Defining Meaningful Outcomes for Patients with Spinal Muscular Atrophy in the Era of Gene Therapy

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Introduction

At the 15th Congress of the EPNS, Jana Haberlová, Charles University, Prague, Czechia, and Motol University Hospital, Prague, Czechia; Francesco Muntoni, University College London, UK, and Great Ormond Street Hospital, London, UK; and Eugenio Mercuri, Gemelli University Hospital, Rome, Italy, all of whom have been involved in a number of studies investigating SMA treatment, reviewed efficacy and safety data from RWE settings of onasemnogene abeparvovec. This is a non-replicating recombinant AAV vector that delivers a fully functional, stable, human SMN transgene to the nuclei of motor neurons via use of an AAV9 capsid that can cross the blood-brain barrier. The SMN1 gene in transduced cells is expected to be stably expressed by post-mitotic cells for an extended time. The AAV9 virus is not known to cause disease in humans.1,2 The experts also discussed benefit/cost considerations for this therapy, and managing patient and caregiver expectations in those eligible to receive it.

SMA occurs at a global incidence of approximately 1 out of 10,000 live births, though this can differ by region.3 The muscular weakness and atrophy indicative of SMA is due to motor neuron loss, as a result of reduced expression of SMN protein. This occurs because of a mutation in the SMN1 gene at chromosome 5q11.1−13.3.4 More recently, progression of, and survival with SMA has been improved by disease-modifying therapies that work by allowing SMN expression, to the extent that if SMA is detected early, some
treatments may enable some patients who are pre-symptomatic to achieve age-appropriate motor milestones.5-7 These therapies include onasemnogene abeparvovec;1,2 nusinersen, a splice-switching antisense oligonucleotide;8 and risdiplam, which binds to SMN2 pre-messenger RNA.9 Onasemnogene abeparvovec is a gene therapy approved for SMA treatment,10 with the European indication being for patients with 5q SMA with a bi-allelic mutation in the SMN1 gene, and either a clinical diagnosis of SMA Type 1, or up to three copies of the SMN2 gene.1

Across clinical trials, managed access programmes and commercial settings, currently over 3,000 children with SMA have been treated with onasemnogene abeparvovec.11 Completed trials include START,12,13 STR1VE-US,14 STR1VE-EU,15 and STR1VE-AP16,17 in patients who are symptomatic, and SPR1NT6,7 in patients who are pre-symptomatic. There are ongoing or recruiting trials including long-term follow-up studies LT-001 and LT-00218 in patients who are symptomatic, and OFELIA19 and SMART20 in symptomatic and previously treated patients. LT-002 also follows up patients who are pre-symptomatic, treated in the core SPRINT trial.18 RESTORE is a sponsored SMA registry of patients treated in RWE in co-operation with the main Academic SMA Registries.21

### Real-World Evidence of Onasemnogene Abeparvovec Efficacy in Spinal Muscular Atrophy Gene Therapy

**Jana Haberlová**

The first objective of the symposium was to discuss how RWE data have expanded the use and understanding of onasemnogene abeparvovec treatment beyond the cohorts investigated in the clinical trials. Haberlová discussed how, up to May 2023, there have been 27 peer-reviewed, independent, RWE publications of onasemnogene abeparvovec, including treatment-naive, and those switched from nusinersen or risdiplam. These involved 574 patients with, where data are available, an age range of 2 weeks–6 years, and a weight range of 2.5−17.0 kg (Table 1).2,22-47

<table>
<thead>
<tr>
<th>SMA type</th>
<th>n (%)*</th>
<th>SMN2 copy number</th>
<th>n (%)*</th>
<th>Other treatment</th>
<th>n (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-symptomatic</td>
<td>59 (10.3)</td>
<td>1 copy</td>
<td>3 (0.5)</td>
<td>Bridge</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Type 0</td>
<td>1 (0.2)</td>
<td>2 copies</td>
<td>320 (55.7)</td>
<td>Switch</td>
<td>324 (56.4)</td>
</tr>
<tr>
<td>Type 1</td>
<td>380 (66.2)</td>
<td>3 copies</td>
<td>146 (25.4)</td>
<td>Add-on/combination</td>
<td>10 (1.7)</td>
</tr>
<tr>
<td>Type 2</td>
<td>73 (12.7)</td>
<td>≥4 copies</td>
<td>17 (3.0)</td>
<td>Naïve</td>
<td>236 (41.4)</td>
</tr>
<tr>
<td>Type 3</td>
<td>1 (0.2)</td>
<td>Not reported</td>
<td>88 (15.3)</td>
<td>Not reported</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Not reported</td>
<td>60 (10.5)</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Not all studies report SMA Type or SMN2 copy number.
†One patient in the combination group received only three of the four loading doses of nusinersen and was excluded from the analysis.

