Nusinersen for spinal muscular atrophy

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Spinal muscular atrophy (SMA) therapy has been challenging for decades when considering the severity of the disorder and functional motor impairment on the one hand and the lack of pharmacological treatment options so far on the other. However, the recently approved antisense oligonucleotide (ASO) nusinersen now provides not only an upcoming and promising treatment option for SMA, but may also represent a general pharmacological approach and mechanism of action relevant for other neurodegenerative disorders.

SMA is an autosomal-recessive neuromuscular disorder with degeneration of alpha motor neurons leading to progressive muscular weakness and atrophy. The clinical phenotype is classified into three main subtypes, ranging from severe to mild with regards to the age of onset and achieved motor abilities.[1] The incidence approaches 1:10,000 live births whereas the most severe SMA type I accounts for 60% of cases.[1,2]

The disorder is caused by deletions or loss-of-function mutations in the survival motor neuron (SMN1) gene on chromosome 5q13.[1] In addition to this SMN1 gene, humans possess a homologue SMN2 gene copy that differs from SMN1 due to a C-to-T exchange in exon 7. Hence, the SMN2 gene undergoes an alternative splicing process, resulting in an mRNA with an absent exon 7 that thereby leads to a small amount of full-length SMN protein.[1] Since the identification of the SMN1 gene locus in 1990 and its homologue SMN2 gene copy in 1995, major effort has been devoted to providing potential therapeutic interventions such as replacing SMN1 or decreasing SMN2 exon skipping to increase the total amount of SMN protein.

First investigations into cell cultures observed that ASOs were effective to modulate splicing of SMN transcripts, followed by *in vivo* experiments in transgenic mice that demonstrated increased SMN protein levels and reduced symptoms of the disease. Based on these results, the new ASO nusinersen was administered to 28 SMA patients (1, 3 and 6 mg dose groups with six patients each; 9 mg in 10 patients) to examine the safety, tolerability, pharmacokinetics and preliminary clinical efficacy within an open-label phase I study.[3] No serious adverse side effects were observed and the results indicated a clinically relevant efficacy of the drug at 9 mg dosage. In an open-label dose-escalation phase II study, 20 infants received either 6 or 12 mg nusinersen by intrathecal application on days 1, 15, 85 and 253 with follow-up treatments every 4 months.[4] The authors observed significant improvements in the achievement of motor milestones and function, survival or independency of permanent ventilation and electrophysiological increase of the compound muscle action potential. Safety assessments revealed adverse events but not or unlikely to be related to the drug. However, 4 of the 20 patients died during the study at the applied dosages. Examination of autopsied tissues in three patients revealed a two- to six-fold increase in full-length SMN2 transcripts and increased SMN protein levels, confirming the results of animal studies regarding an efficient splice correction by the drug in humans. Further, 121 symptomatic SMA patients with infantile onset (age $\leqslant$7 months; symptom onset $<$6 months) were included in a randomized double-blind sham-controlled phase III study that demonstrated a significant improvement regarding the achievement of motor milestones in 51% cases under nusinersen *versus* 0% under sham procedure.[5] A second phase III study enrolled 126 symptomatic later-onset patients (median age of 3 years; symptom onset $>$6 months) and could support these promising results by significant improvements in motor functions under nusinersen whereas those randomized in the sham group declined in line with known natural history data.[6] An ongoing open-label phase II study is investigating 20 presymptomatic SMA infants at the age of 6 weeks or younger and interim analyses revealed an achievement of motor milestones that would not be

expected in SMA type I or II and may correspond to normal motor development.[7]

Considering these encouraging results, the development of the ASO drug can be regarded as a milestone in SMA therapy and, consequently, the FDA approved nusinersen in December 2016 followed by an approval of the EMA in July 2017 for all 5q-associated SMA types. The main pharmacological action mechanism of the 2′-O-methoxyethyl phosphorothioate-modified drug nusinersen consists of an alteration of the SMN2 pre-RMA splicing process by inhibiting splicing factors. This facilitates the integration of exon 7 into the mRNA and thereby enhances full-length SMA protein levels.[3] Following an initial saturation period on days 0, 14, 27 and 63, nusinersen has to be applied every 4 months into the cerebrospinal fluid. In initial studies, repeated lumbar punctures were well tolerated,[8] but in some cases sedation was required due to movements during the procedure. Further, based on current experience, there are no severe side effects of the drug, but nephrotoxicity, blood clotting disorders and thrombocytopenia have to be considered similar to treatment with other ASOs.

