ACTA MYOL 2023;XLII:82-85
doi: 10.36185/2532-1900-356

CASE REPORT

Sequential treatment with nusinersen, Zolgensma® and risdiplam in a paediatric patient with spinal muscular atrophytype 1: a case report

Ilaria Bitetti[1], Maria Rosaria Manna[2], Roberto Stella[2], Antonio Varone[1]

[1] Pediatric Neurology, Santobono-Pausilipon Children's Hospital, Naples, Italy; [2] Rehabilitation Unit, Santobono-Pausilipon Children's Hospital, Naples, Italy

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder that causes muscle atrophy and weakness. While no specific therapies existed until a few years ago, several effective disease-modifying treatments have become available in recent years. However, there are currently no recommendations on the management of therapy sequencing involving these new treatments. A 4-months-old girl with SMA type 1 and two copies of SMN2 was started on treatment with nusinersen resulting in significant improvement in her motor and respiratory function. However, after six doses, treatment was changed to Zolgensma® due to caregiver's decision. In the months following the administration, the patient showed significant clinical improvement in motor performance. After 12 months, the child started therapy with risdiplam in another country. One year after the start of therapy with risdiplam further improvements in both motor and bulbar functions were highlighted. This case report raises a question: is a multiple consecutive theraphy more effective than monotherapy in SMA treatment? These results suggest the need to further explore the potential efficacy of a multidrug treatment.

Key words: gene replacement therapy, nusinersen, neurocognitive function, ona semnogene, abeparvovec, spinal muscular atrophy, risdiplam

Received: March 29, 2023,
Accepted: September 4, 2023

Correspondence
Ilaria Bitetti
Pediatric Neurology, Santobono-Pausilipon Children's Hospital, Naples, Italy
E-mail: Ilaria.bitetti@gmail.com

How to cite this article: Bitetti I, Manna MR, Stella R, et al. Sequential treatment with nusinersen, Zolgensma® and risdiplam in a paediatric patient with spinal muscular atrophytype 1: a case report. Acta Myol 2023;42:82-85. https://doi.org/10.36185/2532-1900-356

Introduction

Spinal muscular atrophy (SMA) is a genetically inherited recessive neuromuscular disease caused by mutations in the survival motorneuron 1 (SMN1) gene located in the 5q13 region on chromosome 5. SMA is characterized by a loss of motorneurons resulting in muscle wasting and weakness. The clinical severity of the disease is strongly related to the copy number of SMN2, an SMN1 paralogue that produces 10-15% of all functional SMN protein [1]. For this reason, SMN2 has become an attractive target for drug development in recent years. In the last few years implementation of the standard-of-care recommendations for SMA and the development and approval of targeted disease-modifying therapies have improved patient survival and modified disease progression [2].

In May 2017, nusinersen became the first drug for the treatment of SMA to be approved by the European Medicines Agency (EMA) [3]. Nusinersen is an antisense oligonucleotide compound that modifies pre-messenger RNA splicing of the SMN2 gene, there by promoting full-length SMN protein production. Its safety and efficacy have been proven by numerous studies [4]. In May 2019, the FDA approved the second drug for the specific treatment of SMA, Onasemnogene abeparvovec, which is an adeno-associated virus (AAV) vector-based gene therapy designed to deliver a functional copy of the human SMN gene.

It is authorized in SMA 5q patients with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1 or up to 3 copies ofthe SMN2 gene in the European Union [5]. The rapid and early benefits of onasemnogene abeparvovec have been demonstrated through numerous clinical trials and real-world studies [6-7]. A new therapeutic option more recently made available is risdiplam, a small molecule that works by modifying the amount of SMN protein that'smade from the SMN2 gene which was approved by the United States Food and Drug Administration in August 2020 [8].

In this exciting era where different treatment options are available for SMA patients, there is still limited data onthe use of different subsequential therapies. We report a paediatric female patient diagnosed with SMA type 1 who received consecutive therapy with nusinersen Zolgensma® and risdiplam.

