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Treatment strategies for patients with spinal muscular atrophy

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1. *Introduction*

Spinal muscular atrophy (SMA) was until recently the most frequent genetic cause of infant mortality. It is caused by homozygous deletions or biallelic pathogenic variants in the survival motor neuron 1 (*SMN1*) gene [1-2], affecting approximately 1 in 15.000 live births [3]. SMN protein deficiency results in a loss of spinal cord alpha motor neurons, causing progressive muscle weakness and atrophy. There is a broad phenotypic spectrum, ranging from the most severe form SMA type 1, presenting before the age of 6 months (around 60% of the cases), to other forms with later onset and less severe disease course. Importantly, all forms of SMA are progressive, which significantly impacts the patients' perspective on their future and thus their quality of life. The main predictor of severity is the number of *SMN2* copies. This highly homogenous gene can partially compensate for the lack of functional SMN, although other factors not generally tested in clinic have also been identified.

2. *Efficacy and safety of SMA treatments on the market*

Three effective but high-cost disease-modifying treatments (DMTs) have been approved by the United States Food and

Drug Administration (FDA) and the European Medicines Agency (EMA) since 2016, changing the SMA landscape significantly. Nusinersen (Spinraza®) and risdiplam (Evrysdi®) increase the level of SMN protein by modification of *SMN2* splicing. Nusinersen is an antisense oligonucleotide administered by repeated intrathecal injections (4 loading doses on day 0, 14, 28 and 63, and thereafter every 4 months for life), limiting its systemic availability [2]. The most common adverse effects are post-lumbar puncture back pain, headaches and vomiting [4]. The small molecule risdiplam has a similar mechanism of action, but is administered orally, once daily, as a syrup (<2 months: 0.15 mg/kg; 2 months – 2 years: 0.2 mg/kg; >2 years and <20 kg: 0.25 mg/kg; >2 years and ≥20 kg: 5 mg/day) [2]. It is evenly distributed throughout the body, including the central nervous system. Rash, diarrhea, aphthous ulcers and nausea are the most commonly reported side effects [4]. Replacement of the *SMN1* gene is obtained with onasemnogene abeparvovec (Zolgensma®), an adeno-associated vector 9 (AAV9)-based gene therapy, which is administered as a one-time intravenous administration of 1.1 x 10^{14} vector genomes/kg, with systemic availability [2]. Patients need to have anti-AAV9 antibody titers below 1:50 prior to infusion, and receive high-dose corticosteroids, from 24 hours before infusion up to several months after infusion, depending on their liver reaction. The most common side effects are pyrexia, nausea, vomiting, thrombocytopenia, and hepatotoxicity-related adverse events. A few fatal outcomes have been reported due to acute liver failure and thrombotic microangiopathy (TMA) [4,5].

3. Early treatment is better

Clinical trials and many real-world datasets have clearly demonstrated that all these DMTs are highly effective in the

treatment of SMA, especially when started very early and preferably before symptom onset. This evidence justifies that newborn screening for SMA is a medical, ethical, and economical imperative [3,6,7]. However, it is very important to realize that these DMTs do not offer a cure, even for some pre-symptomatically treated patients. Patients with ≥3 *SMN2* copies show normal development when treated pre-symptomatically, but patients with 2 *SMN2* copies, even when treated pre-symptomatically, may show some developmental delay and proximal weakness [3]. Furthermore, in addition to treatment with a drug, follow-up according to the internationally agreed standards of care by a multidisciplinary team of professionals with expertise in SMA remains very important to optimize the outcomes of these novel treatments, especially in symptomatic patients [1,8]. These patients still have muscle weakness with impaired motor function and possible secondary orthopaedic complications, and respiratory problems [8]. Moreover, an emerging unmet need is the growing concern about the neuropsychological profile of early symptomatic patients who now survive, but may present autistic features or expressive language delay [9].