Considering that the treatment with nusinersen may become an integral part of clinical care in SMA patients, we assume that an even more reliable experience regarding drug efficacy may be noted shortly along with a better understanding of the side-effect profile. In our view, also a final judgement on dose–response effects cannot be done so far although a fixed-dose scheme (12 mg across all age groups) is recommended so far.[9] Whereas the fascinating results from the mentioned studies necessitate the treatment initiation in infants and children with SMA, it is of note that the effects of the ASO in adolescents or adults with SMA have not been investigated in clinical trials and should be probed in further studies. Here, the identification of therapy monitoring strategies, outcome variables or biomarkers possess not the only considerable challenge. Further, animal studies suggested a critical 'therapeutic time window' for SMN-targeting strategies and increasing SMN protein after the onset of overt symptoms, was accompanied by only little symptom amelioration.[10] In contrast, other animal studies revealed that a restoration of SMN levels in milder SMA[10] and, thus, in clinical SMA types mainly observed in older patients, significantly improved motor abilities and may therefore encourage the treatment initiation with nusinersen also in adolescents or adults not only under ethical considerations.

However, there is an ongoing debate regarding the costs considering a price of US$125,000 per injection and long-term evidence of cost-effectiveness is just as necessary as a critical discussion about fair prices including health insurers, pharmaceutical companies and policymakers.

Nevertheless, nusinersen represents a novel and notable therapeutic option in SMA that would have been barely conceivable a few years ago. The underlying pharmacological mechanisms of ASOs may reflect a proof of concept regarding the treatment of neurodegenerative disorders with a predominant genetic basis such as SMA, Huntington's disease and the 5% of patients suffering from autosomal dominant amyotrophic lateral sclerosis (ALS). These studies may promise an exciting therapeutic future of neurology.

Conflict of interest statement

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References

1. Lunn MR and Wang CH. Spinal muscular atrophy. *Lancet* 2008; 371: 2120–2133.

2. Verhaart IEC, Robertson A, Wilson IJ, *et al.* Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy – a literature review. *Orphanet J Rare Dis* 2017; 12: 124.

3. Chiriboga CA, Swoboda KJ, Darras BT, *et al.* Results from a phase 1 study of nusinersen (ISIS-SMN Rx) in children with spinal muscular atrophy. *Neurology* 2016; 86: 890–897.

4. Finkel RS, Chiriboga CA, Vajsar J, *et al.* Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label,

dose-escalation study. *Lancet* 2016; 388: 3017–3026.

5. Kuntz N, Farwell W, Zhong ZJ, *et al*. Nusinersen in infants diagnosed with spinal muscular atrophy (SMA): Study design and initial interim efficacy and safety findings from the phase 3 International ENDEAR Study (CCI.002). *Neurology* 88(16 Suppl.): CCI.002.
6. Mercuri E, Finkel R, Kirschner J, *et al*. Efficacy and safety of nusinersen in children with later-onset spinal muscular atrophy (SMA): end of study results from the phase 3 CHERISH study. *Neuromuscul Disord* 2017; 27: S210.
7. De Vivo DC, Hwu W-L, Reyna SP, *et al*. Interim efficacy and safety results from the phase 2 NURTURE study evaluating nusinersen in presymptomatic infants with spinal muscular atrophy (S46.003). *Neurology* 88(16 Suppl.): S46.003.
8. Haché M, Swoboda KJ, Sethna N, *et al*. Intrathecal injections in children with spinal muscular atrophy: Nusinersen clinical trial experience. *J Child Neurol* 2016; 31: 899–906.
9. Luu KT, Norris DA, Gunawan R, *et al*. Population pharmacokinetics of nusinersen in the cerebral spinal fluid and plasma of pediatric patients with spinal muscular atrophy following intrathecal administrations. *J Clin Pharmacol* 2017; 57: 1031–1041.
10. Wirth B, Barkats M, Martinat C, *et al*. Moving towards treatments for spinal muscular atrophy: Hopes and limits. *Expert Opin Emerg Drugs* 2015; 20: 353–356.