Case report

A 4-months-old girl diagnosed with SMA type 1 at 3,5 months of age. The onset of the disease occurred at 3 months with generalized hypotonia and loss of head control. Examination by the paediatric neurologist demonstrated tongue fasciculations, oral feeding difficulties due to inefficient sucking patterns, absent reflexes and proximal predominant weakness that was most severe in the lower limbs. Molecular genetic testing revealed deletion of SMN1 and two copies of SMN2 which confirmed the diagnosis. Due to the evidenced dysphagia, PEG tube had been inserted endoscopically. At 4 months of age she was initiated on treatment with nusinersen resulting in significant improvement in her motor and bulbar function. At 9 months of age she has gained head control. At 15 months, she still could not sit up; videofluoroscopy demonstrated good liquids wallowing ability and she began to feed liquids orally again. The children's hospital of Philadelphia infant test of neuromuscular disorders (CHOP INTEND scale) showed improvement in overall motor function (total score from 11 to 41) [9]. However, after six doses, treatment was changed to Zolgensma® due to caregiver's decision. She developed moderate/severe thrombocytopenia (platelet count 32,000 per mm3) 1 week after onasemnogene abeparvovec administration; the deficit was treated with a bolus of Ig vein 0.8 mg/kg, and platelet counts normalized within 2 weeks. Hypertransaminasemia was reported in the third week after treatment (maximum ALT value 262 units/L, maximum AST value 297units/L; alanineamino transferase (ALT) and aspartate aminotransferase (AST) values normalized after modifying the dosage of the immunomodulatory therapy with corticosteroids (prednisone 1,5 mg/kg/day), started at the dosage of 1mg/kg/day one day before the treatment according to the EMA SmPCguideline. In the months following the administration the patient showed significant clinical improvement in motor performance, confirmed by the functional motor tests results measured by the CHOP INTEND scale (see Tab. I for timeline and follow-up results). At 2 years, she began sitting with support, and at 27 months, she acquired independent sitting. She also began to eat semisolids orally. 12 months after onasemnogeneabeparvovec administration the child started therapy with risdiplam in another country. One year after the start of therapy with ris-

