Gene Therapy (2017) **24**, 497

www.nature.com/gt

EDITORIAL

Spinraza—a rare disease success story

Gene Therapy (2017) **24,** 497; doi:10.1038/gt.2017.59

Classified as a rare disease, spinal muscular atrophy (SMA) is a genetic condition that chiefly affects motor neurons and is the leading genetic cause of death in infants worldwide. The disease is chronic, severe and currently has no cure. More than 30 years of research and combined efforts of several stakeholders have brought us to the current understanding of the disease and very recently led to the approval of the first-ever therapy for SMA—the drug called Spinraza. The outcomes from initial clinical testing and approval of Spinraza provide great encouragement not only to the patients but also to the entire SMA community. Moreover, in a broader context, Spinraza is an exemplar success story for rare disease research.

Just a little before Christmas last year, the United States Food and Drug Administration (FDA) announced the regulatory approval of Biogen's drug Spinraza for the treatment of all types of spinal muscular atrophy—a landmark for the entire SMA community. Spinraza is the brand name for the gene therapy drug, nusinersen, and is the first and only treatment now commercially available to treat SMA. The FDA's approval came based on results from clinical studies in more than 170 patients, many of whom showed remarkable improvements in motor functions and survival.

SMA is a rare neurological genetic disease that affects muscle strength and movement. In its most fatal form—which makes up to half of all people affected—infants have a life expectancy of around 2 years of age. About 1 in 6–10 000 babies are born with SMA worldwide each year, making it the leading genetic cause of death in infants. The basis of the disease is the deficiency in survival motor neuron (SMN) protein. This protein is present in all cells but, as the name suggests, it is critical for the maintenance and survival of the nerve cells that control muscles. Therefore, loss of the SMN protein causes muscles to atrophy over time, making motor functions like walking, sitting, breathing and swallowing extremely challenging.

The severity of the disease correlates with the amount of SMN protein present. People with type 1 SMA, with a life expectancy of 2 years, produce very little SMN protein. Patients cannot sit upright without support and ultimately lose the ability to breathe unaided. People with type 2 and 3 SMA, the intermediate and mild forms, produce greater amounts of SMN. Although their symptoms are less severe in comparison to the type 1 form, the disease does have life-changing effects.

Most of the SMN protein is produced from a gene of the same name—*SMN1*. SMA arises when there is a defect in this gene or when the gene is missing. However, you cannot live without any SMN protein at all. Humans harbour a second, almost identical, copy of the *SMN1* gene called *SMN2*, which acts as a backup making low amounts of SMN protein. However, it is an inefficient backup system, making much less protein than the *SMN1* gene. Typically, SMA patients carry two or more copies of the *SMN2* gene: the more the *SMN2* genes, the less severe the disease outcome. However, since the amount of protein formed is low, even multiple copies of *SMN2* do not fully stop the disease. This is precisely what Spinraza targets. Spinraza is a short string of synthetic genetic material directed to the product of the *SMN2* gene, making it generate more of the functional SMN protein. In doing so, it bypasses the *SMN1* gene, compensating for the shortfall.

Spinraza is designed as an intrathecal injection directly into the cerebrospinal fluid, the liquid surrounding our spinal cord, so it reaches the motor neurons. Biogen recommends four single-injection doses—the first three at 14-day intervals and the fourth dose 30 days after the third—followed by a maintenance dose every 4 months thereafter. Patients will presumably take Spinraza for the rest of their lives. The mode of administration, although invasive, was well tolerated in the clinical studies.

As per the clinical evidence presented by Biogen at the British Pediatric Neurology Association annual conference held in January this year, infants treated with Spinraza compared to untreated infants showed a significant reduction in the risk of death or permanent ventilation. The most common adverse reactions that occurred in at least 20% of Spinraza-treated patients were respiratory infection and constipation.

Whether there are limitations, Professor Sendtner from the University of Wuerzburg, Germany, says 'This is not clear yet. From previous animal experiments, therapy should work better the earlier it starts'. This has ethical implications for SMA patients, families and clinicians, as in when to start the treatment and for how long. 'The other limitation', says Professor Sendtner, 'is the mode of administration and potential limits in biodistribution which are also not perfectly understood yet, in particular when children under treatment become older. There are also no clear data on long term tolerability and whether in the long run immune response could interfere'.

Approval of Spinraza is a historic achievement for the entire SMA community. 'It is a proof that therapy is possible, and a proof that current concepts to interfere with disease are on the right track', commented Professor Sendtner. It also showcases the endeavours and perseverance of several stakeholders. It was more than a decade ago that the target site for Spinraza was first identified by researchers with seed funding from Cure SMA, a patient charity. From there it went on to be developed by pharma companies Biogen and Ionis. Biogen filed for FDA approval in September 2016 and soon after with the European Medicines Agency (EMA). The FDA's approval came through on 23 December 2016 with a broad label to treat all types and stages of SMA. The EMA's recommendation for licensing Spinraza in Europe was approved and a marketing authorisation granted on June 1, 2017.

Spinraza is at the leading edge of SMA treatments. In the pipeline lies promising gene therapy from AVEXIS to directly express SMN protein from a new copy of the *SMN1* gene. The drug has already been granted the ground-breaking Orphan Drug Designation with human clinical trials ongoing in SMA type-1 infants. Separately, 17 treatments are currently being developed, with 5 in clinical trials. This progress, which would not have been possible without the perseverance of researchers, families, charities and industry, gives hope that we are close to having meaningful treatment options for this horrific disease.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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