Spinal Muscular Atrophy

Educational Material*, Third Quarter, 2020

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Summary:

Spinal muscular atrophy (SMA) is a genetic disorder that starts in the central nervous system (CNS) and affects all the muscles in the body. Due to the degenerative nature of the disease, people with SMA experience a decline in muscle strength over time, although the rate and severity can vary among individuals. Gene therapy options are now available for patient with SMA to help minimize the progression of the disease and improve survival.

Objective(s):

1. Overview of Spinal Muscular Atrophy (SMA)
2. Explain the differences between SMA types
3. Discuss the complications and impact of SMA
4. Review current drug therapies approved for the treatment of SMA

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*As required by Medicaid Mega Reg

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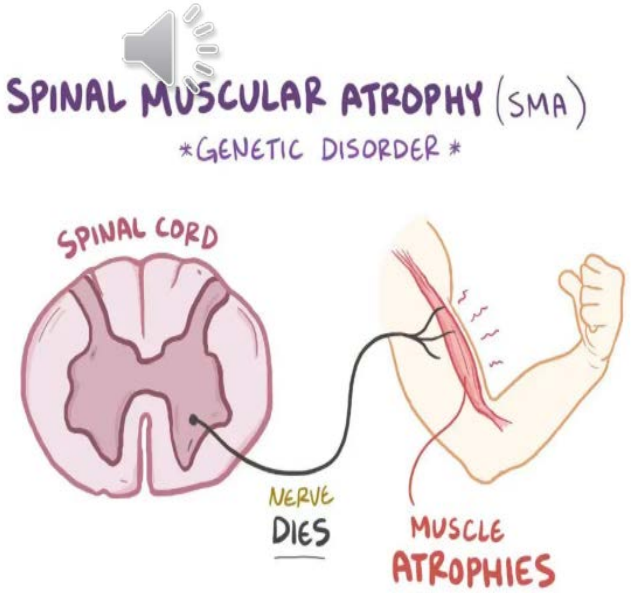
September 2, 2020

Objectives

- Overview of Spinal Muscular Atrophy (SMA)
- Explain the differences between SMA types
- Discuss the complications and impact of SMA
- Review current drug therapies approved for the treatment of SMA

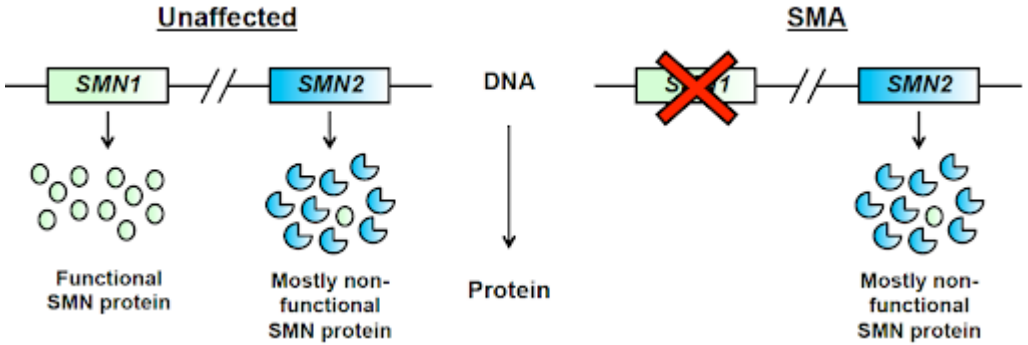
What is Spinal Muscular Atrophy (SMA)?