Several other drugs are in clinical or pre-clinical development [10]. The most advanced are certainly anti-myostatin for which three late-stage trials, including two pivotal phase 3 trials, are ongoing. Anti-myostatin aims to promote skeletal muscle mass growth by inhibiting myostatin. Positive results of a phase 3 have been publicaly disclosed in October 2024. Nevertheless, it is still unclear if myostatin can constitute a robust molecular target in older and weaker patients with SMA, as it seems that the pathway is down-regulated in these patients [11]. Another add-on approach that has reached the patient's bedside, concerns neuromuscular junction modulation, either by drugs

that are already approved, such as pyridostigmine, or new agents such as chloride channel blockers [12].

All drugs for SMA have been developed in the context of standards of care [2,5]. Exercise and physiotherapy are paramount in the management of SMA, and recent studies have suggested that regular respiratory exercises may improve respiratory function in treated patients [13].

Finally, limited evidence has been provided for potential improvement in patients undergoing spine stimulation [14].

4. Expert opinion: What treatment to choose?

Back-to-back comparisons between approved medications are currently not available, so the choice of therapy is based on the condition and characteristics of the patient (age, phenotype, genotype, duration of the disease), the label, country-specific reimbursement criteria, practical considerations and parental preferences [2]. Outside the current existing population of symptomatic patients with SMA type 1-4, the population of patients detected by newborn screening is growing, but not all of them are pre-symptomatic. Around 40-50% of patients screened with 2 *SMN2* copies already have symptoms when treatment is started [3]. In addition, patients with point mutations are not detected by newborn screening, and there are still many patients born in countries where newborn screening is not yet implemented.

Patients identified pre-symptomatically or by newborn screening (*pre-symptomatic and early symptomatic*) should receive DMT as soon as possible [15]. Onasemnogene abeparvovec is the most commonly prescribed drug in these patients, but it is not available for patients with ≥4 *SMN2*

copies. The injection can be delayed because of high anti-AAV9 antibody titers or administrative procedures. In these cases, and given the urgency especially in patients with 2 *SMN2* copies, bridging by risdiplam (or nusinersen) to cover the delay before gene therapy is entirely justified [6].

Most of the patients diagnosed before the era of DMTs (2016), were initially treated with nusinersen, as this was the first treatment approved and available. However, in these *late symptomatic* patients as in patients not identified by NBS the development of scoliosis still frequently occurs [8], compromising intrathecal administration. Switching to more convenient oral intake of risdiplam should be discussed in a timely manner with these patients and their families.

For *new symptomatic cases* of SMA, depending on age and country-specific reimbursement criteria, the 3 DMTs may be available. Onasemnogene abeparvovec administration comes with a significant risk in older (≥24 months) and heavier (>13.5 kg) patients, and the benefit to risk ratio should be clearly explained to the parents of these patients [6].

Patients and families often advocate for combination therapies, although evidence of additional benefit remains to be formally demonstrated. In addition, the very high cost of the approved DMTs could question the cost to effectiveness ratio of associating *SMN2*-based approaches with *SMN1* restoration.

In addition, it is important to recognize that management of SMA does not only rely on drug treatment. Optimal outcomes can only be reached when there is a global vision that includes early identification [15] and treatment, and continued multidisciplinary management, including empowering the patients and promoting activity. The importance of long-term

follow-up and standard of care should be underlined in the context of patients travelling abroad to receive a one-shot therapy.

Finally, management of expectations forms a key element in the (success) story. High cost of combination therapies and potential limited efficacy in patients who already have severe atrophy and secondary complications such as contractures and scoliosis, should prompt the physician to communicate clearly and transparently with the patient and the family.

5. Conclusion

The SMA landscape has significantly changed since three disease-modifying drugs (nusinersen, risdiplam and onasemnogene abeparvovec) have become available for these patients. The efficacy and safety of these three products has been shown in clinical trials to be more or less comparable, but in the 'real world' not all three products are always available, and patients often differ from the selected trial subjects. Moreover, not only the condition and characteristics of the patient should be taken into account, but also the label, country-specific reimbursement criteria, practical considerations and parental preferences.

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Declaration of Interest

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