Dawn of a new therapeutic era for spinal muscular atrophy

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The original studies reporting defects in the survival of motor neuron 1 (*SMN1*) gene as the underlying cause of spinal muscular atrophy were published more than 20 years ago.[1] At the time, the identification of spinal muscular atrophy as an essentially mono-genetic disorder was heralded as a major research breakthrough that would lead to the rapid development of new therapies. Yet, despite over two decades of intensive basic and pre-clinical research, no approved treatment options are currently available. Against this background, the open-label, phase 2 clinical study by Richard S Finkel and colleagues[2] in *The Lancet* is a major milestone on the journey towards a viable therapy.

Mutations in the *SMN1* gene render it incapable of generating full-length survival motor neuron (SMN) protein.[3] The continuing presence of low concentrations of SMN protein in patients with spinal muscular atrophy results from the expression of a near-identical *SMN2* gene, the copy number of which affects disease severity.[4] This backup *SMN2* gene has a C to T substitution at an exon splice enhancer site that regulates exon 7 inclusion. As a result, less than 25% of *SMN2* transcripts contain exon 7 and are capable of producing full-length SMN protein. However, the retained presence of an *SMN2* gene in patients offers an opportunity for the development of therapies aimed at increasing concentrations of functional SMN protein, a strategy found to have potential in pre-clinical animal studies.[5,6]

Finkel and colleagues[2] report on the delivery of nusinersen, a 2′-O-methoxyethyl phosphorothioate-modified antisense drug designed to alter splicing of *SMN2* pre-mRNA and subsequently increase concentrations of SMN protein. Although data from a phase 1 trial of nusinersen in patients with less severe forms of spinal muscular atrophy have already been published,[7] this study is the first robust demonstration of safety and tolerability, as well as a positive pharmacokinetic profile, for nusinersen after multiple intrathecal doses in infants with the most severe form of spinal muscular atrophy (type I). Most importantly, the study confirmed uptake of nusinersen into motor neurons throughout the spinal cord, as well as other neuronal populations throughout the nervous system, leading to increased *SMN2* mRNA exon 7 inclusion and SMN protein concentrations. This establishes a crucial proof-of-principle that it is possible to target *SMN2* to raise SMN protein concentrations across a range of affected cell types in patients with spinal muscular atrophy, without major adverse consequences.

Finkel and colleagues[2] also present preliminary evidence suggesting that nusinersen can deliver incremental improvements in motor function for patients with severe forms of spinal muscular atrophy. Although these findings need to be interpreted cautiously in the context of the limitations of a small, open-label, interventional trial, they should generate substantial encouragement that raising SMN protein concentrations could be of therapeutic benefit to patients with spinal muscular atrophy. Conclusions cannot yet be drawn concerning the potential ability of nusinersen to affect broader aspects of the spinal muscular atrophy phenotype, such as a requirement for permanent ventilation or age of death. This is largely due to the relatively small number of patients enrolled in the study and the need to draw quantitative comparisons with an unrelated, natural history case series. Indeed, it should be noted that promising clinical responses were not uniformly observed across all infants enrolled on the study. However, the overall direction is encouraging, with future studies (including phase 3 trials) likely to generate the additional clinical data required to gain a full appreciation of the potential therapeutic benefits of nusinersen treatment.

As predicted from pre-clinical animal studies, the current study indicates that restoration of SMN protein can modify disease severity, but does not represent a complete cure. Thus, ongoing efforts to develop a second generation of therapies for spinal muscular atrophy are likely to be key for developing fully effective treatments applicable to patients with all subtypes of the condition. These include efforts to restore SMN protein earlier in disease progression (during a crucial therapeutic or developmental time-window[8]), to facilitate systemic delivery of therapies throughout a range of additional peripheral tissues and organs,[9,10] and to target additional SMN-independent pathways.[11,12] However, the promise of nusinersen shown by Finkel and colleagues[2] is a first step forward, indeed a new dawn, in developing safe and effective therapy options for spinal muscular atrophy that are urgently required.

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I am Chair of the Scientific Advisory Board of the SMA Trust and serve on scientific and clinical advisory boards for SMA Europe and Association Française contre les Myopathies. I am named on a patent application submitted by the University of Edinburgh for the use of β-catenin inhibitors for the treatment of spinal muscular atrophy.

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