- Rare, degenerative neuromuscular disease characterized by progressive muscle weakness and atrophy
- Leading genetic cause of infant death
- Estimated incidence of SMA in the United States is 1 in 11,000 live births
- Estimated prevalence is around 1 to 2 in 100,000 persons

Pathophysiology

- Survival motor neuron (SMN) proteins facilitate proper signaling between CNS motor neurons and muscles in the body
- SMA is an autosomal recessive condition caused by deletions or mutations in the SMN1 gene, resulting in a shortage of SMN protein
  - SMN2 gene produces a small amount of functional length SMN protein, and an increase in copy number may decrease severity of disease but cannot fully compensate for the loss-of-function of SMN1



SMA Types

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SMA Type Prevalence	SMN2 copies	Age of Onset	Features
Type 1 (~60%)	2 – 3	Birth – 6 months	• Flaccid paralysis, rapid progression of symptoms • Weak cry, poor suck/swallow reflex, aspiration risk • Progressive respiratory failure, paradoxical breathing • Most die before 2 years of age
Type 2 (~ 20%)	3	3 – 15 months	• Often able to achieve sitting unassisted, but not independent standing/walking • Restrictive lung disease, scoliosis, respiratory muscle weakness, and dysphagia • Lifespan variable
Type 3 (~30%)	3 – 4	18 months – adult	• Often achieve ambulation, but potential loss of ability to stand/walk independently over time • Limited scoliosis and/or respiratory muscle weakness • Normal lifespan
Type 4 (<5%)	4+	Late onset	• All motor milestones achieved • Normal lifespan

Complications and Impact

- Respiratory
  - Potential dependence on cough assist devices, BiPAP (bilevel positive airway pressure)/CPAP (continuous positive airway pressure) machines, ventilator/tracheostomy
- Feeding/Nutrition
  - Impacted ability to feed self and swallow, risk of aspiration, and potential progression to G-tube/gastric button
- Activities of daily living (ADL)
  - Potential loss of ability to live independently, may become reliant on home health nursing, DME (durable medical equipment) use, other assistance
- Decline in motor function abilities

Spinal Muscular Atrophy Treatments

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	SPINRAZA® (nusinersen) injection 12 mg/5 mL	zolgensma® (onasemnogene abeparvovec-xioi)	Evrysdi™ risdiplam 60 mg powder for oral solution
FDA Approved	December 23, 2016	May 24, 2019	August 7, 2020
Route of Administration	Intrathecal Injection	Intravenous Infusion	Oral Solution
Frequency	Initial: every 2 weeks for three doses, then 4th loading dose 4 weeks after 3rd dose Maintenance: every 4 months	One-time	Once daily
Estimated Annual Cost	$550,800	$510,000	$407,705

Spinraza ® (nusinersen)

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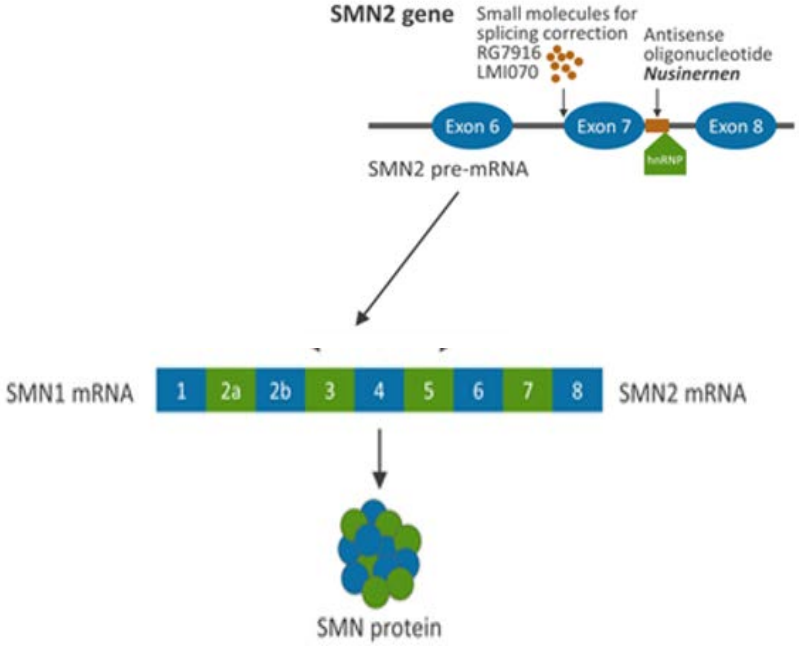
- **Mechanism of Action:** survival motor neuron-2-directed antisense oligonucleotide that increases exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts to produce full-length SMN protein
- **Indication**: treatment of SMA pediatric and adult patients
- **Dose:** 12mg <u>intrathecally</u> every 14 days for first 3 loading doses, then 4th loading dose 30 days after 3rd dose, then a maintenance dose once every 4 months



