CLIPPINGS

Evaluation of putative CSF biomarkers in paediatric spinal muscular atrophy (SMA) patients before and during treatment with nusinersen (J Cell Mol Med. 2021 Jul 27. Online ahead of print)

Nusinersen, being the longest validated therapy for SMA, requires biomarkers to validate its therapeutic effects. This single-centre pilot study analyzed CSF candidate biomarkers (phosphorylated heavy chain (pNf-H), light-chain neuro-filaments (NfL), total tau protein (T-Tau), neurogranin, α secretase BACE-1 and alpha-synuclein) in 193 CSF samples of 44 pediatric SMA types 1, 2 and 3 patients before and under nusinersen treatment and related them to standardized clinical outcome scores. pNf-H and NfL correlated with disease severity and activity, emphasizing their relevance as marker of neuronal loss and clinical outcome. T-Tau was significantly correlated with motor function scores in SMA type 1 making it an interesting marker for treatment response. Additionally, baseline T-Tau levels were elevated in most SMA patients possibly reflecting the extension of neuronal degeneration in pediatric-onset SMA.

Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy (Muscle Nerve. 2021 Jun 30.Online ahead of print).

Onasemnogene abeparvovec is an adeno-associated virus-based gene replacement therapy. It delivers functional human SMN through a one-time intravenous infusion. In addition to substantially improving survival, onasemnogeneabeparvovec was found to increase motor milestone attainment and reduce the need for respiratory or nutritional support. This expert opinion provides recommendations and practical considerations on the patient-centered decisions like the need for patient-centered multidisciplinary care, patient selection to identify those with underlying medical conditions or active infections, importance of retesting patients with elevated anti-adeno-associated virus serotype 9 antibodies, guidelines for prednisolone tapering and monitoring for potential adverse events, including hepatotoxicity and thrombotic microangiopathy.

Risdiplam-treated infants with type 1 spinal muscular atrophy versus historical controls (N Engl J Med. 2021;385:427-35)

Type 1 SMA is characterized by onset before 6 months of age and such children are unable to sit. This study was an open-label study of risdiplam on 41 infants with type 1 SMA who were 1 to 7 months of age at enrolment. After 12 months of treatment, 12 infants (29%) met the primary end point and were able to sit without support for at least 5 seconds, a milestone not attained in this disorder in natural course. Other secondary end points measured by CHOP-INTEND, HINE-2 and survival without permanent ventilation were also significantly different in the study group as compared to historical controls.

Early Cost-Effectiveness of Onasemnogene Abeparvovec-xioi (Zolgensma) and Nusinersen (Spinraza) Treatment for Spinal Muscular Atrophy I in The Netherlands With Relapse Scenarios (Value Health. 2021;24:759-69**)**

The goal of this study was to perform a cost-effectiveness analysis of treatment of SMA I patients with Onasemnogene Abeparvovec-xioi (AVXS-101) in The Netherlands including relapse scenarios. An individual-based state-transition model was used to model treatment effect and survival of SMA I patients treated with AVXS-101, nusinersen and best supportive care (BSC). The model included five health states: three health states according to SMA types, one for permanent ventilation and one for death. Based on this model, treatment with AVXS-101 was found unlikely to be cost-effective under Dutch willingness-to-pay reference values.

Treatment of infantile-onset spinal muscular atrophy with nusinersen: final report of a phase 2, open-label, multicentre, dose-escalation study (Lancet Child Adolesc Health. 2021;5:491-500)

Spinal muscular atrophy (SMA) is a fairly common autosomal recessive, neurodegenerative disease caused by biallelic mutations in the survival motor neuron 1 (SMN1) gene. SMA is characterized by motor neuron degeneration, resulting in progressive muscle weakness, immobility and appreciable morbidities and mortality. Currently, three disease modifying therapeutic options are approved for treatment: Nusinersen (Spinraza), the antisense oligonucleotide given through intrathecal route; Risdiplam, an orally administered splicing modifier of motor neuron 2 (SMN2) and Onasemno-geneabeparvovec (Zolgensma), an adeno-associated virus-based gene replacement therapy.

Nusinersen is the oldest and the most well studied medication among them. It had showed a favourable benefit-risk profile in participants with infantile-onset spinal muscular atrophy at the interim analysis of a phase 2 clinical study. In the above study, authors present the final analysis, assessing the efficacy and safety of nusinersen over 3 years. It recruited 20 symptomatic infants aged between 3 weeks and 6 months with two or three *SMN2* gene copies, between May 3, 2013, and July 9, 2014. Participants received multiple intrathecal loading doses of 6 mg equivalent nusinersen (cohort 1) or 12 mg dose equivalent (cohort 2), followed by maintenance doses of 12 mg equivalent nusinersen. Median time on study was 36·2 months. In the 13 participants with two SMN2 copies treated with 12 mg

nusinersen, the HINE-2 motor milestone total score increased steadily from a baseline mean (SD) of 1·46 (0·52) to 11·86 (6·18) at day 1135, representing significant clinical improvement. At study closure (Aug 21, 2017), 15 (75%) of 20 participants were alive. All five deaths (one in cohort 1 and four in cohort 2) were likely to be related to spinal muscular atrophy disease progression.

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