NEURODEGENERATIVE DISEASE

Early treatment is a lifeline for infants with SMA

In the phase 3 SPR1NT trial, pre-symptomatic gene therapy demonstrated impressive clinical outcomes in infants with a genetic diagnosis of spinal muscular atrophy (SMA); long-term safety follow-up of these patients must now be a key priority.

Charlotte J. Sumner and Thomas O. Crawford

Onasemnogene abeparvovec (OA) is an in vivo viral-mediated gene therapy — one of only two such therapies in clinical use — which is approved for one-time intravenous administration to infants under 2 years of age with spinal muscular atrophy (SMA). Despite the small number of in vivo gene therapies in clinical use, more than a hundred are in clinical trials (www.clinicaltrials.gov). The greatest benefit from these rapidly emerging treatments is likely to come when initiated prior to disease onset, particularly when disease progression claims non-replicating cells such as neurons — as is the case for SMA. In paired papers in this issue of *Nature Medicine*, Strauss et al. report the two-year outcomes of the phase 3 trial (SPR1NT) in which infants with SMA were treated with a single intravenous dose of the OA gene therapy prior to overt disease manifestation[1,2].

SMA is an early-onset motor neuron disease caused by recessive loss-of-function mutations of the survival motor neuron 1 (*SMN1*) gene and retention of a paralogous alternatively spliced *SMN2* gene, with consequent insufficient expression of SMN protein. SMA-associated genotypes vary in copy number of the *SMN2* gene. Infants with just two copies of the gene experience profound muscle weakness of the trunk and limb muscles with failure to achieve any motor milestones including head control, rolling, or sitting; while infants with three copies of *SMN2* generally achieve the ability to sit and sometimes to stand. Three treatments that increase SMN levels are now approved for treating infants with SMA, having shown some benefit in patients with symptomatic disease: the splice-switching antisense oligonucleotide nusinersen, the small molecule risdiplam, and OA. OA consists of a *SMN* cDNA transgene whose expression is driven by a human cytomegalovirus enhancer and β-actin promoter, packaged within an adeno-associated virus 9 (AAV9) capsid. Following a single intravenous administration of OA, persistence of a functional *SMN* transgene offers the potential for lifelong SMN expression in motor neurons (Fig. 1).

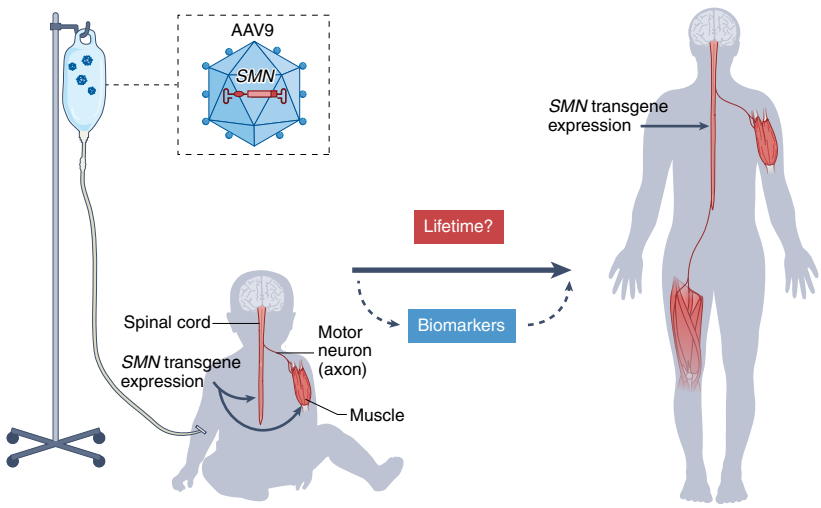

Fig. 1 | OA for presymptomatic spinal muscular atrophy. Onasemnogene abeparvovec (OA), an adeno-associated virus 9 (AAV9) *SMN* gene replacement therapy, is administered as a one-time intravenous injection. Transduction of motor neurons likely results in improved motor neuron development, function, and survival with the potential for near-normal attainment of motor milestones. Whether OA remains effective and safe throughout life requires further assessment.

Strauss et al. treated infants with genetically confirmed, presymptomatic SMA — including 14 infants with 2 copies of *SMN2* at a median age of 21 days (ref. [1]), and 15 infants with 3 copies at a median age of 32 days (ref. [2]). Remarkably, by 18 months of follow-up, 79% of those with two copies achieved independent standing and 64% achieved independent walking, compared to only 3–5% of postsymptomatically treated genotype-matched infants treated at a median age of around 4 months[3,4]. For infants with three copies of the gene (also treated presymptomatically), 93% walked independently in the 24-month post-treatment observation period. It is worth noting that these markedly enhanced outcomes with presymptomatic treatment are strikingly similar to those observed in trials of pre-symptomatic infants treated with the other two SMN-enhancing therapies, nusinersen[5] and risdiplam[6]. This suggests that the optimal levels of SMN induction can be achieved with any of the three therapies when given very early, despite their distinct molecular mechanisms and biodistributions. With the recent approval of risdiplam for neonatal use (and nusinersen already approved in this setting), families now have the choice of starting one of three distinct SMN-enhancing treatments at the time of newborn diagnosis.