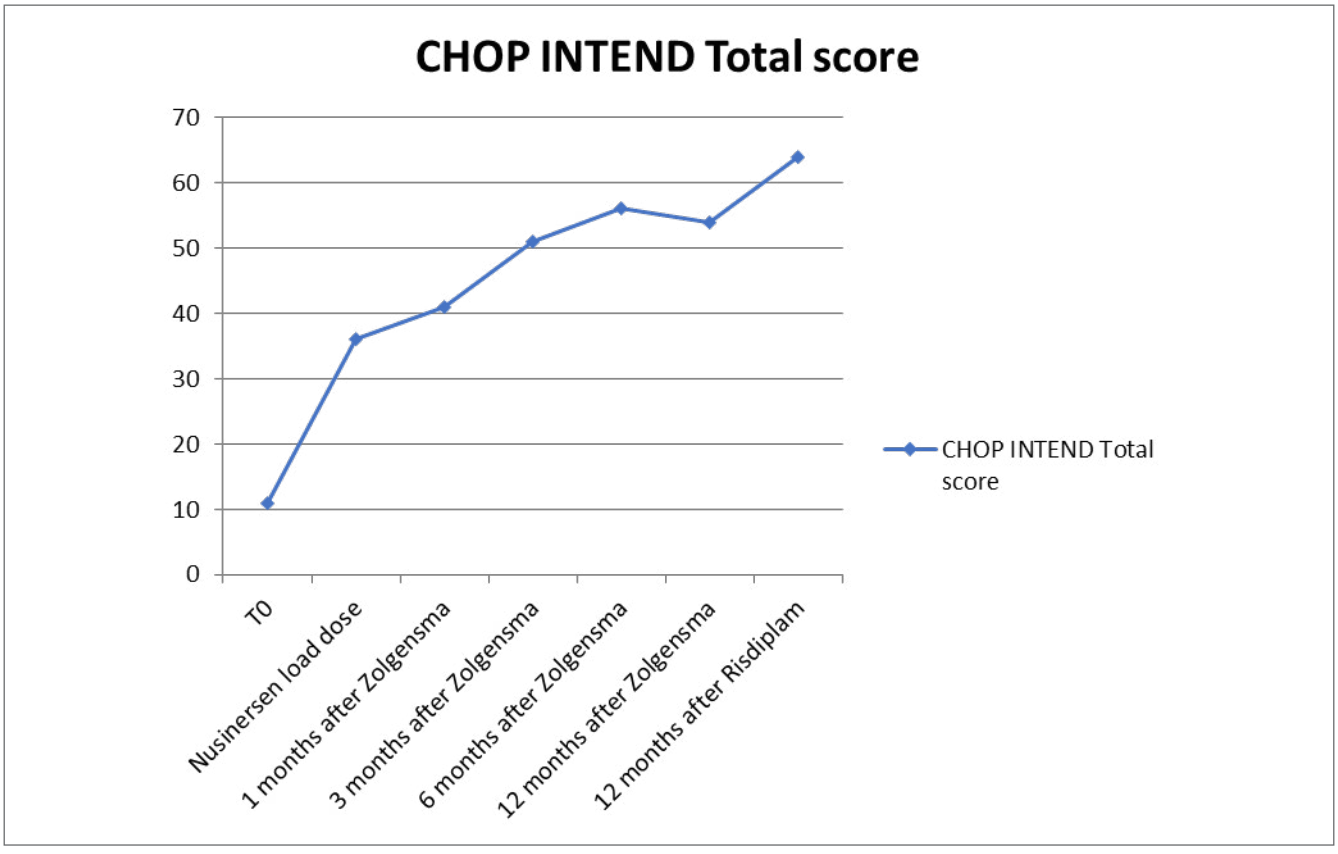

Figure 1. Figure 1. Motor function assessed by CHOP-INTEND scale (total score) during follow-up.

Table I. Patient characteristics treatment and follow-up periods.

	Medication received up to that point	Full blood count, biochemistry, coagulation	Functional Motor Scales assessment				PEDI paediatric evaluation of disability Inventory Computer adaptive test)	Motor milestones	Hospitalization for respiratory complications	Nutrition
			CHOP	HINE 2	HMFSE	RULM				
Baseline (06/2020)	**0**	**Normal**	**11**	**1**	**NA**	**NA**	**NA**	**No head control**	**0**	**Peg**
Nusinersen started										
August 2020	4 dose (12 mg)	Normal	36	3	NA	NA	NA	Head control	0	Peg
April 2021	6 dose (12 mg)	Normal	41	4	NA	NA	NA	Head control	0	Peg/oral intake liquids
Onasemnogene abeparvovec dose (July 2021)										
1 month		Hypertransaminasemia; hypoplatelasemia	43	8	NA	NA	TOT:112 Act: 36 Mob:27 SC: 49	Head Control	0	Peg/oral intake liquids
3 months		Normal	51	9	NA	NA	NA	SWS	0	Peg/oral intake liquids
6 months		Normal	56	12	NA	NA	NA	SWS	0	Peg/oral intake liquids
12 months		Normal	54	13	NA	NA	NA	SWS	0	Peg/oral intake semisolids
Risdiplam started (July 2022)										
12 months after started	4 mg (0,20 mg/kg)	normal	64	16	24	18	TOT:2015 Act: 48 Mob: 49 SC: 60 W: 60	Stands with support	0	Peg/oral intake semisolids

NA = not assessed; SWS = sitting with support; SWNS = sitting without support; Act = Activity; Mob = Mobility; SC = Social and Cognition; W = Wheelchair; PEDI = Pediatric Evaluation of disability inventory, Computer adaptive test.

diplam, further improvements in both motor and bulbar functions were highlighted, reaching the maximum score on the CHOP INTEND scale (64/64) (Tab. I, Fig. 1). Bulbar functions improved with mostly oral semisolid feeding and no respiratory exacerbations reported. A marked improvement in communication-social skills and adaptive skills was also highlighted, confirmed by the administration of the PEDI test (*Pediatric Evaluation of disability inventory, Computer adaptive test).*

