COMMENTARY

Response to Provincial Governments' Decisions Regarding Monitoring for Adults with Spinal Muscular Atrophy

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As Canadian neuromuscular specialists caring for adults with spinal muscular atrophy (SMA), we write to express our opinions in response to provincial governments' requirements for outcome assessments in monitoring response to therapy.

SMA is an autosomal recessive motor neuron disease caused by dysfunction of the SMN 1 gene. This results in progressive weakness of limb, bulbar, and respiratory function. SMA types 1–4 are characterized by their age of onset and disease severity. The number of copies of the SMN 2 gene varies among individuals and impacts the disease phenotype. Although typically diagnosed in childhood, adult neuromuscular specialists care for patients with SMA, often in multidisciplinary motor neuron disease clinics which are ideally suited to address these patients' complex needs. Guidelines for care of SMA have indicated that a multidisciplinary approach in a clinic with expertise in motor neuron disease is standard of care.[1]

Recent positive trials of therapies in children with SMA have revolutionized care, with significant impacts on survival and quality of life.[2–4] The efficacy of treatment is optimal when patients are treated soon after or before symptoms become apparent. No SMA treatment trials have been performed in a dedicated and strictly adult population. While recent real-world evidence suggests benefits for adults with SMA,[5,6] it must be noted that these were open label observational studies which lacked a concurrent control arm, with a high risk of bias.

There are divided opinions in the medical community as to the potential benefit of SMA therapies in adults; while some say that real-world studies provide the necessary data offering support for use, others worry that the inherent bias of an open label study and the training effect of regularly applied outcome measures is insufficient to support decision-making. Ultimately, it is beyond the scope of this article to address the utility of SMA therapies in adults. Rather, the focus of this paper is to discuss the monitoring regulations for those adults whose nusinersen treatments have been approved by payers.

At this time of writing, nusinersen (Spinraza), an antisense oligonucleotide, is the only disease-modifying therapy approved by Health Canada for SMA. Although widely available for children, it has recently become available for adults with SMA in many Canadian provinces. After Health Canada approval for all types of SMA in all ages in June 2017, Quebec was the first province to provide adult coverage in December 2018. This was then followed (from April 2019 to January 2020) with case-by-case adult coverage in Saskatchewan, Ontario, Alberta, New Brunswick, Yukon, Nova Scotia, Manitoba, BC, and the Northwest Territories. Additional SMA-modifying therapies currently under review by Health Canada include the gene replacement onasemnogene abeparvovec-xioi (Zolgensma) for children under 2 years of age (all studies done without a concurrent control group and already approved in the USA and in Europe), and the splice modifier RG 7916 (Risdiplam – studies done in infants without concurrent control group and in patients 2–25 years with a placebo group).

These approvals bring hope to patients and families suffering with a disabling, and at times, deadly disease. However, certain questions and challenges arise, particularly since there have been limited studies focused on adults with SMA.[5–7] In an age of finite health care resources, how will decisions around "case-by-case" adult approvals be made given the very significant cost of these drugs? Which monitoring measures are most appropriate? How will decisions be guided that a treatment is unsuccessful and should be discontinued? Importantly, how will neuromuscular clinics cope with the additional monitoring, therapeutic, and clinical care requirements? While provincial governments have

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Table 1: Provincial adult coverage and monitoring for nusinersen

