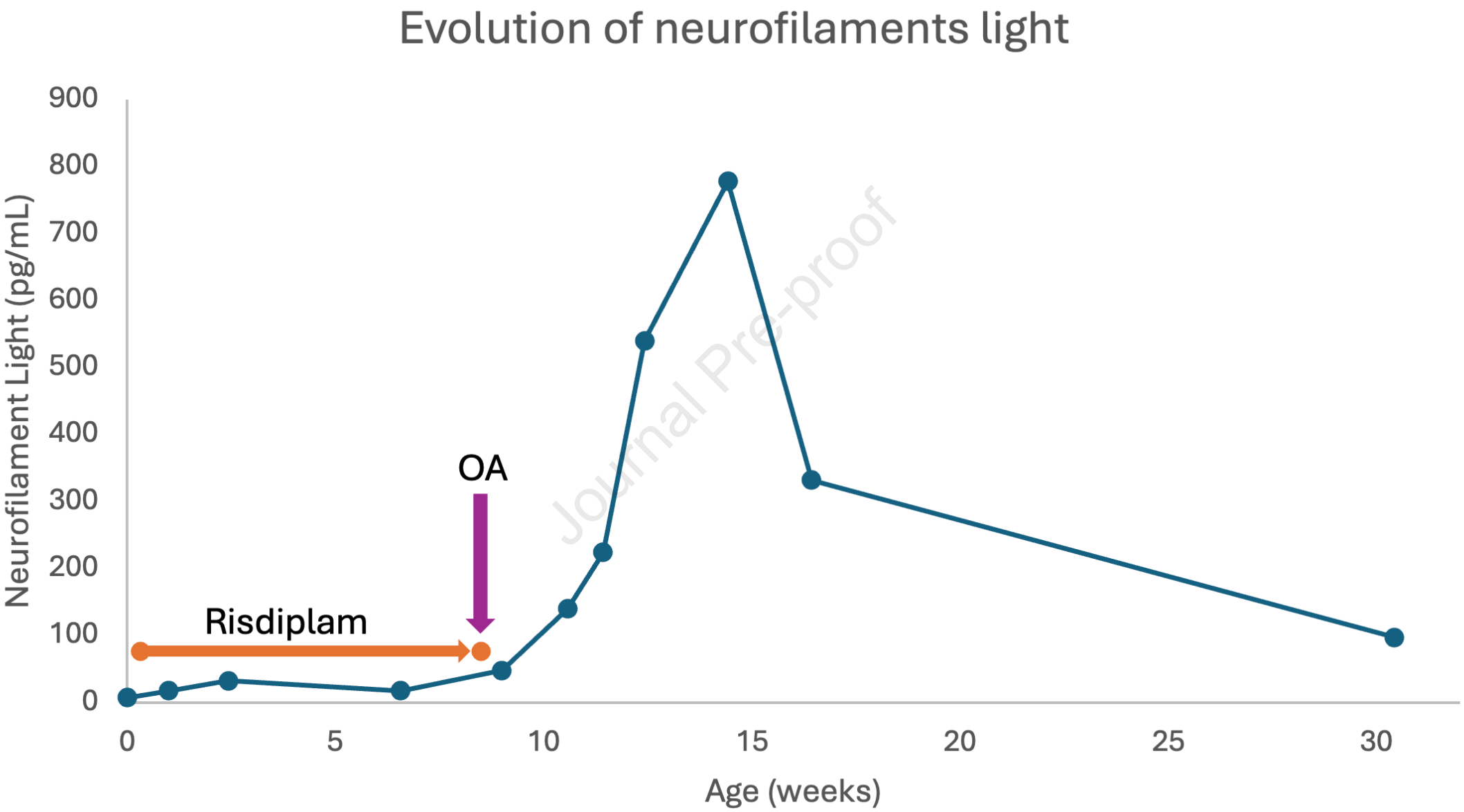
List of figure captions

Figure 1: Evolution of neurofilament light chain values. OA: Onasemnogene Abeparvovec.



Dangouloff and colleagues report a case showing that elective late-preterm delivery enables earlier postnatal treatment for fetuses with spinal muscular atrophy. Their findings suggest that planned preterm birth may offer a pragmatic alternative to in utero therapy, supporting timely neuroprotective intervention while avoiding prenatal treatment risks.