Discussion and conclusions

In the reported case, a child diagnosed with SMA 1 and subjected to sequential therapy with nusinersen, Zolgensma® and risdiplam showed continuous improvements in terms of motor function, bulbar function, adaptive behaviors and ADL. Nusinersen and risdiplam had no side effects. Zolgensma® caused hypertransaminasemia and thrombocytopenia, which resolved after week 4. This is the first report of a therapeutic switch from nusinersen to onasemnogene abeparvovec to risdiplam in a child with SMA type 1. Previous studies suggest that onasemnogene abeparvovec may be safe even in patients previously treated with risdiplam [10]. However, this case report raises a question: Is consecutive multiple therapy more effective than monotherapy in the treatment of SMA? It is interesting to underline that both the switch from nusinersen to Zolgensma® and from Zolgensma® to risdiplam was due to decision by the caregiver. Indeed, there are no clear and equal guidelines for all countries regarding the choice of therapies in SMA, where there are indications for all 3 drugs and often the final decision is left to the patient or to the caregiver. Furthermore, the indications differ between countries and the parent may decide to move to another country to change therapy, as happened in the case reported.

While the patient's outcomes are extraordinary even compared to other real-world experiences [6,7], we cannot know whether the patient would have achieved the same goals with monotherapy. So is it right to totally entrust the choice of the drug to the family and what the effects totally delegated to the care giver?

These results suggest on the one hand the need to further explore the potential efficacy of a multidrug treatment, on the other they highlight the need for clearer therapeutic decision-making guidelines for physicians.

Conflict of interest statement

The Authors declare no conflict of interest.

Funding

No financial assistance was received for the study.

Authors' contributions

IB, MRM, and RS provided substantial contributions to the data collection. IB drafted the initial manuscript. AV supervised the project. All authors contributed to the concepts presented, and revised and edited the manuscript.

Ethical consideration

All procedures were in accordance with the standards of the bioethical committee and the Declaration of Helsinki.

References

1 Mercuri E. Spinal muscular atrophy: from rags to riches. Neuromuscul Disord 2021;31:998-1003. https://doi.org/10.1016/j.nmd.2021.08.009

2 Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and managementofspinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. NeuromusculDisord. 2018;28:103-115. https://doi.org/10.1016/j.nmd.2017.11.005

3 Spinraza. European Medicines Agency 2021.

4 Coratti G, Cutrona C, Pera MC, et al. Motor function in type 2 and 3 SMA patients treated with nusinersen: A critical review and meta-analysis. Orphanet J Rare Dis 2021;16:430-442. https://doi.org/10.1186/s13023-021-02065-z

5 European Medicines Agency. Zolgensma (onasemnogeneabeparvovec). https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma.

6 Mercuri E, Muntoni F, Baranello G, et al. Onasemnogeneabeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol 2021;20:832-841. https://doi.org/10.1016/S1474-4422(21)00251-9

7 Bitetti I, Lanzara V, Margiotta G, et al. Onasemnogene abeparvovec gene replacement therapy for the treatment of spinal muscular atrophy: a real-world observational study. Gene Ther 2023;30:592-597. https://doi.org/10.1038/s41434-022-00341-6

8 Dhillon S. Risdiplam: First approval. Drugs 2020;80:1853-1858. https://doi.org/10.1007/s40265-020-01410-z

9 Glanzman AM, Mazzone E, Main M, et al. The children's hospital of Philadelphia infant test of neuromuscular disorders (CHOP INTEND): test development and reliability. Neuromusc Disord 2010;20:155-161. https://doi.org/10.1016/j.nmd.2009.11.014

10 Tosi M, Catteruccia M, Cherchi C, et al. Switching therapies: safety profile of Onasemnogene abeparvovec-xioi in a SMA1 patient previously treated with Risdiplam. Acta Myol 2022;41:117-120. doi:10.36185/2532-1900-077