Organization/ province	Expanded coverage date	Adult coverage	Standard of care assessment schedule (months)	Required monitoring schedule (months)
Health Canada	June 28, 2017	All SMA	–	–
CADTH	February 27, 2019	None (type 1 and 2, 12 years and under)	–	–
INESSS (Québec)	December 18, 2018	Types 1, 2, and 3 of all ages	12	12
Saskatchewan	April 22, 2019	Physicians encouraged to submit application for those 18 years of age and older and/or who walked independently	12	4
Ontario	June 12, 2019	Adults can be approved exceptionally on a case-by-case basis	12	4
Alberta	July 5, 2019	May be considered on an exceptional basis	12–18	6
New Brunswick	August 26, 2019	Requests considered on a case-by-case basis	12	n/a
Yukon	August 8, 2019	Case-by-case basis, based on clinical status and SMA disease course, age at symptom onset, ventilation status, motor outcome score, and patient-specific goals	#	
Nova Scotia	October 1, 2019	Individuals over the age of 18 may be considered on a case-by-case basis	12	n/a
Manitoba	October 22, 2019		12–18	
British Columbia	December 16, 2019	None (case-by-case for types 1 and 2, 12 years and under)	12–24	n/a
Northwest Territories	January 1, 2020		#	
Prince Edward Island	–			
Nunavut	–		#	

CADTH = Canadian Association of Drugs and Technologies in Health; INESSS = Institut National d'Excellence en Santé et Services Sociaux.
# = no provincial/territorial multidisciplinary motor neuron disease clinic.

allocated funds for the medication, no additional funds have been funnelled to the neuromuscular clinics that care for these patients.

At this time, there is significant variability in provincial requests for the timing and frequency of monitoring. Some provinces are mandating a clinical assessment be performed every 4 months (Saskatchewan and Ontario), while others are content to request yearly monitoring (Québec), which is in keeping with the usual practice of most neuromuscular clinics which follow adult patients with SMA across Canada (Table 1).

The Canadian Adult SMA neuromuscular community is committed to providing standard of care treatment and monitoring for patients with SMA. We have significant concerns around the current state of monitoring and resource allocation as provincial negotiations for nusinersen occur and would respectfully submit the following observations.

Evidence for Frequency of Monitoring

The natural history of SMA in adults is that of a slowly progressive functional decline, where the common motor outcome assessment Hammersmith Functional Motor Scale Expanded (HFMSE) decreases by 0.5 points per year.[8] Existing evidence and the marker of clinically meaningful change used in clinical trials for the HFMSE are 3 points. Based on the natural history and meaningful change on the HFMSE, this suggests patients not on therapy may require 6 years to demonstrate "statistically significant" decline. Recent evidence suggests that in response to nusinersen therapy for adult patients, clinically meaningful change on the HFMSE is seen in only 28%, 35%, and 40% of cases at 6, 10, and 14 months, respectively (5). Statistically significant changes were also observed for the Revised Upper Limb Module (RULM) and 6-minute-walk-test (6MWT) at these time points. This is consistent with the smaller prior observational study in adults demonstrating benefit of nusinersen at day 180 (6MWT and peak cough flow) and day 300 (6MWT and RULM).[6] All motor outcome assessments currently used are expected to demonstrate clinically meaningful change only after a 1- to 2-year period. A concern is that a decline in outcome measures on treated patients in the span of 4 months is more likely to be secondary to inter- or intra-examiner variability or patient effort than a true effect. This potential artificial decline in outcome measure scores could lead to inappropriate termination of therapy provision based on stop criteria.

Human Resource Strain and Patient Burden

In certain jurisdictions where regular 4 monthly monitoring has been mandated, resource allocation is a concern as these motor outcome assessments are time-consuming and personnel intensive. Certain assessments must be performed by physical therapists, others by respiratory therapists; this coordinated assessment is not readily available outside of multidisciplinary motor neuron disease clinics or some rehabilitation center clinics for this population. Additionally, therapists must be trained in these measures to perform them accurately thus compounding limitations on personnel. There are ethical concerns when provincial governments mandate that scarce resources be utilized to provide frequent monitoring for largely stable patients for whom such

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frequent testing is not clinically relevant, nor evidence-based. This leaves fewer resources available for patients with other forms of motor neuron diseases or other neuromuscular conditions who may be rapidly progressing and in need of significant supports.

Additionally, frequent clinic visits can be challenging for patients; they are fatiguing, time-consuming, and sometimes costly depending on the degree of travel involved.