N/A: not applicable.
Overall, these RWE data found that administration of onasemnogene abeparvovec in patients with SMA led to stabilisation or improvement of motor function and achievement of motor milestones, and stabilisation or improvement of respiratory function. Also shown was that the efficacy and safety of onasemnogene abeparvovec can be affected by several factors, including clinical status, weight, age, previous treatment, and disease severity at the time of infusion.

Many of the published data of SMA use the CHOP-INTEND measure to ascertain baseline function and track changes over time. CHOP-INTEND was developed to capture specific targeted motor skills that are clinically significant for the SMA-I population. Each of the 16 motor skills, including neck flexion, rolling, hand grip, and spontaneous movement, is scored from 0–4, from none to full ability, for a total possible score of 64. In regard to the efficacy of onasemnogene abeparvovec, RWE data of patients who are pre-symptomatic appear to attain the highest mean increase in CHOP-INTEND scores compared with patients with SMA Type 1 or 2, with motor function outcomes not influenced by SMN2 copy number or sex in patients who are pre-symptomatic. In patients with SMA Type 1 treated with onasemnogene abeparvovec, while an increase in motor function is observed in all age groups, the level of improvement is best predicted by baseline CHOP-INTEND score and age at treatment initiation. For patients who have been previously treated with a disease-modifying therapy, onasemnogene abeparvovec infusion can lead to further respiratory function improvement or stabilisation, and/or achievement of new motor milestones.

From data gathered in the RWE data, Haberlová concluded that, further to clinical trial data, onasemnogene abeparvovec shows efficacy in patients with SMA in terms of symptom stabilisation and improvement.

Adeno-Associated Virus-Based Gene Therapy Benefit/Risk Profile

Francesco Muntoni

Although the benefits of viral vector therapy include how targeted it can be to the cause of a disease (in this case, onasemnogene abeparvovec replaces the missing SMN1 gene and boosts SMN production), there are potential treatment-associated, but manageable, adverse events. An immune response to the vector can arise as, while the virus itself is not pathogenic, a high viral load is needed for AAV-based gene therapies. Due to such potential adverse events, close monitoring is required for a number of weeks pre- and post-onasemnogene abeparvovec infusion. With this in mind, Muntoni discussed how knowing and understanding the overall benefit/risk profile of onasemnogene abeparvovec can help healthcare professionals when making treatment decisions for patients with SMA. Muntoni also stressed the necessity prior to and during an onasemnogene abeparvovec infusion of having a network of colleagues that have been educated with regard to gene therapy, and pre-warned prior to the infusion. “It is critical,” Muntoni said, “that other colleagues, such as physicians and nurses, are aware of what you are doing, because not everyone necessarily has expertise in this field.” Muntoni highlighted the need to “prepare the hospital team, even if 99% of the time they are not involved.”

To aid in identifying typical events following onasemnogene abeparvovec infusion, Muntoni highlighted how, in the first week, events indicative of activation of innate or adaptive immunity includes flu-like symptoms, such as malaise, loss of appetite, and fever, along with vomiting and troponin increase. In the first 2 weeks, an early humoral response and/or an innate immune response against the viral capsid proteins is observed in some patients. This can cause complement activation consistent with thrombotic microangiopathy (TMA), low platelets, troponin release from cardiac muscle and platelets, and kidney and liver injury. Cardiogenic shock has been reported with other AAV therapies; however, Muntoni reported that they had not personally seen this with onasemnogene abeparvovec. In the first month, liver toxicity and inflammation may be indicative...
of a T cell-mediated immune response against the viral capsid.\textsuperscript{51} In the following months, heart muscle inflammation, which can be indicative of a humoral and T cell-mediated immune response against the transgene protein, has been reported with other AAV therapies, but has not been observed with onasemnogene abeparvovec.\textsuperscript{51}

