New Treatments Of Spinal Muscular Atrophy (SMA)

BY

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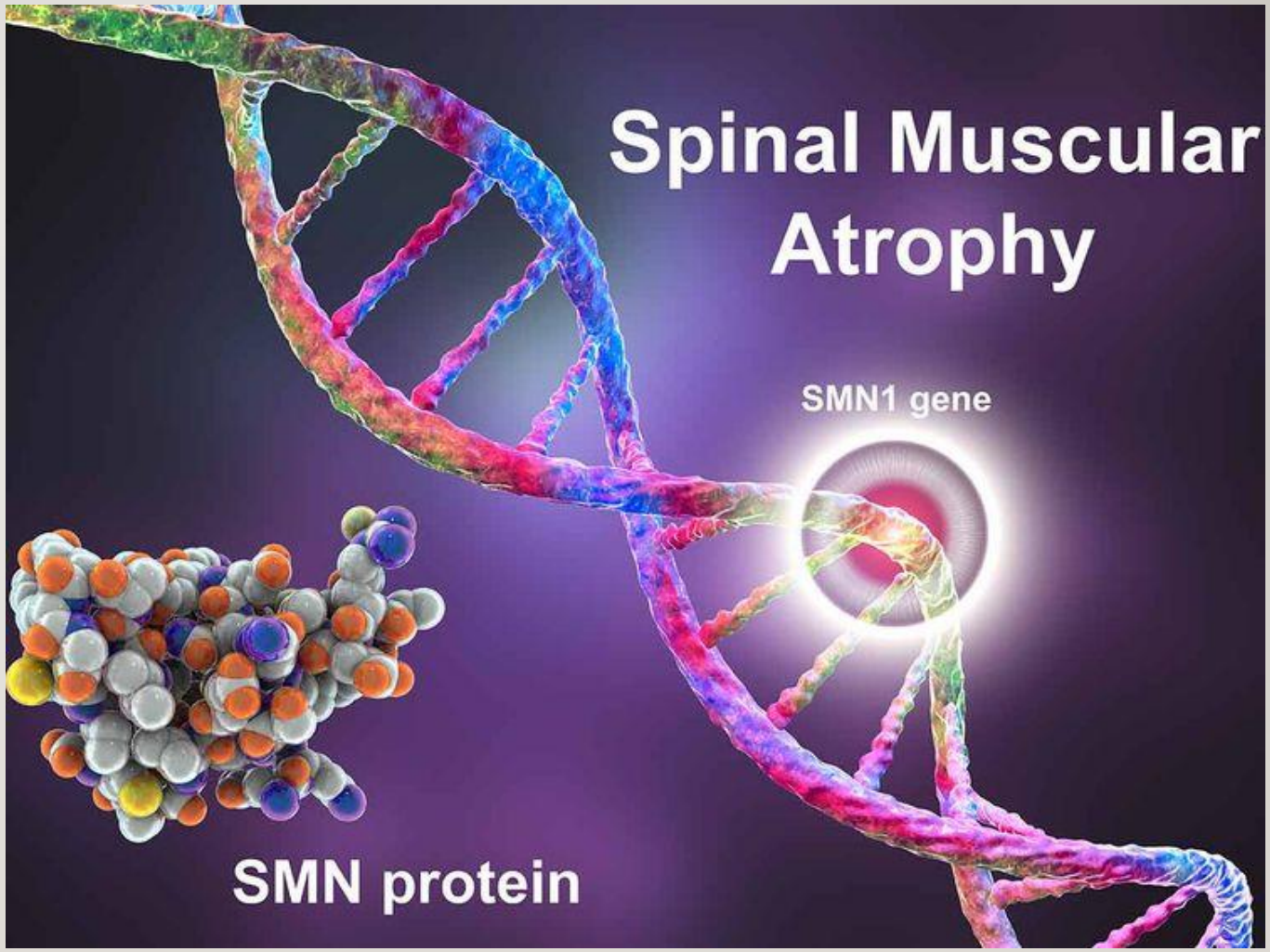
1400/12/12

