Case Report: Nusinersen for the treatment of Spinal Muscular Atrophy Type 3 in an adult

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Objective

To describe the use and effect of nusinersen as a treatment for an adult diagnosed with Spinal Muscular Atrophy (SMA) Type 3 at a major public hospital.

Clinical Features

A 45-year old male patient with a new diagnosis of SMA Type 3 was initiated on nusinersen by the Neurology team in collaboration with the Interventional Radiology department.

Table 1: Impact of muscle weakness on function according to onset and SMA type

SMA Type	Usual age of symptom onset	Impact of muscle weakness on sitting/walking that would occur without treatment
Type I	< 6 months	Unable to sit or roll independently
Type II	6 – 18 months	Able to sit, but not walk independently
Type IIIa	18 months – 3 years	Able to walk, though may lose this ability over time
Type IIIb	3 – 18 years	Able to walk, though may lose this ability over time
Type IV	> 18 years	Mild walking difficulties

The patient had developed gradual bilateral weakness in both arms and legs since childhood, affecting his ability to only walk up to 1 kilometer without a walking aid.

Neurogenetics panel testing completed in 2019 showed the patient had homozygous deletion of exon 7 and 8 of the SMN1 gene, and he had three copies of exon 7 and 8 of the SMN2 gene. Therefore, the patient was diagnosed with SMA type 3.

Nusinersen (Spinraza®) was first listed on the Australian Pharmaceutical Benefits Scheme (PBS) in November 2018 and is the first and only treatment of its kind to be listed for SMA.

In December 2020, the PBS listing was extended to include pre-symptomatic initiation treatment of patients genetically diagnosed with SMA who have 2 or less copies of SMN2. The current PBS clinical criteria requires genetic confirmation of 5q homozygous deletion of SMN1 gene OR deletion of one copy of the SMN1 gene in addition to a pathogenic variant in the remaining single copy of the SMN1 gene[1].

Literature Review

SMA is an autosomal recessive neuromuscular disorder that results in progressive muscle atrophy and weakness.

It is caused by a homozygous deletion in the gene encoding survival motor neuron 1 (SMN1) at locus 5q13, which results in a decreased expression of the survival motor neuron (SMN) protein.

A paralogous gene, survival motor neuron 2 (SMN2), also encodes the SMN protein, however only 5-10% can produce a functional full-length SMN protein due to aberrant splicing[2,3].

Nusinersen is a modified antisense oligonucleotide drug that modifies pre-mRNA splicing of SMN2 to promote the expression of full-length SMN protein[2,3].

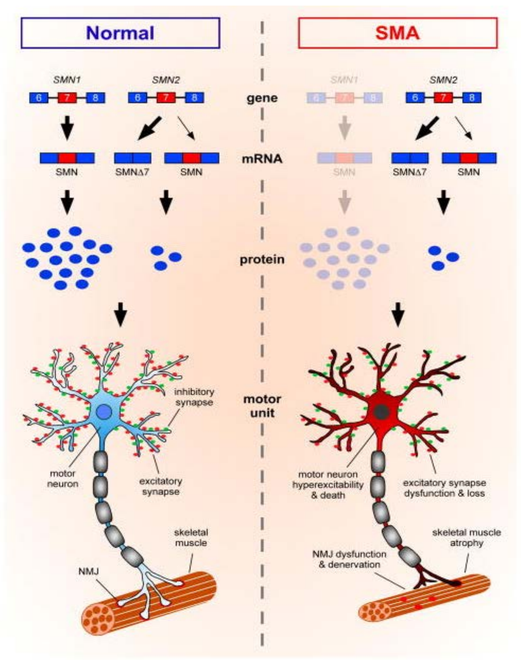

Figure 1. Genetic and cellular defects underlying motor system dysfunction in SMA. Data sourced from Current Opinion in Neurology (2016).

Clinical trials of nusinersen only included infants and children prior to approval for the market. The infants and children with SMA that received nusinersen were more likely to have clinical improvements in motor function compared to those in the control group[2,3].

Adults with SMA Type 3 that received nusinersen showed evidence of safety and efficacy including clinical improvements in motor function irrespective of their ambulatory status[4,5].

