

Switching therapies: safety profile of Onasemnogene abeparvovec-xioi in a SMA1 patient previously treated with Risdiplam

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Three disease-modifying drugs (Nusinersen, Risdiplam and Onasemnogene abeparvovec) have been approved for SMA type I. Onasemnogene abeparvovec (GRT) can be administered in naïve patients or patients who are already being treated with Nusinersen or Risdiplam. Safety data on GRT in naïve patients or previously treated Nusinersen have been extensively described whereas any case of switch therapy from Risdiplam to GRT has been reported yet. We report on a SMA type I patient treated with Risdiplam by 2 months and switched to GRT at 5 months. She manifested the more common and awaited side effects that resolved in 3 months. The follow-up after 9 months from GRT infusion showed normal blood count, renal and cardiac function. She had great improvement in motor outcome, and no respiratory and bulbar problems as well as normal neurocognitive profile. This case suggests that the GRT may be safe also in patients previously treated with Risdiplam.

Key words: Risdiplam, Onasemnogene abeparvovec, safety, switching therapies

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease, caused by homozygous mutations of the survival motor neuron 1 (*SMN1*) gene, leading to degeneration of alpha motor neurons which results in progressive proximal muscle weakness and paralysis ¹. The disease severity is classified in three main phenotypes from type I to type III on the basis of age of onset and highest motor function achieved ¹. In recent years, three disease-modifying drugs have been approved ². Nusinersen, an anti-sense oligonucleotide (ASO) that acts as an *SMN2* splicing modifier, was the first therapy approved for the treatment of all types of SMA in 2017 ². Onasemnogene abeparvovec (GRT), a gene therapy product devised to insert a functional *SMN1* copy in motor neurons using an adeno-associated viral vector (AAV9), was approved in 2020 for treatment of SMA patients (with different indications by FDA and EMA) ². Risdiplam, the latest approved therapy for all types of SMA, is a small pyridazine derivative molecule, which modifies the splicing of pre-mRNA from the

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SMN2 gene promoting the expression of full-length mR-NA and higher levels of functional SMN protein ².

While mid- and long-term (at least 12 months) follow-up from SMA patients treated with Nusinersen or GRT are available as well as safety data on their combinations or switch ^{3,4}, to date, there is no safety data about the switch from Risdiplam to GRT. Here we report on a SMA type 1 baby treated with Risdiplam from the age of 2 months who switched to GRT at 5 months. To the best of our knowledge, this is the first report describing the safety profile and the clinical outcome of a switching from Risdiplam to GRT.

Case report

The baby was the first child born of unrelated parents coming from an eastern European country. The pregnancy was uneventful. The vaginal delivery was at term and the neonatal period was reported as normal until the age of 30 days, when parents noted a reduction in leg movements. Soon after the neurological examination, a genetic test was performed demonstrating the absence of *SMN1* with two copies of *SMN2*, thus confirming the diagnosis of a SMA type 1. At the age of two months, the baby started treatment with Risdiplam at a dose of 1.6 ml/day that was gradually implemented, according to weight in the following months.

Our first neurological evaluation was performed at the age of 3 months. The child was alert, reactive, showing good visual tracking and interaction with the examiner. In supine traction, the child still did not control her head but she was able to balance her head quite well when sitting with support. She had minimal distal leg movements, and she had subgravity movements at forearms and hands. She presented diaphragmatic breathing without a chest deformity and bulbar function was completely preserved. She fed herself by mouth, without difficulties in swallowing or drooling. The CHOP-INTED score was 32/64. Compound muscle action potential (CMAP) registered from ulnar nerve showed a low voltage (0.4 mV, normal values > 1.7 for age 1-5 months ⁵). In the following months, parents enquired the access to GRT because they planned to move to their country of origin where Risdiplam was unavailable. Thus, extensive blood tests including cells blood count, serum transaminases, serology for hepatotropic viruses and antibody titer for AAV9 were performed, resulting in normal range. The child met all the eligibility criteria, and at the age of 5 months, after a washout period of 3 days from Risdiplam, she received the treatment with Onasemnogene abeparvovec (7.7×10^{14} vg, based on a weight of 6.8 kg). As recommended she started treatment with prednisolone at 1 mg/kg/day the day before the GRT infusion ⁶.