BACKGROUND

- Spinal muscular atrophy (SMA) is one of the heterogeneous hereditary and progressive neuromuscular disease associated with a progressive degeneration of motor neurons in the spinal cord and brainstem that causes paralysis, muscle weakness and progressive loss of movement.
- SMA is the leading genetic cause of infant death and the second most common autosomal recessive disorder after cystic fibrosis.
- It is most commonly caused by deletions or biallelic mutations of the survival motor neuron gene (SMN1) at locus 5q13.2 (also known as 5q SMA);

- The majority (>95%) of SMA mutations are due to homozygous SMN1 deletions.

- Higher copy numbers of a nearby SMN2 gene is associated with a milder phenotype, as it is able to express 10 to 20% of the full-length survival motor neuron (SMN) protein.



SMA CLASSIFICATION

SMA is classified into subtypes by age on disease onset and the maximum motor milestones achieved.

SMA I: 60 %, the most severe subtype vs. SMA IV is the mildest. Notably, children with SMA are cognitively bright and sociable.

Subtypes:

• 1-SMA I, (Werding-Hoffman) presents before 6 months, patients never acquire a sitting position, and life expectancy due to respiratory failure is ≤ 2 yrs. without treatment.(with significant muscle weakness, hypotonia, and areflexia leading to progressive feeding and respiratory insufficiency)

• 2-SMA II (Intermediate) between 6 and 18 months, patients can sit but not walk independently, and patients develop respiratory involvement that requires noninvasive ventilation, as well as orthopedic complications and the condition can be associated with reduced life expectancy.

• 3- SMA III (Juvenile type or kuglberg-welander) presents 18-36 M (after 18 months) with the ability to walk unassisted; progressive weakness may result in loss of independent ambulation, but a normal life span can be expected and patients achieve independent walking and variable clinical course.

• 4- SMA IV (Adult-Onset) means later onset of disease(After age 30), Autosomal recessive. At least 4 copies of SMN 2, an uncommon adult form with mild weakness and slowly progressive, Proximal limb weakness and diaphragm; Although eventually wheelchair-bound but normal life expectancy and usually have no life-threatening events.

SMA CLASSIFICATION

On the other hand, some experts believe that SMA is clinically classified into five subtypes, based on the age of symptom onset and the maximum attainable gross motor function (see Table). SMA type 0 is a rare in utero-onset disease, with reduced fetal movements and severe weakness leading to respiratory insufficiency at birth, and death before six months of age.

SMA types, features and life expectancy

Type	Onset	Indicators	Clinical features	Life expectancy
0	Prenatal, at birth	No head control, Can't sit	General weakness, muscle weakness, respiratory failure, poor feeding, con-tractures	Death within weeks of birth
I	0-6 months	Cannot sit	Weakness close to the middle of the body, respiratory in-sufficiency, poor feeding, tongue muscle twitch	Death by age 2
II	6-18 months	Never stands or moves about, sits independently	Weakness close to the middle of the body; tongue muscle twitch; invol-untary, jerky trem-or-like movements, sideways curvature of spine	Age 2-25 years
III	18 months - 3years.	Walks independently	Predominant weak-ness in middle, lower extremity; abnormal gait	Normal lifespan
IV	>30 years	Walks independently	Leg weakness and tremor in the fingers	Normal lifespan

INCIDENCE & THE EPIDEMIOLOGIC BURDEN OF SMA

- **Currently, the incidence and prevalence of SMA is unknown, not only in Iran but also in many advanced countries such as Canada.**
- **For example, based on the number of live births in Canada (393,102 in 2016) and the estimated SMA incidence of 1 per 11,000 newborns, the estimated number of new cases is about 35 per year, including 21 (60%) new cases of SMA Type I.**
- **So, SMA occurs (estimated to be around) in 1 : 6,000 to 1 : 11,000 in live births, with a prevalence of 1–2 per 100,000 persons, and a carrier frequency of 1 in 50 people (1 in 40 to 67 adults is a carrier of the autosomal recessive gene.)**
- **"However, the epidemiologic burden of SMA differs among the subtypes,". SMA III has a lower incidence compared with the other subtypes.**

COSTS

- SMA is associated with direct and indirect costs of approximately $1 billion annually in the United States. Given the rarity of SMA, the direct and indirect costs per capita are close to $200,000.

