Yeo and Darras: Extraneuronal Phenotypes of Spinal Muscular Atrophy

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Recently, the splicing modulator risdiplam was approved by the US Food and Drug Administration (FDA) for spinal muscular atrophy (SMA) in adults and children 2 months of age and older. Risdiplam is the third disease modifying treatment for SMA and only the second for children above the age of 2 years and adults with SMA. Before the approval of the antisense oligonucleotide nusinersen in 2016 for all types of SMA, regardless of age, and adeno-associated virus serotype 9-mediated *SMN1* gene replacement therapy onasemnogene abeparvovec-xioi in 2019 for children 2 years of age and younger, SMA was invariably fatal in the most severe form of SMA, SMA type 1. With intrathecal administration of nusinersen every 4 months after a loading regimen, a single dose intravenous administration of onasemnogene abeparvovec-xioi, and now daily oral administration of risdiplam, infants and children below the age of 2 years with SMA type 1 can now survive to childhood and probably up to adulthood. Data are just emerging about treatment tolerability and efficacy in different clinical settings and age groups, and long-term adverse effects of treatment are yet unclear. Children above the age of 2 years and adults with SMA now have two FDA-approved therapies, nusinersen and risdiplam, for less severe but still significantly limiting forms of SMA. Treatment efficacy and expectations in adults, where the motor neuron pool is already severely depleted, is under debate. The exponential growth of precision medicine in SMA, and the significant costs of approved gene therapies, bring sharply into the forefront pressing questions related to treatment efficacy and iatrogenic phenotypes, which adult and pediatric neurologists have an ethical obligation to understand and counsel our patients on. In this timely two part ANA Highlights program, Dr. Basil Darras (Boston Children's Hospital and Harvard Medical School) and Dr. Crystal Yeo (Boston Children's Hospital, Harvard Medical School, LKC School of Medicine, EDDC, IMCB) explain the extraneuronal phenotypes of SMA, clinical implications in patients being treated with innovative therapies, and avenues for future research.

In part 1 of the program, Dr. Basil Darras explains that SMA is a genetic disorder driven by degeneration and loss of motor neurons in the anterior horns of the spinal cord and brain stem of children and adults. SMA is typically characterized as a motor neuron disease; however, extraneuronal phenotypes have been noted in severely affected patients and animal models. Data from autopsies, case studies, and limited cohort studies in patients with severe SMA correspond with animal models of SMA, showing dysfunction in almost every peripheral organ system, including the skeletal muscle, heart, kidneys, liver, pancreas, spleen, bones, connective tissues, and immune systems, and providing evidence in support of SMA being a multisystem disorder.[1,2] In part 2 of the program, Dr. Crystal Yeo explains why neurologists and neuroscientists need to be aware of the evolving therapeutic

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25930

Received Aug 17, 2020, and in revised form Oct 11, 2020. Accepted for publication Oct 12, 2020.

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landscape and the potential emergence of extraneuronal phenotypes in treated patients with SMA. Survival motor neuron (SMN) protein is ubiquitously expressed in almost every peripheral organ, necessary for embryonic development and necessary for the development and function of many organs and tissues.[3] Extraneuronal phenotypes in animal models support a "threshold" model in which cells and tissues have differential requirements for SMN and corresponding susceptibilities to SMN depletion. With patients with severe SMA phenotypes living longer due to SMN protein augmenting therapies, impaired function of the peripheral tissues and organs may become significant future comorbidities in patients who receive only central nervous system-directed treatments. Animal data are conflicted on whether the expression of the survival motor neuron protein in motor neurons alone is necessary and/or sufficient for preservation of motor function and/or overall survival.[1] There are animal studies that show that non-motor neuron cell autonomous SMN rescue is necessary and/or sufficient for motor neuron function and overall survival, and may be related to the regulation of systemic neurotrophic or toxic factors secreted from peripheral organs, such as insulin-like growth factor 1 (IGF-1).[4] This implies a therapeutic window for SMN rescue treatment even in late stages of disease when many motor neurons are already lost in pediatric and adult patients with SMA.[5] Nusinersen, onasemnogene abeparvovec-xioi, and risdiplam primarily target the motor neurons, which drive death in SMA; however, due to systemic modes of administration, onasemnogene abeparvovec-xioi and risdiplam also act on peripheral tissues. It is important to consider the therapeutic window, define cell targets of gene therapies, and decide on therapeutic regimes based on our understanding of SMA pathology. The next logical steps in clinical management and research are to consider expanding multidisciplinary clinical teams to include additional subspecialties, plan clinical trials using combination therapies, evaluate peripheral organ function over time, develop clinical biomarkers correlating with neurological function and overall outcome, and develop centralized network databases to extract outcomes from real-world datasets.

Conclusion

With recent FDA approval of risdiplam, there are now three SMN protein augmenting drugs for SMA: risdiplam, costing US $340,000 per year, nusinersen, costing US $750,000 in the first year and US $375,000 each year thereafter, and onasemnogene abeparvovec-xioi, costing US $2.15 million for a single infusion. Data from patients and animal models with SMA suggest that SMA is probably a multisystem disease, consistent with ubiquitous expression of SMN protein in almost every peripheral tissue and organ, and affecting almost every peripheral organ in severe SMA phenotypes. Iatrogenic complications may emerge as extraneuronal phenotypes. Risdiplam and to some extent onasemnogene abeparvovec-xioi have peripheral effects, with the latter dependent on peripheral cell replication. Neurologists should consider drug cell targets, efficacy, and durability of SMN protein augmentation, potential iatrogenic phenotypes, and financial/ethical issues when providing patients with informed consent for innovative therapies. A systemic approach to SMN augmentation therapy is likely to most effectively maximize clinical outcomes and result in a phenotype without extraneuronal manifestations. Future research can explore to what extent pathology of each peripheral organ contributes to the overall pathology of SMA and whether motor neuron dysfunction in SMA is cell-intrinsic or depends on neurotrophic factors secreted by peripheral organs, such as IGF-1. Exploring neurotrophic factors can provide downstream treatment avenues for SMA and other motor neuron diseases, such as amyotrophic lateral sclerosis (ALS) and Kennedy's disease.

Suggested Supplemental Material

URL for ANA Highlights module: https://myana.org/education/ana-highlights-bite-size-learning-cme.

Part 1 of module: https://vimeo.com/434158288.

Part 2 of module: https://vimeo.com/435164016.

QRCode for part 1:

QRCode for part 2:

Acknowledgments

The authors thank all patients and families who have been the inspiration for their work, and Jennifer Hurley and the American Neurological Association for producing the podcast. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

C.Y. and B.D. were responsible for the concept of the program and gave the talks.

Potential Conflicts of Interest

Dr. Darras has served as an ad hoc scientific board member for Biogen, AveXis, Roche, and Genentech, the pharmaceutical companies that manufacture nusinersen, onasemnogene abeparvovec-xioi, and risdiplam. Dr. Darras is also the FIREFISH study Steering Committee Chair for Roche, which manufactures risdiplam.

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