Spinraza & Spinal Muscular Atrophy: Moving Toward Treatment, But Not for Everyone

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In October 2018, the government of British Columbia announced that it will fund a life-saving pharmacotherapy called nusinersen (Spinraza), providing the first effective treatment to be approved for spinal muscular atrophy (SMA), a chronic neuromuscular degenerative condition.[1] SMA is categorized into three main subtypes: type 1 (severe), type 2 (intermediate), and type 3 (mild).[2] The age of onset for type 1, type 2, and type 3 SMA are 0-6 months, 7-18 months, and greater than 18 months, respectively. Moreover, the estimated age of mortality is approximately less than two years for type 1 patients, greater than two years for type 2 patients, and greater than eighteen years for type 3 patients. The incidence of the condition approaches one in 10,000 live births with type 1 accounting for 60% of cases.[3] SMA symptomatology includes muscle weakness, decreased muscle tone, limited mobility, delayed gross motor skills, spontaneous tongue movements, scoliosis, and problems with breathing, eating, and swallowing.[2,4]

SMA is caused by a homozygous deletion on the survival of motor neuron 1 (*SMN1*) gene, leading to a loss of SMN proteins and the eventual degradation of spinal motor neurons followed by paralysis.[5] Diagnosis is achieved through genetic testing, which is conducted to detect the absence of *SMN1*. However, the precise role of the loss of SMN proteins in driving SMA pathogenesis has not been characterized.

Adrian Krainer, professor and chair of the cancer and molecular biology program at Cold Spring Harbor Laboratory, spearheaded advancements in SMA treatment by shifting attention towards the role of *SMN2* as a possible therapeutic target.[6] The *SMN2* gene differs from the *SMN1* gene by a single base pair in one exon of the transcript product, leading to the production of mostly unstable, non-functional SMN protein. However, the *SMN2* gene also produces a small proportion of functional SMN protein, and a short antisense oligonucleotide developed by Krainer—nusinersen—augments this production and rescues the loss of *SMN1* function associated with SMA. Specifically, nusinersen attaches to a region of the *SMN2* transcript product, effectively blocking the splicing of exon 7 and preventing the frameshift mutation that would otherwise render the SMN protein from *SMN2* non-functional.

In the past, clinical trials that focused on developing pharmacotherapies for SMA included an investigation into the therapeutic potential of riluzole (Rilutek), a medication used to treat amyotrophic lateral sclerosis, and salbutamol (Ventolin), a β2 adrenergic agonist used to treat asthma and chronic obstructive pulmonary disease.[7] Although these drugs, among others, failed to demonstrate clinical efficacy in the treatment of SMA, researchers have continued to investigate other avenues for treatment, one of them being nusinersen. Namely, Phase 3 of the clinical trial "ENDEAR" demonstrated that SMA type 1 infants treated with nusinersen displayed significant improvements in motor-milestones compared to infants that had not received nusinersen.[8] In particular, 51% of infants treated with nusinersen achieved the desired motor-milestone response compared to 0% of infants in the control group. Among the infants that received nusinersen treatment, 22% exhibited full head control, 10% demonstrated the ability to roll over, and 8% demonstrated the ability to sit independently. Relative to the control group, infants treated with nusinersen experienced fewer severe adverse events (56% vs. 80%), serious adverse events (76% vs. 95%), and mortality (16% vs. 39%). However, this trend was reversed for constipation (35% vs. 22%) and some respiratory events, including upper respiratory tract infection (24% vs. 9%) and pneumonia (23% vs. 7%).

With clinical trials producing encouraging results, nusinersen was approved as a treatment option for SMA by Health Canada in June 2017. While many are celebrating the drug's availability, the prohibitive cost of nusinersen presents a significant limitation to patient access. In Canada, the cost of the first year of treatment is listed at $708,000 followed by $354,000 annually.[9] This cost perpetuates existing health disparities because public funding for nusinersen is generally limited to type 1 patients who are less than six months old (seven months in British Columbia), leaving type 2 and 3 patients of all ages without adequate access to treatment.[10] With many people questioning the government's decision to restrict access to nusinersen, a recent report by the Canadian Agency for Drugs and Technologies in Health may provide some answers. This report made cost-effectiveness predictions using the data from three previous studies: the ENDEAR, CHERISH, and CS2+CS12 trials for SMA types 1, 2, and 3, respectively. Using this information, nusinersen was predicted to increase life expectancy of patients with SMA types 1 and 2, but not for type 3.[9] Additionally, the cost per quality-adjusted life years (an indicator of cost–effectiveness) for the treatment of SMA type 2 was significantly greater than that of type 1 ($24.4 million vs. $9.2 million), with type 3 lacking sufficient clinical data for an accurate estimate. Furthermore, research supporting the therapeutic value of nusinersen treatment for adult populations is currently lacking and requires further investigation.