DIAGNOSIS

Tests during pregnancy

Chorionic Villus Sampling (CVS)a sample of cells from the placenta are tested, during weeks 11 to 14 of pregnancy

Amniocentesis a sample of amniotic fluid is tested, usually during weeks 15 to 20 of pregnancy

Both these tests can slightly increase chances of a miscarriage .

Tests after birth

PH.EX

EMG/NCV

A **Genetic blood test**.

Very occasionally, other tests may be needed, too. For example:

MBx a small sample of muscle is taken for analysis

Clinical factors can guide to predict treatment response

In presymptomatic patients who have yet to develop clinical symptoms, the SMN2 copy number is the best available predictor of future disease severity. The SMN2 copy number determination is challenging especially when a high copy number is present.

In symptomatic patients, the clinical classification of disease into subtypes is not a sufficient predictor of trajectory of the response to treatment, with a wide spectrum and overlap across types. An earlier age of onset predicts a more severe phenotype with likely prenatal loss of motoneurons. A longer duration of symptoms, lower level of current functioning, and dependence on ventilatory and nutritional support represent more advanced stages of disease where treatment response expected will be smaller.

Clinicians should be aware of these factors potentially influencing treatment response and counsel families accordingly.

THERAPEUTIC OPTIONS

There are now multiple therapeutic options available.
(3 licensed SMA therapies increase SMN levels, but are not a cure).
Other strategies to increase SMN levels are still under development.

I-SPINRAZA (NUSINERSEN)

NUSINERSEN (SPINRAZA)

- The first FDA-approved for SMA was nusinersen (Spinraza), an antisense oligonucleotide (a SMN splicer or ASOs directed against an intron splice silencer (ISS) in the *survival motor neuron 2* (*SMN2*) gene to alter the splicing of a gene and the amount of full-length SMN transcript in the nervous system, restoring SMN to levels that could correct SMA).
- Approved in December 2016,the European Medicines Agency (EMA) and Health Canada approved it in June 2017.
- These trials showed improvements in motor function, a prolonged time to death, and a prolonged time to needing permanent ventilation. Both trials were ended early because of their positive results.
- Spinraza ® (nusinersen) is a DMT approved for all patients with SMA and is IT injection Q 4 months after a series of loading doses.
- Nusinersen is an antisense oligonucleotide therapy (a SMN2 directed antisense oligonucleotide) that enhances production of full-length survival motor neuron (SMN) protein and slows the progression of the disease by increasing SMN expression from the SMN2 gene.

SPINRAZA ® (NUSINERSEN) PRICE

- Spinraza is among the most expensive drugs in the world. A price of $626,000 to $750,000 for the first year of Tx, but that doesn't make it cheaper compared to Zolgensma. Because unlike Zolgensma, which is a one-time drug, Spinraza has recurring costs. From the second year onwards, its price drops to $375,000 per year and continues so for the remainder of the patients' lives, making it effectively costlier than Zolgensma (The single dose of Zolgensma can end up costing half as much as this chronic course of SMA therapy).
- The 2018 published price of a single dose is around €75,000, or approximately £66,000, however government buyers normally negotiate significant discounts on drugs.