Summary of Clinical Trials – Spinraza

Infantile-Onset

	ENDEAR
Design	Phase 3, randomized, double-blind, placebo-controlled
# of patients	SMA Type 1, N = 121
Age Range	7 months of age and younger
Results	• 51% treated vs 0% untreated were motor milestone responders at 9 months • HINE-2: head control, rolling, independent sitting, standing • 63% reduced risk of mortality in Spinraza group
Status	Completed

Summary of Clinical Trials – Spinraza
Late-Onset

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	CHERISH	CS2/CS12
Design	Phase 3, randomized, double-blind, placebo-controlled	Open-label, 3-year study
# of patients	SMA Type 2/3, N = 126 (84 treated; 42 untreated)	SMA Type 2, N = 21 SMA Type 3, N = 7
Age Range	2 – 9 years old	2 – 16 years old
Results	• Spinraza treated group improvements over 15 months • RULM: 4.2 points treated vs. 0.5 points untreated • HFMSE: 3.9 points treated vs. – 1 point untreated	Type 2: • 4 point increase from baseline in upper limb function (ULM) • 10.8 point increase from baseline in motor function (HFMSE) • 1 gained ability to walk Type 3: • 1.8 point increase from baseline in motor function (HFMSE) • 2 regained ability to walk

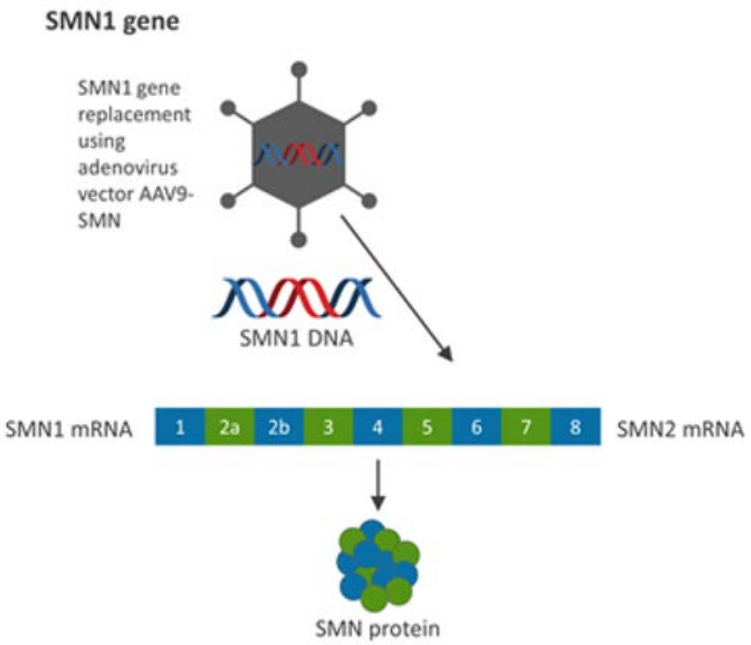
Summary of Clinical Trials – Spinraza

Ongoing

	NURTURE
Design	Phase 2, open-label, single-arm
# of patients	Pre-symptomatic SMA, N = 25
Avg. Age	6 weeks of age or younger
Results	• 100% (25 of 25) not requiring permanent ventilation at 2.9 years • 100% achieved sitting without support • 92% achieved walking with assistance • 88% achieved walking independently

Zolgensma® (onasemnogene abeparvovec)