Despite the aforementioned reasons, Canada should still strive towards increasing patient accessibility to nusinersen by adapting strategies from countries such as Germany, Portugal, and Romania among others that currently provide broader funding.[11,12] Additionally, Canada should endeavor to fund and support research initiatives that are centered around other therapeutic options. For example, vector-based gene replacement therapy is one initiative that has shown promise as a viable alternative to nusinersen that would expand the scope of SMA treatment, both in terms of patient population and clinical efficacy.[13] In conclusion, though the funding of nusinersen by the government of British Columbia (and Canada more broadly) presents promise for the treatment of SMA, its potential as a therapeutic agent is eclipsed by its limited accessibility for patients.

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References

1. Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, *et al.* Identification and characterization of a spinal muscular atrophy-determining gene. *Cell.* 1995 Jan 13;80(1):155 65.
2. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. *Neurol Clin.* 2015;33(4):831 46.
3. Wurster CD, Ludolph AC. Nusinersen for spinal muscular atrophy. *Ther Adv Neurol Disord.* 2018 Mar 13;11.
4. Boston Children's Hospital. Spinal muscular atrophy (SMA) | symptoms and causes [Internet]. Boston Children's Hospital [date unknown] [cited 2019 Feb 17]. Available from: http://www.childrenshospital.org/conditions-and-treatments/conditions/s/spinal-muscular-atrophy-sma/symptoms-and-causes
5. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, *et al.* Diagnosis and management of spinal muscular atrophy: part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord.* 2018 Feb;28(2):103 15.
6. Corey DR. Nusinersen, an antisense oligonucleotide drug for spinal muscular atrophy. *Nat Neurosci.* 2017 Apr 13;20(4):497 99.
7. Calder AN, Androphy EJ, Hodgetts KJ. Small molecules in development for the treatment of spinal muscular atrophy. *J Med Chem.* 2016 Nov 23;59(22):10067 83.
8. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, *et al.* Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med.* 2017 Nov 2;377(18):1723 32.
9. CADTH common drug review pharmacoeconomic review report [Internet]. Ottawa: CADTH; 2018 [cited 17 February 2019]. Available from: https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0525_Spinraza_PE_Report.pdf
10. BC Gov News. British Columbia to fund life-changing spinal muscular atrophy treatment [Internet]. Victoria [updated 2012 Oct 2; cited 2019 Feb 18]. Available from: https://news.gov.bc.ca/18174
11. Spinal Muscular Atrophy UK. SMA Community Update March 2019 [Internet]. United Kingdom: Spinal Muscular Atrophy UK; 2018 [cited 2019 Apr 17]. Available from: https://smauk.org.uk/files/files/Research/SMA%20Community%20Update%20March%202019.pdf?fbclid=IwAR2VUe2t10PsPGirxzhCKEk0sBZR-9XG0pr1MKp_Xh1E_BGBt2SC3b9G0tA
12. McCourt DF. Why aren't children with rare diseases getting access to treatment? [Internet]. Toronto: Personal Health News; 2018 [cited 2019 Feb 17]. Available from: http://www.personalhealthnews.ca/patient-perspective/why-arent-children-with-rare-diseases-getting-access-to-treatment?fbclid=IwAR0yr47rbMeEV-tYaywi3j8m0ZIeHxmhN_nHlPcR9R7a-wBhg7ApjnEz5qg
13. Scoto M, Finkel RS, Mercuri E, Muntoni F. Therapeutic approaches for spinal muscular atrophy (SMA). *Gene Ther.* 2017 Sep 29;24(9):514 19.