DOSAGE FORM & INTERVALS

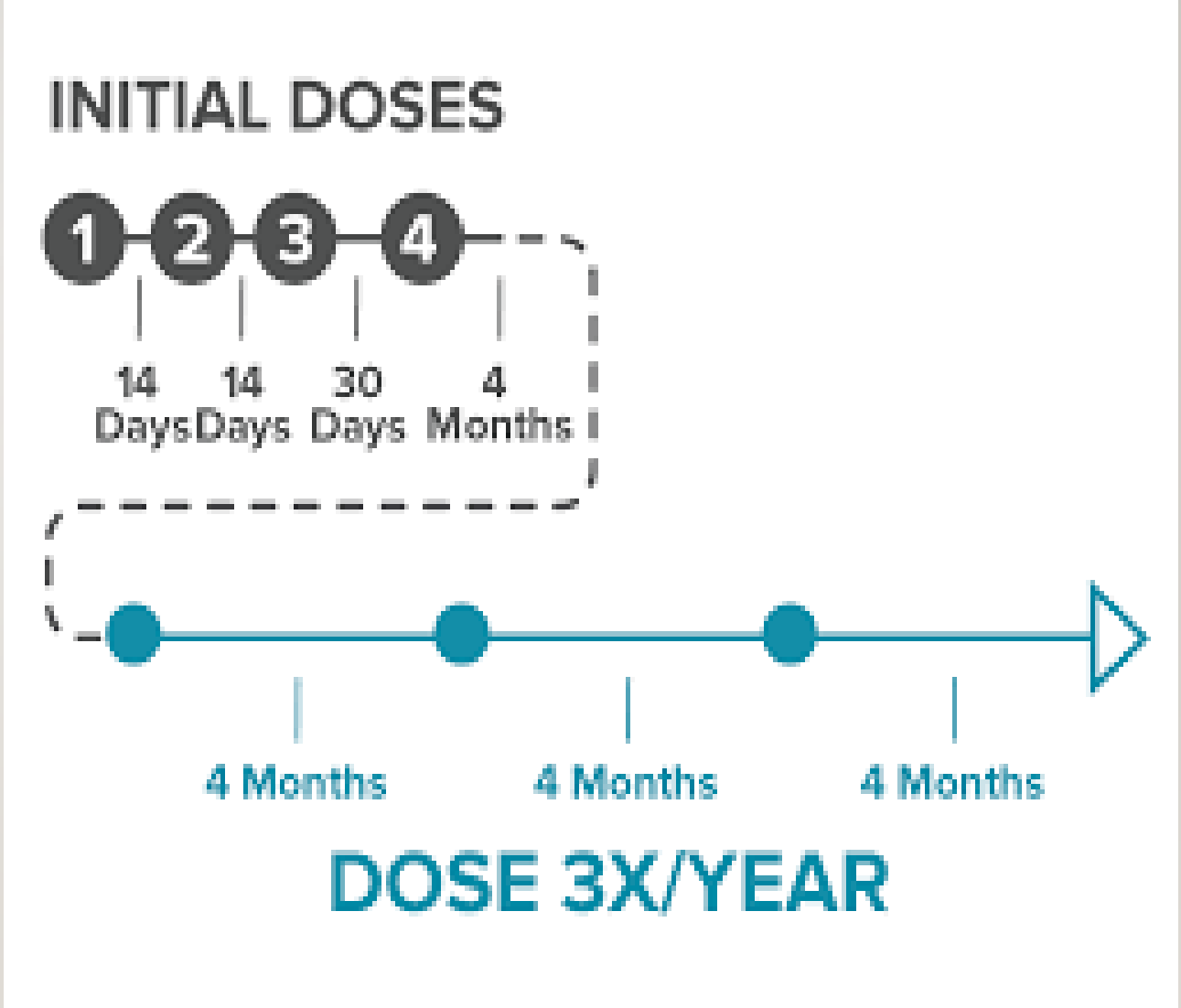
Solution for intrathecal injection

- 12mg/5mL single-dose vial

Indicated for SMA in children and adults (New born -16 yrs.) 12 mg IT per administration

Initial: 4 loading doses; administer the first 3 doses at 14-day intervals and the fourth dose 30 days after the third dose

Maintenance: One dose Q4M



AGE LIMIT

Clinical studies of SPINRAZA included patients from 3 days to 16 years of age at first dose, but did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients.