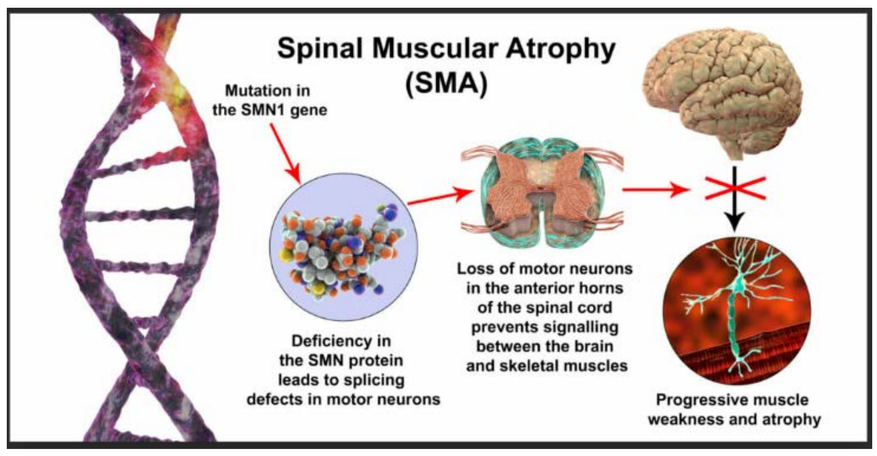

Figure 2. Spinal muscular atrophy pathophysiology. Data sourced from Rare Disease Advisor (2021).

Pharmacist Interventions, Case Progress and Outcomes

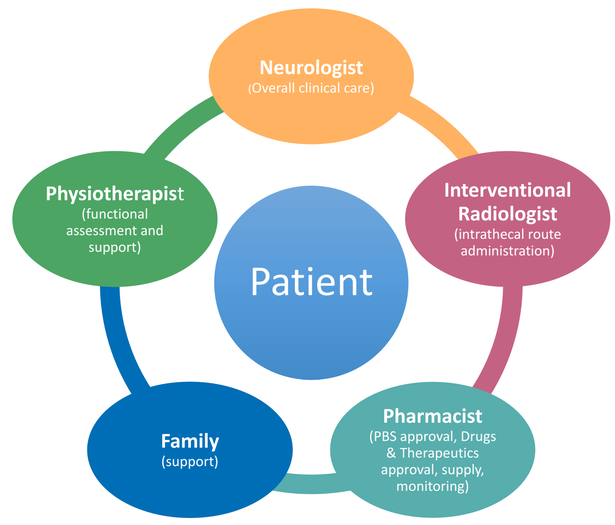

Figure 3: Multidisciplinary team collaboration to support SMA patient

- Our Associate Director for Operations at the Pharmacy Department requested formulary approval via the hospital Drugs and Therapeutics Committee. Once obtained - a supply of Spinraza® 2.4mg/mL solution for injection was organized and scheduled with the team and patient. Each vial cost $110,000.

- The patient received the first dose via intrathecal bolus injection in February 2023 with minimal complications. The patient had completed his loading doses in April 2023 with a plan for ongoing maintenance doses.

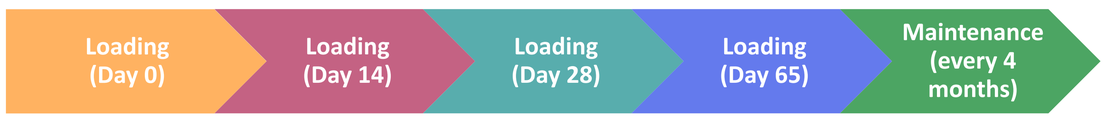

Figure 4: Dosing regimen for Nusinersen

- A Manual Muscle Test was conducted at baseline pre-intervention and again post loading dose completion.

Table 2: Comparison table of manual muscle test pre and post-loading dose of nusinersen

Manual Muscle Test	Score (baseline)	Score (post-loading doses)
Neck flexion	5	5
Neck extension	5	5
Shoulder abduction	4	4+
Shoulder adduction	4	4
Elbow flexion	4	4
Elbow extension	3+	3+
Wrist flexion	5	5
Wrist extension	5	5
Finger flexion	4	4+
Finger extension (Left)	4	4
Finger extension (Right)	4	3+
Interosseous function (Left)	4	3+
Interosseous function (Right)	4	4
Hip flexion	2	2
Hip extension (Left)	5	5
Hip extension (Right)	4	4
Knee extension	2	2
Knee flexion (Left)	4	4
Knee flexion (Right)	4	4
Foot dorsiflexion	5	5
Plantar flexion	5	5

- The outcome has not shown to be significant, however, this may be due to early stages of the treatment. Nusinersen has shown to have improvements after 15 months of treatment.
- The patient does report an improvement in his endurance and ability to work for extended periods of time as a result of treatment.

Conclusion

To our knowledge, this is the first Australian case report published of nusinersen as a treatment of an adult diagnosed with SMA type 3. It is anticipated this patient will continue treatment long-term with pharmacy's involvement to ensure timely supply of a high-cost drug, and safe and effective use through appropriate monitoring and management.

References

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