- **Mechanism of Action:** recombinant AAV9-based (adeno-associated virus vector) gene therapy that delivers a copy of SMN1 gene encoding functional SMN protein
- **Indication**: treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene
- **Dose**: 1.1 x 10^{14} vector genomes(vg)/kg single-dose intravenous infusion over 60 minutes



Summary of Clinical Studies - Zolgensma

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	START	STR1VE
Design	Phase 1, open-label, dose-finding	Phase 3, open-label, single-arm
# of patients	SMA Type 1, N = 15	SMA Type 1, N = 22
Avg. Age	6.3 months / 3.4 months	3.7 months
Results	High dose group (N = 12): • 100% (12 out of 12) not requiring permanent breathing support at 24 months • 75% achieved ability to sit for 30 seconds without assistance • 16.6% achieved standing/walking independently Low dose group (N = 3): • 1 required permanent breathing support • None achieved independent sitting, standing or walking	• 90.9% (20 out of 22) not requiring permanent breathing support at 14 and 18 months • 1 passed away at 7.8 months from unrelated causes to treatment • 59% achieved ability to sit for 30 seconds without assistance at 18 months • 95% achieved or maintained a CHOP-INTEND score of at least 40 • Average increase of 6.9 points

Evrysdi™ (risdiplam)

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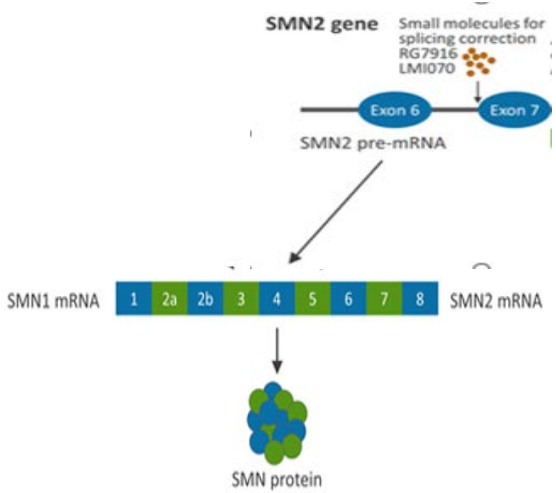
- **Mechanism of Action:** SMN2 gene splicing modifier that systemically distributes small molecules that enhance exon 7 inclusion into SMN2 messenger ribonucleic acid (mRNA) to produce more functional SMN protein
- **Indication:** treatment of SMA in patients 2 months of age and older
- **Dose:** oral solution administered daily
  - 0.2 mg/kg for patients 2 months to less than 2 years old
  - 0.25 mg/kg for patients 2 years of age and older, < 20 kg
  - 5 mg for patients 2 years of age and older, ≥ 20 kg



Summary of Clinical Trials - Evrysdi

	FIREFISH	SUNFISH	JEWELFISH	RAINBOWFISH
Design	Open-label, 2-part pivotal trial	2-part, double blind, placebo controlled pivotal trial	Open-label exploratory trial	Open-label, single arm, multicenter study
SMA Population	Type 1 Infants	Type 2-3 2 – 25 years old	SMA (All types) previously treated 6 months – 60 years old	Type 1 Pre-symptomatic Birth to 6 weeks of age
Status	Phase 3 Enrollment part 2 completed 11/2018	Phase 3 Part 1 data presented June 2020	Recruitment completed	Currently recruiting
Primary Endpoints	Part 1: Assessing safety profile in infants and dose for Part 2 Part 2: Assessing efficacy by proportion of infants able to sit without support after 12 months of treatment	Part 1: Determined dose for Part 2 Part 2: Evaluated motor function after 12 months of treatment using Motor Function Measure 32	Assessing safety, pharmacodynamics data, and accessibility in a broad population of patients that have been previously treated	Evaluating efficacy, safety, pharmacokinetics, pharmacodynamics in babies