Cautions

1-Coagulation

- Coagulation abnormalities and thrombocytopenia, may be at increased risk of bleeding.
- Obtain platelet count and coagulation laboratory testing at baseline and prior to each administration and as clinically needed.

2- Renal toxicity

- Nusinersen is present in and excreted by the kidney
- Renal toxicity, including potentially fatal glomerulonephritis

Intrathecal Administration

Consider sedation as indicated by the clinical condition of the patient.
Consider U/S or other imaging to guide intrathecal administration of, particularly in younger patients.

Prior to administration, remove 5 mL of CSF
Administer as an intrathecal bolus injection over 1-3 minutes using a spinal anesthesia needle.

Do not administer in areas of the skin where there are signs of infection or inflammation.

NUSINERSEN AND PRESYMPTOMATIC STAGE

April 14, 2020; 94 (15 Supplement) SUNDAY, APRIL 26

Nusinersen in Infants Who Initiate Treatment in a Presymptomatic Stage of Spinal Muscular Atrophy (SMA): Interim Results From the Phase 2 NURTURE Study (993)

Richard S. Finkel, Darryl C. De Vivo, Kathryn J. Swoboda, Enrico Bertini, Wuh-Liang Hwu, Richard Foster, Ishir Bhan, Stephanie Fradette, Wildon Farwell

First published April 14, 2020.

Other treatment strategies

The most important other treatment strategies, including vector-based gene replacement and small molecule therapies.

Patients with the disease cannot produce sufficient amounts of a protein called 'survival motor neuron' (SMN), which is essential for the normal functioning and survival of motor neurons. Without this protein, the motor neurons deteriorate and eventually die. This causes the muscles to fall into disuse, leading to muscle wasting (atrophy) and weakness.

The SMN protein is made by two genes, the SMN1 and SMN2 genes. Patients with spinal muscular atrophy lack the SMN1 gene but have the SMN2 gene, which mostly produces a 'short' SMN protein that cannot work properly on its own.

A one-time intravenous administration of Zolgensma supplies a fully functioning copy of the human SMN1 gene enabling the body to produce enough SMN protein. This is expected to improve their muscle function, movement and survival of children with the disease.

2-ZOLGENSMA


onasemnogene abeparvovec-xioi
ZOLGENSMA
Rx ONLY
DO NOT SHAKE
DO NOT REFREEZE
5.5 mL
onasemnogene ab
ZOLGENSMA
Rx ONLY

Zolgensma ®

Zolgensma ® (onasemnogene abeparvovec-xioi) is a gene replacement therapy that uses a viral vector to deliver a functional copy of the SMN1 gene.

Zolgensma is administered as a one-time IV infusion and is only approved for the treatment of children ≤ 2 years in May 2019 by FDA because of current limitations of dosing (i.e. viral titers and increased likelihood of immune response) and the fact that this drug has only been tested for this age group.

The most common side effects: Increases in liver enzymes (transaminases). This is an effect of the immune response to the treatment.

ZOLGENSMA@

EMA's recommendation is based on the preliminary results of 1 completed clinical trial and 3 supporting studies in patients with SMA with different stages. These included genetically diagnosed and pre-symptomatic patients.

A clinical trial conducted in 22 patients who were <6 months of age at the time of the gene replacement therapy with Zolgensma.
The survival of patients treated with Zolgensma exceeded than untreated patients with severe SMA.
Out of 22 patients, 20 patients (91%) were alive and did not need permanent ventilatory support at 14 months of age.
At 14 months of age only 25% of patients are still alive.

These patients also achieved motor milestones, which are usually not achieved in the natural history of the disease.
14 patients (64%) reached the milestone of independent sitting before 18 months of age.
One patient (4%) reached the milestone of walking unassisted before reaching 16 months of age.
Patients with less motor deterioration appeared to benefit the most from the treatment with Zolgensma.

Dosage

Give as a slow IV infusion over 60mins. <2yrs: 1.1×1014 vg/kg.