Where safety and tolerability was assessed in onasemnogene abeparvovec RWE settings, TEAEs were reported fairly frequently, but with different degrees of severity.\textsuperscript{2,22,23,28,30,31,36,40-43,46,47} The most common risk associated with AAV-based gene therapies is hepatotoxicity,\textsuperscript{52} as evidenced by liver enzyme elevation.\textsuperscript{2,22,23,28,30,31,36,40-42,46,47} This may be due to the AAV9 vector in onasemnogene abeparvovec having tissue tropism to the liver, as well as to skeletal muscle, the heart, and the brain.\textsuperscript{53} It may also be due to an immune system primed by prior exposure to wild-type AAV, which can result in T cell and humoral immunity against the vector in the liver.\textsuperscript{30,53} With onasemnogene abeparvovec, there appears to be a lower risk of liver transaminase elevation in patients who are younger and/or have a lower body weight, and a higher risk in older, previously treated patients.\textsuperscript{2,23,24,40,41,44,45} According to Muntoni: “More severe liver involvement than usual may be observed in some patients who experience quite significant elevation of transaminases. Although liver failure is exceptional, it can potentially occur.”\textsuperscript{28}

Corticosteroids are used prior to and following onasemnogene abeparvovec infusion, as they can block the T cell response to capsid-derived peptides presented by transduced hepatocytes, and have a role in protecting hepatocytes against apoptosis and preventing cytolysis of ballooned hepatocytes.\textsuperscript{54,55} According to Muntoni: “Corticosteroids appear to be effective in removing the most significant peaks of transaminitis.” Indeed, studies show that elevations in liver enzyme resolve in most cases following such treatment,\textsuperscript{2,23,36,37,40,41,44} and that most patients do not require corticosteroid treatment long term.\textsuperscript{24,30,40,41,44}

Scheduling of corticosteroid administration is detailed in onasemnogene abeparvovec prescribing guidelines.\textsuperscript{1} This includes starting oral prednisolone (or equivalent) at 1 mg/kg/day 24 hours prior to infusion, then continuing this dose for 30 days, followed by 28 days’ tapering if liver enzyme values are below two-times the upper limit of normal.\textsuperscript{1,56} Where liver-related AEs have occurred, short-term treatment with high-dose corticosteroids is advised in the prescribing information of a number of gene therapies, including onasemnogene abeparvovec.\textsuperscript{1,49,57,58} Muntoni confirmed that, “if the patient is having bigger liver problems than you expect, there are protocols for using high doses of steroids, including intravenous administration.” During the panel discussion, when asked if the initial dose should be 2 mg/kg/day prednisolone (or equivalent), Muntoni noted how, in their centre’s experience, this higher starting dose did not make a difference, although it can be used if liver enzymes increase. Mercuri commented how the higher dose may also lead to liver complications; hence, not being suitable for every patient.

Other TEAEs reported following onasemnogene abeparvovec infusion are transient, mild increases in troponin I levels with no aberrant cardiac assessment report;\textsuperscript{2,23,36,41} pyrexia;\textsuperscript{2,23,28,30,36,41,42,47} vomiting; loss of appetite; and diarrhoea.\textsuperscript{2,23,28,30,41-43,47} RWE evidences showed transient thrombocytopenia (where this was assessed) in 16−100% of patients, which generally normalised without intervention.\textsuperscript{2,23,36,37,40,41,44} Also observed, though rare, is TMA.\textsuperscript{42,43} “This is the adverse event that is most important in terms of morbidity,” said Muntoni, “but only exceptionally is it very significant, and it is not difficult to monitor for.” During the panel discussion, Muntoni explained how TMA usually occurs in the first 2 weeks after infusion, but stressed that a patient needs to be monitored very carefully for a potential TMA in the first 3 months.

