

A consensus survey of neurologists and clinical geneticists on spinal muscular atrophy treatment in Singapore

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Dear Editor,

Just a decade ago, spinal muscular atrophy (SMA) was considered a debilitating, progressive neuromuscular disease that inevitably led to chronic disability and a shortened lifespan. Now, it is treatable with nusinersen, onasemnogene abeparvovec (OAV) and risdiplam—the 3 disease-modifying drugs approved by the US Food and Drug Administration, the European Medicines Agency and most recently, the Health Science Authority in Singapore.¹ Clinical trials and real-world data have consistently shown improvement in motor milestones for all 3 drugs, especially if introduced early in the disease course.²⁻⁴ More significantly, presymptomatic treatment has enabled age-appropriate development of motor milestones, leading to improved respiratory, orthopaedic and nutritional outcomes.⁵⁻⁸

However, there remains a multitude of challenges facing SMA patients in Singapore, in particular, the equitable access to these hyper-expensive therapies. OAV carries a hefty price tag of SGD 2.4 million (approx. USD 1.7 million), nusinersen costs approximately SGD 330,000 per year (after the initial SGD 660,000 for the first 4 loading doses) and risdiplam costs up to SGD 375,000 per year. None of these drugs are yet eligible for governmental subsidies under existing healthcare financing models, and patients have to rely on either private philanthropic donations or public crowdfunding to raise sufficient funds for treatment.

To identify a consensus for SMA treatment in Singapore, we surveyed 14 clinicians comprising 6 paediatric and 4 adult neurologists, and 4 paediatric clinical geneticists, all who directly care for SMA patients (Table 1). These are the key takeaways:

(1) The most important determinants for treating symptomatic patients were type of SMA or *SMN2* gene copy number, disease stage, ventilatory requirement, family support and compliance to multidisciplinary care.

(2) A total of 72% of respondents supported treatment over best supportive care in patients under 2 years of age with 2 or 3 *SMN2* copy numbers, with all 10 respondents preferring OAV to *SMN2* gene modifiers. Additionally, 72% also supported treatment for patients older than 2 years with 2 to 3 *SMN2* copies if they were not ventilated. Support for those with 4 or more *SMN2* copy number was more equivocal, with a slightly higher preference to treat if they were ambulant.

(3) A total of 93% of respondents supported presymptomatic treatment, with 77% choosing OAV as first choice. All supported newborn screening, with the vast majority electing to treat patients with up to 3 *SMN2* copies (>85%). Only 21% would consider treating 4 *SMN2* copy number patients.

(4) Respondents were willing to consider combination therapy if there was potential to wean off ventilatory support, ambulate independently, feed orally or delay scoliosis surgery.

The nuanced responses indicate a cognisance that systemic implementation of this new standard of care is being hindered by the lack of a strategic funding framework at present in Singapore. As such, a stricter criterion that limits use to those assessed to potentially yield the greatest benefit may be necessary to balance the competing needs of the wider collective. Yet these benchmarks may be hard to define fairly.⁹

Expert consensus currently prioritises early OAV treatment for presymptomatic and symptomatic patients with 2 to 3 *SMN2* copy number below 2 years of age as these patients are deemed to benefit the most from treatment. Support for disease-modifying treatment such as nusinersen or risdiplam in those above 2 years with 2 to 3 *SMN2* copy number only without ventilator dependence also underpins this pragmatism. Patients with milder disease (4 *SMN2* copy number) may need to be individually considered based on the magnitude

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Table 1. Consensus survey on spinal muscular atrophy (SMA) treatment in Singapore (March to April 2023).

Regarding symptomatic treatment*	Agree, no. of votes (%)
Factors influencing decision to start treatment	
Type of SMA/ <i>SMN2</i> copy number	14 (100)
Requirement for ventilatory support	13 (92.9)
Stage of disease	13 (92.9)
Family support	11 (78.6)
Compliance to multidisciplinary care	11 (78.6)
Requirement for assisted feeding	8 (57.1)
Financial status	8 (57.1)
Comorbidities, e.g. scoliosis	8 (57.1)
Factors influencing decision to exclude from treatment	
Previous hypoxic-ischaemic injury/cognitive impairment	11 (78.6)
Poor family compliance	10 (71.4)
Permanent ventilation/tracheostomy dependence	8 (57.1)
Cardiomyopathy	6 (42.9)
Chronic diseases	6 (42.9)
Psychiatric illness	5 (35.7)
Liver dysfunction	3 (21.4)
Swallowing dysfunction requiring feeding tube >1 month	1 (7.1)
Scoliosis	1 (7.1)
Factors influencing decision to stop treatment	
Poor compliance	13 (92.9)
Unacceptable side effects of drugs	12 (85.7)
Progression to ventilatory support	11 (78.6)
Persistent decline in motor function scores (>10% drop across 3 visits)	8 (57.1)
Increase in ventilatory support for >3 months	6 (42.9)
Progression to NGT feeding/gastrostomy	5 (35.7)
Frequent respiratory infections requiring hospitalisations ≥3x/year	4 (28.6)
No improvements in motor function scores	4 (28.6)
Loss of patient-reported functional skills	4 (28.6)
Progressive scoliosis (Cobbs angle >40°)	2 (14.3)
Clinical worsening of swallowing function	1 (7.1)
Drop in weight across ≥2 centiles	1 (7.1)
Reasonable minimum treatment period for efficacy assessment	
6 months	2 (14.3)
9 months	1 (7.1)
12 months	10 (71.4)
2 years	1 (7.1)
Regarding presymptomatic treatment	Agree, no. of votes (%)
I support presymptomatic treatment over best supportive care	13 (92.9)
First-line treatment	
Nusinersen	1 (7.1)
OAV	10 (71.4)
Risdiplam	2 (14.3)
I support newborn screening	14 (100)
Opt-out	8 (57.1)
Opt-in	6 (42.9)
I support treatment for these patients:	
1 <i>SMN2</i> copies	12 (85.7)
2 <i>SMN2</i> copies	14 (100)
3 <i>SMN2</i> copies	13 (92.9)
4 <i>SMN2</i> copies	3 (21.4)
>4 <i>SMN2</i> copies	1 (7.1)
Funding should be prioritised for:	
Carrier screening	3 (21.4)
Preconception screening	1 (7.1)
Newborn screening	10 (71.4)