Summary of Clinical Trial Results - Evrysdi

	FIREFISH	SUNFISH
SMA Population	Type 1 Infants	Type 2-3 2 – 25 years old

Results	Part 1 (N = 21):
	• Median treatment duration 14.8 months [0.6 to 26 months]
	• After 12 months of treatment:
	  • Recommended (higher) dose 0.2 mg/kg/day, N = 17: 41% able to sit independently for 5 seconds or more
	  • 90% of all patients were alive without permanent ventilation
	• After 23 months of treatment:
	  • 81% of all patients were alive without permanent ventilation
		Part 2 (N = 180):
		• Type 2 (71%) vs Type 3 (29%)
		• Evrysdi recommended dose vs placebo 2:1
		  • MFM32 score change from baseline at month 12: 1.36 vs -0.19
		  • Proportion of patients with a change from baseline MFM32 total score of 3 or more at month 12: 38.3% vs 23.7%
		  • Change from baseline in total score RULM at month 12: 1.61 vs 0.02

Institute for Clinical and Economic Review (ICER) Analysis

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- Analysis published May 2019
  - At the time, Zolgensma was not FDA approved
  - Specific to SMA Type 1
- In the United States, thresholds of $100,000 or $150,000 per QALY gained have been suggested as a reasonable upper bound for an intervention to be deemed cost effective
- Zolgensma has an incremental cost-effective ratio of $139,000 per QALY compared to Spinraza

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$2,231,000	$1,653,000	$3,884,000	3.24	7.64	$1,112,000	$590,000
BSC	$0	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,657,000	$3,657,000	12.23	18.17	$243,000	$182,000
BSC	$0	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$3,630,000*	$1,671,000	$5,301,000	13.46	19.76	$139,000	$117,000
Spinraza	$2,231,000	$1,653,000	$3,884,000	3.24	7.64	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Includes the Zolgensma costs (placeholder price of $2 million) and additional Spinraza costs.

Conclusion

- Spinal muscular atrophy has a huge impact on utilization of health care services, durable medical equipment, costs, and caregiver/family care
- The development of disease modifying therapies that enhance the production of functional SMN protein has completely changed the way SMA is approached and treated
- Impact of novel agent Evrysdi to be seen:
  - Utilization of Spinraza and Zolgensma
  - Patients previously treated with SMN enhancing therapy
  - Development of future agents for the treatment of SMA
- Overall efficacy and cost of treating SMA

Glossary

- ADL – Activities of Daily Living
- CHOP-INTEND – Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
- CNS – Central Nervous System
- HFMS(E) – Hammersmith Functional Motor Scale (Expanded)
- HINE – Hammersmith Infant Neurological Examination
- ICER – Institute for Clinical and Economic Review
- MFM32 – Motor Function Measure 32 motor function test
- MOA – Mechanism of Action
- QALY – Quality Adjusted Life Years
- RULM – Revised Upper Limb Module
- SMA – Spinal Muscular Atrophy
- SMN – Survival Motor Neuron
- ULM – Upper Limb Module

References

- https://www.ncbi.nlm.nih.gov/books/NBK533981/ (Accessed August 7, 2020).
- https://www.avexis.com/us/Content/pdf/prescribing_information.pdf (Accessed July 31, 2020).
- https://www.zolgensma.com/clinical-studies (Accessed August 2, 2020).
- https://www.spinraza.com/content/dam/commercial/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf (Accessed July 31, 2020).
- https://www.spinraza.com/en_us/home/why-spinraza/later-onset-studies.html (Accessed August 2, 2020)
- https://icer-review.org/material/sma-final-evidence-report (Accessed July 31, 2020).
- https://pubmed.ncbi.nlm.nih.gov/30044619/ (Accessed July 31, 2020).
- https://www.curesma.org/risdiplam/ (Accessed July 31, 2020).
- https://www.agah.eu/wp-content/uploads/Mueller__Lutz.pdf (Accessed July 31, 2020).
- https://www.gene.com/download/pdf/evrysdi_prescribing.pdf (Accessed August 24, 2020).
- https://www.uptodate.com/contents/spinal-muscular-atrophy?source=mostViewed_widget#H2206210403 (Accessed July 31, 2020).