Due to potential TEAE, patients should be followed-up every 6 months to a year following the initial infusion and have liver function tests as, said Muntoni: “We have an obligation to follow these patients clinically.” Muntoni discussed how vital it is that the family of the patient understand the immediate post-infusion time. “When you describe and discuss [the treatment], managing expectations with the family is important, so they do not receive an AAV gene therapy then disappear for 6 months.” Haberlová confirmed that, in their practice, even cases identified via newborn screening, so treated while pre-symptomatic, are followed up for at least 10 years.
Understanding and Discussing Long-Term Outcomes with Onasemnogene Abeparvovec Across Different Spinal Muscular Atrophy Patient Populations

Eugenio Mercuri

The final objective of this symposium was to explore treatment expectations, and which outcomes are most meaningful for patients and their families. Mercuri discussed how improving understanding of gene therapy predictors and outcomes can aid treatment decisions, and help with expectation management.13,24 Mercuri utilised the results of the recent RWE publication from the Italian experience in treating patients with SMA with onasemnogene abeparvovec in a clinical setting, which they had been involved in Italy to discuss.

In this paper, predictors of the efficacy and safety of onasemnogene abeparvovec were investigated in both treatment-naïve patients (n=19) and those switched from nusinersen (n=46) or risdiplam (n=2). All 67 patients had at least 6 months’ follow-up and an available safety profile, with 46 followed up for 12 months. Patients varied with respect to age (22 days–58 months, with one child of 72 months), weight (3.2–13.5 kg, with the older child being 17.0 kg), and disease severity.24 Mercuri highlighted how these ranges, especially at the higher end, were much broader than those in clinical trials.12–21,59 Most (63 out of 67) patients were symptomatic with SMA Type 1 (94.0%), and four were identified through neonatal screening and were pre-symptomatic. Just over two-thirds (68.7%) of the patients had a CHOP-INTEND assessment at the time of treatment, and at 12 months from first infusion.24

As can be seen from Table 2, independent sitting after onasemnogene abeparvovec infusion was achieved by all patients who were pre-symptomatic, and most of those who were symptomatic but had received another treatment prior to onasemnogene abeparvovec, even if they had not achieved this functional milestone with such treatment. Of the four patients who achieved standing, two were pre-symptomatic and also acquired independent walking at 16 and 17 months; one was symptomatic and treatment-naïve and stood independently at 12 months; while the other was symptomatic and pre-treated, and achieved this motor milestone at 34 months.24

For many patients, their CHOP-INTEND scores did not fall from baseline over the follow-up period, and for some there was an increase from baseline at 12 months. For example, most patients with a baseline CHOP-INTEND score <40 achieved a 12-month score ≥40, with some achieving a score ≥60. The best predictor of change in CHOP-INTEND scores was patient age, with the greatest change in those aged <6 months and the least change in those aged >24 months.24

“It is very important when we counsel families to try to keep their expectations under control,” said Mercuri. In regard to these findings and treatment expectations, Mercuri discussed how “it is important to look at the variability of responses because, while a number of patients did achieve sitting at the time they were taking onasemnogene abeparvovec, some, though very few, never achieved sitting, even if they had been on both [onasemnogene abeparvovec and another] therapies.” Conversely, Muntoni commented in the panel discussion that while the baseline CHOP-INTEND score is useful, these results show that “you could have a low CHOP-INTEND score in a [young] child with a very short disease duration, and significant improvement is still possible.”

Safety findings in this RWE publication reflected those shown in clinical trials12–21,59 with TEAEs within 7 days of onasemnogene abeparvovec infusion, including pyrexia (22.4%), vomiting (20.9%), a two-fold increase in aspartate transferase (AST; 39%), and a two-fold increase in alanine transaminase (ALT; 29.9%). The risk of elevated liver enzymes increased with age and weight, with a 5.76x greater risk of abnormal AST and a 11.08x greater risk of abnormal ALT in patients aged >24 months compared to those aged <6 months (where ‘abnormal’ is defined as two-times the upper limit of normal). No major serious TEAEs were observed.24 Mercuri stressed how the age stratification regarding tolerability and safety results “does not mean we should not treat patients if they are aged over 24 months, but we should be extra careful.”