NGT: nasogastric tube; OAV: onasemnogene abeparvovec

* Case scenarios to investigate treatment threshold in separate unpublished appendix (available upon reasonable request from the corresponding author).

and urgency of the individual's clinical need. Consideration for add-on therapy to patients previously treated with OAV may warrant clear, objective improvements given the absence of adequate data justifying the additional cost.

Several studies have sought to determine the cost-effectiveness of drugs by calculating the cost of treatment relative to the benefit of supportive care, known as the incremental cost-effectiveness ratio (ICER). These benefits are mostly quantified by health-related quality-of-life (QoL) indices known as quality-adjusted life-years (QALYs). However, QALYs may neither fully capture all treatment benefits nor take into account the QoL of caregivers, especially in the areas of caregiver fatigue and mental health.¹⁰ Some studies have demonstrated an unsustainably high ICER for all 3 drugs, but when applied to presymptomatic treatment versus later symptomatic treatment, there was significant cost savings and improved health outcomes, with particular sensitivity to treatment strategy (gene therapy over *SMN2* modifiers) and disease severity (treating those with 3 or more *SMN2* copy number).^{11–13} This provides a strong argument for nationwide implementation of newborn screening to maximise cost-effectiveness, although the threshold of treatment will still need to be addressed. A total of 28.5% of the respondents also prioritised preconception/carrier screening over newborn screening, reflecting differing views on the efficacy of disease prevention and management in the population in the light of high treatment costs.

In the absence of presymptomatic testing and treatment, it is imperative to understand that while symptomatic treatment provides a means of modifying a previously debilitating condition to one that achieves an acceptable level of functional independence, it is not curative. Differences in outcomes primarily depend on disease severity and timing of therapy. Even as we acknowledge tangible benefits in treated patients, families need to be made aware of disease complications and availability of palliative options. This requires a continuing process of clear communication and value exploration between healthcare professionals and families to define their shared goals of care and manage expectations.

However, it is difficult to quantify the value of life and life experiences, with physicians, policymakers and insurance payers likely having differing perspectives from patients and their families. In a qualitative study of 123 adult SMA patients and their physicians, definitions of meaningful change were highly variable between

patients, and was relative to their current functional ability rather than a simple increase in motor scores.¹⁴ Extending the lifespan of a patient with SMA Type 1 may add many years of treasured experiences, even if patients remain on ventilatory support. Reducing hospital admissions or prolonging distal hand function in patients with SMA Type 2 enables them to continue working, which gives meaning to their lives. Preventing wheelchair-dependence in patients with SMA Type 3 prolongs functional independence. It may be difficult for society to articulate the value of some of these aspirations over others.

Ultimately, decision-making needs to be collaborative between physicians, caregivers and patients based on evidence-based knowledge of their condition, and the changing risks and benefits of treatment. In our survey, poor compliance, unacceptable adverse effects from disease-modifying drugs, progression to ventilator dependence and persistent decline in motor function were the top considerations for treatment withdrawal. Physicians will need to individualise treatment strategies considering each patient's disease type, family resources and personal beliefs.

SMA is presently one of the rare genetic diseases that has viable life-changing treatments. There is clear support among experts in Singapore for these therapies but until a structured funding framework is developed, access will likely be inequitable and limited only to those who have the resources and the wherewithal to engage in public fundraising. This consensus survey will go some way in standardising treatment decisions for the patients most in need, but there remains an urgent need for a systemic funding framework to be introduced to facilitate timely treatment in this devastating disease. Difficult ethical considerations may also require oversight from an independent core committee.

Given the ongoing advances in genetic therapies, SMA is the first of many other treatable genetic disorders, which will incur enormous financial cost to patients and society. As a disease entity, it forms the ideal model for discussion of treatment and early diagnosis as the genetics are homogeneous with predictable and measurable disease types and severity. Not all diseases and their treatments will be as clearly defined, especially if there are alternative therapies available. The differing durability of treatment effect will also be a major concern. Against this backdrop, decisions about which disease and which patient to treat will need to be considered in light of the lessons learned from treating SMA.

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Data availability statement

Data are available upon reasonable request from the corresponding author.

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