Collection of Real-World Evidence

Through the Canadian Neuromuscular Disease Registry (CNDR), an observational initiative to collect real-world evidence on SMA patients, both pediatric and adult SMA working groups comprised of expert investigators across the country have agreed to q6–q12 monthly monitoring of patients irrespective of therapeutic status. The registry is set up with a clear plan to assess effectiveness of novel therapies in a broad population.

The Canadian adult SMA physician working group are evaluating specific assessments by way of a Delphi model to incorporate best practices for the Canadian landscape (manuscript in preparation).

Proposition for Appropriate Monitoring

A recent CNDR meeting (January 20, 2020) convened adult experts in SMA from across Canada to agree on recommendations for frequency of monitoring. Final consensus included baseline visit, 6-months post-therapy initiation, and annually thereafter.

This proposed monitoring regimen allows for appropriate clinical monitoring, is congruent with the available evidence in treated adults, and does not put undue burden on provincial and clinic resources. Importantly, this standardized approach to SMA monitoring in Canada may prevent over-burdening patients and their families, for whom frequent clinic attendance is tiring, costly, and disruptive. The shared goal of the health care system is to provide a standard of care which is acceptable for patients, maintains appropriate resource allocation for all populations, and is feasible for the clinics. We believe our proposed monitoring system achieves these goals.

Declarations

Dr. Hodgkinson reports personal fees from Biogen, Roche, Sarepta outside the submitted work. Dr. Chapman reports personal fees from Biogen, Roche, outside the submitted work. Dr. Izenberg reports personal fees from Biogen, Roche, Akcea, Alexion, Takeda, Alnylam, Genzyme, outside the submitted work. Dr. Lochmuller reports grants and personal fees from Amplo Biotechnology, AMO Pharma, Biogen, Desitin, Fulcrum Therapeutics, GW Pharma, Milo Biotechnology, Pfizer, PTC Therapeutics, Roche, Santhera, Sarepta, Satellos, Ultragenyx, outside the submitted work, and Editor-in-chief, Journal of Neuromuscular Diseases (IOS Press). Dr. O'Connell reports personal fees from MT Pharma, grants and personal fees from Canopy Growth, personal fees from IPSEN, grants from Cytokinetics, grants from Mallinckrodt, grants from Orion, personal fees from Shoppers Drug Mart, outside the submitted work. Dr. O'Ferrall reports personal fees from PTC Therapeutics nmDMD Advisory Board; grants from Sanofi Genzyme, grants from Acceleron, grants from SAnofi Genzyme, grants from Grifols, outside the submitted work. Dr. Oskoui reports grants from Fonds de Recherche Sante du Québec, grants from Kids Brain Health Network, grants from Canadian Institutes of Health Research, grants from SickKids Foundation, grants from Cerebral Palsy Alliance Research Foundation, Fondation du Grand Defi Pierre Lavoie, outside the submitted work and served as site investigator on SMA clinical trials by Biogen, Roche, Cytokinetics. Dr. Pfeffer has nothing to disclose. Dr. Plamondon reports personal fees from Biogen, outside the submitted work. Dr. Rodrigue reports personal fees from Biogen, Roche outside the submitted work. Dr. Shoesmith reports other from Biogen, outside the submitted work, and Dr. Shoesmith's spouse is employed by Roche. Dr. Warman Chardon has nothing to disclose. Dr. Brais reports other from Biogen, Roche, outside the submitted work. Dr. Korngut reports grants from Biogen, Sanofi Genzyme, Cytokinetics, personal fees from Alexion, Novartis, Mitsubishi Tanabe, Sarepta, Biogen, CSL Behring, outside the submitted work. Dr. Schellenberg reports grants from Allergan, Genzyme, Mitsubishi Tanabe, personal fees from Akcea, Genzyme, EMD Serono, Alexion, Biogen, Mitsubishi-Tanabe, Roche, outside the submitted work.

Statement of Authorship

VLH and KS wrote the letter. All authors reviewed and approved the final letter.

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