These impressive results have encouraged increasing newborn screening for SMA internationally. But even with such early diagnosis, optimal outcomes may be difficult to achieve. In the studies by Strauss et al., 14 out of 44 screened newborns were excluded due to evident symptoms. Furthermore, although all infants enrolled in the study were 'presymptomatic' by clinical neurological examination at the time of dosing, those infants with two

copies of *SMN2* fared less well than those with three copies. Scored on the Bayley Gross Motor Scale, one-third of infants with two copies scored below the normal range at the study end, suggesting that pre-treatment pathology emerges in the form of mild motor impairment by this age. All those with three copies scored within the normal range. These observations, mirrored in the presymptomatic trials of other therapies, emphasize that the timing of treatment initiation and the magnitude of neurodegeneration at that time are key drivers of therapeutic response — possibly even more so than the choice of specific treatment. Evidence from autopsy studies[7] and analyses of serum neurofilament levels (a marker of active neurodegeneration)[5] indicate that disease-associated pathology in infants with two copies of *SMN2* begins in utero with rapid degeneration occurring neonatally, even before overt symptoms. In this group it is truly a race against time, and we strongly encourage initiation of any one of the therapeutics as soon after birth as possible. Biomarkers that can predict functional outcomes within the range manifest for each of the genotype groups, as defined by their *SMN2* copy number, are urgently needed. Serum neurofilaments have shown promise as safety and efficacy biomarkers in interventional studies of SMA[5] and other neurodegenerative diseases; these were not measured in the SPR1NT study, but warrant investigation in this context.

Characteristics of early childhood suggest particular promise for gene transfer therapies[8] because the nervous system is still developing and highly plastic at this age, the immune system is relatively tolerant, and broad transgene biodistribution may be enhanced by small body size and an immature blood–brain barrier. OA offers the potential advantage of a single dose as compared to other SMA treatments. But an important potential disadvantage of OA is that once administered, treatment cannot be withdrawn. Clinical trials and early post-marketing surveillance have identified short-term toxicities including acute liver toxicity and rare thrombotic microangiopathy. But these post-market, short-term assessments are ill-suited for identifying potential long-term toxicities that might arise[9,10]. Although AAV gene therapies generally do not integrate in the genome, if this occurs at low frequency there would be associated concern over insertional oncogenesis. There are also ongoing concerns about potential toxicity from SMN overexpression, epigenetic silencing of recombinant AAV-encapsulated genomes[11], or slow progressive loss of OA transgenes by other means. With this in mind, the follow-up of just 2 years for a putative lifelong treatment is relatively short.

Although challenging, long-term studies will be essential for both assessment of safety and to identify ways to improve efficacy[9]. The establishment of an infrastructure to obtain autopsy tissues from individuals treated with SMN-enhancing therapies would be particularly valuable and informative. So far, autopsies have been reported for only two patients treated with OA[12], nine treated with nusinersen[13], and none treated with risdiplam.

The reversal of a relentless degenerative disorder of infancy with a one-time treatment is an extraordinary accomplishment; now is the time to build on this foundation with vigilant follow-up and biomarker studies. ❐

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Competing interests

C.J.S. has been a consultant for Novartis, Ionis Pharmaceuticals, Biogen, PTC Therapeutics, Roche, Genentech, Cytokinetics, Sarepta, Nura Bio, Atalanta, Shift, Argenx, Biomarin, Scholar Rock, GenEdit, Epirium, and Capsigen. C.J.S. has received research grant from Ionis Pharmaceuticals and currently receives grant support from Roche and Biogen. C.J.S. is a coholder of 2 pending patent applications (BIOL0274USA and BIOL0293WO) with Ionis Pharmaceuticals for antisense oligonucleotides targeting SMN-AS1. C.J.S. receives royalties from Elsevier for the book *Spinal Muscular Atrophy: Disease Mechanisms and Therapy* (eds Sumner, C. J., Paushkin, S. & Ko, C. P.; Elsevier, 2017). T.O.C. has been a consultant for Avexis/Novartis, Biogen, Catalyst, Cytokinetics, Erydel, Genentech, Ionis, and Scholar Rock. He is/has been a site principal or co-principal investigator for the Biogen EMBRACE, NURTURE, and DEVOTE clinical trials, the Avexis/Novartis STR1VE and STRONG clinical trials, and individual clinical trials with Catabasis, Catalyst, Cytokinetics, Santherra, and Sarepta.

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NEURODEGENERATIVE DISEASE

Comorbidities confound Alzheimer's blood tests

The concentrations of two key blood biomarkers for Alzheimer's disease are affected by some medical conditions, which could potentially lead to misdiagnosis.

Suzanne E. Schindler and Thomas K. Karikari

Alzheimer's disease (AD) is the most frequent cause of dementia in older individuals and is defined not by the clinical symptoms but by the presence of amyloid plaques and tau tangles in the brain. Cerebrospinal fluid (CSF) biomarkers and amyloid positron emission tomography (PET) tests can accurately detect AD brain pathology, but the perceived risks, costs, and lack of availability of these tests have contributed to a low rate of AD biomarker testing in the clinic.