While shorter term clinical trial and RWE results are promising for onasemnogene abeparvovec, Mercuri commented that “one concern is whether...
these children are going to lose what they have acquired in the first year." LT-001 and LT-002 are two long-term follow-up studies of patients treated with onasemnogene abeparvovec across five clinical trials. LT-001 includes 13 patients with SMA Type 1 enrolled in the START clinical trial, which was carried out between May 2014–December 2017. Participants are planned to be followed up for 15 years with annual visits for 5 years, then annual phone contact for 10 years. The current data cut-off is up to 7.5 years post-dosing. LT-002 includes 38 patients with symptomatic SMA Type 1 (from the STR1VE-US, n=12;14 STR1VE-EU, n=24;15 and STR1VE-AP, n=216,17 trials, run up to February 2020), with the 15-year follow-up consisting of biannual visits (years 0–2), then annual visits (years 3–5), then annual phone contact for up to 10 years. The current data cut-off is up to 4.3 years post-dosing.

Interim data from these studies show the efficacy of onasemnogene abeparvovec up to 7.5 years post-treatment. In LT-001, all included patients who received a therapeutic dose of this drug (n=10), achieved or maintained head control and independent sitting (sitting up straight with their head erect for ≥10 seconds without using arms or hands for balance or support), and two out of 10 (20%) maintained independent walking.

"When we have long-term follow-up, it is also possible to see whether there are additional [safety] concerns which were not addressed in the clinical trial," said Mercuri. "During the 90 days is when we really focus on adverse events," they continued, “but past this time frame, there was no evidence of any new safety signals, even up to 7.5 years post-dosing.” In LT-002, two TEAEs

![Table 2: Achievement of motor milestones following onasemnogene abeparvovec infusion according to patient subgroup (n=66*).](image)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Independent sitting†</th>
<th>Independent standing</th>
<th>Independent walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-symptomatic</td>
<td>100.00% (4/4)</td>
<td>75.00% (3/4)</td>
<td>50.00% (2/4)</td>
</tr>
<tr>
<td>Symptomatic, treatment naïve</td>
<td>37.50% (6/16)</td>
<td>6.25% (1/16)</td>
<td>N/A</td>
</tr>
<tr>
<td>Symptomatic, pre-treated*</td>
<td>82.60% (38/46)</td>
<td>2.17% (1/46)</td>
<td>N/A</td>
</tr>
<tr>
<td>Before onasemnogene abeparvovec</td>
<td>36.80% (14/38)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>After onasemnogene abeparvovec</td>
<td>63.20% (24/38)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*One patient is not included due to non-treatment related fatality.
†Ability to sit without support and without a brace for at least 3 seconds.
N/A: not applicable.
(bronchiolitis and pneumonia) occurring in one patient were deemed potentially treatment-related, but in both studies there were no serious TEAEs that led to study discontinuation, and there were no adverse events of special interest.\textsuperscript{18,60}

In conclusion, Mercuri discussed how RWE\textsuperscript{24} and long-term follow-up\textsuperscript{16,66} data may help clinicians to work with caregivers to set appropriate expectations around gene therapy outcomes in children of different ages. “These data are important,” Mercuri said, “as we all face families who want to switch therapy and the expectations are generally based on the clinical trials, so RWE and long-term evidence help us, as clinicians, to communicate and set up best expectations.” Muntoni also, during the panel discussion, stressed that when counselling parents with a child who has noticeable motor dysfunction, including a low CHOP-INTEND score, bulbar involvement, and respiratory dysfunction, it is important to explain that while they may improve, it may not be to the same extent as a child without this baseline. However, they said, “any outcome is meaningful when it’s different from progression and death, so it’s just a matter of having the right expectations.”

### Conclusion

RWE data of onasemnogene abeparvovec\textsuperscript{2,22-47} support the clinical trial data\textsuperscript{6,7,12-17} and suggest that a wide range of patients with SMA can gain motor and respiratory function stabilisation or improvement following a single infusion. While TEAEs appear to be mostly transient, careful monitoring and long-term follow-up are needed.\textsuperscript{2,22-47} These findings may help healthcare professionals with the treatment decision-making process for patients with SMA.

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**References**


Symposium Review


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