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Editorial

Good News Never Hurts

On 23rd December 2022, we celebrated the 6-year anniversary of the FDA's approval of nusinersen, the first drug authorised for the treatment of spinal muscular atrophy (SMA). With the subsequent approval of 2 other drugs, and the gradual implementation of newborn screening programs around the world, the prognosis of this previously untreatable disease has dramatically improved. However, significant unmet needs and unanswered questions remain.

First and foremost, the long-term efficacy and safety of SMA treatments remain a challenging aspect of discussions with a patient and their family. SMA clinical trials have so far reported data up to 2 years, on a limited and well-selected population. The occurrence of serious adverse events, including acute liver failure and thrombotic microangiopathy following treatment with onasemnogene abeparvovec [1] (which had not previously been reported in three separate clinical trials), is illustrative of the need for sustained vigilance in the implementation of new innovative treatments.

A recurring question raised by parents when discussing nusinersen treatment is about the potential risks of long-term repeated intrathecal injection. The question is pertinent, as recent examples of adverse events reported due to central and peripheral nervous system inflammation in amyotrophic lateral sclerosis [2] or Angelman syndrome [3] have raised significant concerns that have hampered ongoing clinical development [3]. In nusinersen-treated patients, concerns regarding cerebrospinal fluid (CSF) inflammation were raised by the description of cases of aseptic meningitidis [4] or nusinersen-containing macrophages.

In a cohort of 38 patients with different forms of SMA who received 5 injections of nusinersen, Scheijmans and colleagues reported 3 patients with an occasionally elevated leucocyte count in their CSF associated with IL10 (and IL6 and IFNG in one patient) elevation [5]. Neither cytorachia, CSF protein, or IL10 elevation were consistent across samples or associated with significant clinical manifestations. In addition, the authors observed a mild but consistent rise in MCP1 in all but 2 patients with SMA types 2 and 3, which suggests a neuroprotective action of nusinersen treatment. Similar reports of predominantly transient elevation of CSF leucocytes, or of CSF protein, or both, during treatment with or without clinical symptoms have been reported by other groups [4].

Elevated leucocyte count and protein in CSF can understandably raise safety concerns and clinicians may consider interrupting treatment until CSF normalisation. However, missed or delayed doses can have a significant long-term negative impact, particularly on patients with SMA1, or with 2 copies of *SMN2* identified through neonatal screening. The results of this study will therefore help reassure clinicians that they should continue nusinersen treatment when a patient presents with asymptomatic elevation of CSF leukocytes or protein.

Nevertheless, the question remains whether intrathecally-injected antisense oligonucleotides have inflammatory effects. Further studies are therefore needed to clarify whether the clinically significant inflammation observed in other programs [2,3] are caused by disease, or by the chemical backbone -, dose-, or manufacturing process of the drug.

At the end of 2022, approximately 14,000 patients worldwide had begun treatment with nusinersen. The good news for them is that this study further strengthens a growing body of evidence demonstrating the excellent safety profile of the drug.

References

[1] R.H. Horton, D. Saade, T. Markati, et al., A systematic review of adeno-associated virus gene therapies in neurology: the need for consistent safety monitoring of a promising treatment, J. Neurol. Neurosurg. Psychiatry 93 (2022) 1276–1288.
[2] T.M. Miller, M.E. Cudkowicz, A. Genge, et al., Trial of antisense oligonucleotide Tofersen for SOD1 ALS, N. Engl. J. Med. 387 (2022) 1099–1110.
[3] T. Markati, J. Duis, L. Servais, Therapies in preclinical and clinical development for Angelman syndrome, Expet Opin. Invest. Drugs 30 (2021) 709–720.
[4] O. Moshe-Lilie, L.P. Riccelli, C. Karam, Possible recurrent aseptic meningitis associated with nusinersen therapy, Muscle Nerve 62 (2020) E79–E80.
[5] F.E.V. Scheijmans, I. Cuppen, M.M. Zwartkruis, et al., Inflammatory markers in cerebrospinal fluid of paediatric spinal muscular atrophy patients receiving nusinersen treatment, Eur. J. Paediatr. Neurol. 42 (2022) 34–41.

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