There were no immediate adverse effects. Two days after the infusion, the patient presented fever (T max 38.6°C) and loss of appetite. Five days after infusion, blood chemistry tests showed the presence of hyper-transaminasemia (AST 170 U/L, ALT 131 U/L, normal range > 33 U/L), thrombocytopenia (62.000/uL, normal range 150.000-450.000/uL) and hyper-ferritinemia (4809 ng/ml, normal range 13-150 ng/ml), thus prednisolone was doubled at 2 mg/kg/day. Her liver enzymes and platelet count have gradually normalized, and we proceeded with progressive steroid's reduction until complete suspension after 95 days. Liver ultrasound was always normal.

The last clinical evaluation was performed 9 months after the gene therapy administration. The baby was 14 months old and she presented significant improvement in motor function. She acquired a stable sitting position, she maintained the kneeling position with anterior support and she was able to stand unaided with upper limbs support. Her CHOP-INTEND score was 59/64 and HFMSE score 18/66. No respiratory problems bell-chest or paradoxical breathing were observed. The neurocognitive and speech profile was normal. The blood tests showed normal blood count, renal and cardiac function. She fed by mouth and no swallowing problems were reported, nor chewing fatigue or drooling were observed. She had a good body-weight growth. The ulnar CMAP < 1 mv, showed an increased amplitude (0.6 mV).

Discussion

To the best of our knowledge, this is the first report of a therapeutic switch from Risdiplam to Onasemnogene abeparvovec in a SMA type 1 child.

Monotherapy using Nusinersen, Risdiplam or GRT results in motor milestone achievements, and prolonged survival in symptomatic infants with SMA type 1.

The safety profiles of these modifying therapies are quite well known. The most common side effects related to intrathecal injection of Nusinersen, observed in clinical trials and in clinical practice, are: headache, post-puncture syndrome, back pain, nausea, vomiting, rash, and pyrexia; whereas the most reported risdiplam-related adverse events in clinical trials (FIREFISH and SUNFISH) are fever, diarrhea, mouth and aphthous ulcers, arthralgia, urinary tract infection, constipation, that are seemingly associated with progression of or complications related to the underlying condition, rather than the drug ³.

Common and almost awaited side effects related to GRT are vomiting, loss of appetite, thrombocytopenia and liver enzymes elevation ⁷. These complications are most often mild and self-limiting; however some safety concerns related to GRT include severe liver failure, caused by hepatotoxicity secondary to a hyperinflammatory re-

action and thrombotic microangiopathy, a rare, acute, and life-threatening condition, characterized by microangiopathic hemolytic anemia with thrombocytopenia. These fatal complications occurred in a very low percentage of treated patients⁸.

Following the approval of Onasemnogene abeparvovec, increasingly often, families ask for combined treatments or therapeutic switches. Clinical trials data on combination therapies are lacking whereas in the last two years several observational studies have been published reporting safety and efficacy profiles of SMA type 1 patients who switched from Nusinersen to GRT or viceversa⁹⁻¹².

Risdiplam has been the latest treatment approved for SMA and, up to date, no switching from Risdiplam to GRT has been still reported in SMA type 1.

This has been our first clinical experience of switching from Risdiplam to GRT in a young SMA type 1 patient. The switch was well tolerated; the baby experienced the expected side effects (high transaminases, fever, and thrombocytopenia) that resolved in 3 months under prednisolone treatment. We are certainly aware that the age and the weight as well as the clinical status at the time of infusion have played a crucial role in the good clinical outcome in our patient. However, this case shows that the switch from Risdiplam to Onasemnogene abeparvovec is safe, as already demonstrated for Nusinersen.

The clinical decision regarding the opportunity in switching and the timing of administration of a second therapy is always challenging. Currently, there are no published guidelines or clinical recommendations regarding the switch of therapies in SMA type 1 patients, so it is left to the decision of the clinician if, how and when to proceed.

It is known that Risdiplam and Nusinersen have different mechanisms of action than GRT, but it is unclear whether the combination of these therapies can really increase the SMN expression levels above the monotherapy approach. Moreover, the long-term effects of their concurrent administration in terms of efficacy and safety are not yet known.

In our opinion, it is extremely important to continue collecting safety and efficacy data to answer these questions.

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Conflict of interest statement

AD, MC and EB has received honoraria as scientific consultant and compensation for congress participations from Sanofi Genzyme, Roche and Biogen; AD and EB received honoraria for advisory board activities from Biogen, Roche and Novartis.

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Author contributions

MT, MC: performed data analysis and their interpretation, drafted the manuscript; CC, IM, AC: collect clinical data and evaluate the patient; ADA: planned the study, performed data analysis and their interpretation, revised and submitted the manuscript.

Ethical consideration

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by Ethics Committee of Bambino Gesù Hospital.

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