ZOLGENSMA is provided in a kit containing 2 to 9 vials, as a combination of 2 vial fill volumes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of 2.0 × 1014 vector genomes (vg) per mL. Each vial of ZOLGENSMA contains an extractable volume of not less than either 5.5 mL or 8.3 mL.

Starting one day prior to Zolgensma infusion: give systemic corticosteroids equivalent to oral prednisolone 1mg/kg/day for 30 days, then taper dose gradually over the next 28 days if LFTs are unremarkable.

Adverse Effects

The most common adverse reactions (incidence ≥ 5%) were elevated aminotransferases and vomiting.

1->10%
Elevated aminotransferases (>ULN) (27.3%)

2-10%
Vomiting (6.8%)

Precaution & Warnings

- Acute serious liver injury, acute liver failure, and elevated ALT/AST can occur
- Patients with preexisting liver impairment may be at higher risk
- Before infusion, assess liver function of all patients by clinical examination and laboratory testing (eg, AST/ALT, total bilirubin, prothrombin time)
- Administer systemic corticosteroid to all patients before and after infusion
- Continue to monitor LFT for at least 3 months after infusion

PRICE


TOP 10 MOST EXPENSIVE DRUGS
These are the costliest drugs (single dose) in the world
1 Zolgensma
$2.12 M
2 Zokivny
$1.03 M
3 Danyelza
$977,664
4 Myalept
$889,904
5 Luxturna
$850,000
6 Folotyn
$793,870
7 Brineura
$730,340
8 Blincynto
$712,672
9 Ravicti
$695,970
10 Soliris
$678,392
Calculated based on the total annual cost of a typical course of therapy for each drug.


ZOLGENSMA
(Onasemnogene abeparvovec)
$2.1
Million
Per injection

3-RISDIPLAM

The most recent treatment approved by the FDA on August 7,2020 & then shortly after EMA on August 17 is Evrysdi ® (risdiplam), an orally administered, SMN2 splicing modifier for patients 2 months of age and older.

RISDIPLAM

Improves motor function and is taken as a syrup medicine once a day after meals. It is the first non-injectable Tx for SMA and can be taken at home and is available for SMA 1, 2 and 3.

Evrysdi ® (risdiplam)

Mechanism of Action:

The liquid drug works by modifying the SMN2 gene ((SMN2) mRNA splicing modifier) to produce increase amounts of SMN protein- essential for the health of nerve cells that control muscle movement.

In fact, the drug increases exon 7 inclusion and thus full-length SMN protein production from the SMN2 gene.
Absorption:

Peak plasma time: 1-4 hr
Steady-state reached: 7-14 days

RISDIPLAM

In England, the drug has a list price of nearly £8,000 per dose, but following a deal struck between the manufacturer Roche and NHS England, the health service will have access to the drug at a price that is fair for taxpayers.

Babies as young as two months can be treated with the drug, with a Dx of SMA types 1, 2 or 3 or with one to four SMN2 copies.

One case from London, has SMA type 3 and was the first patient from the UK to receive risdiplam through a clinical trial, he is now aged nine, started the drug when he was five.

The liquid drug works by modifying the SMN2 gene to produce increase amounts of SMN protein- essential for the health of nerve cells that control muscle movement. Evrysdi (risdiplam) will be priced so the highest annual cost will be $340,000.

Dosage Forms & Strengths

Powder for oral solution

- 60mg/bottle

Indication:

For Tx of SMA, including types 1, 2, and 3

5 mg PO q/d (6-7 cc)

Administer at approximately the same time each day after a meal.

Risdiplam must be taken immediately after it is drawn up into the oral syringe; if not taken within 5 minutes, discard the drug from the oral syringe and prepare a new dose.

Do not mix with formula or milk.

DOSAGE MODIFICATIONS

Renal impairment

Renal impairment is not expected to alter risdiplam exposures

Hepatic impairment

Safety and efficacy have not been studied in hepatic impairment

Avoid use (Hepatic impairment may potentially increase risdiplam exposures)

Adverse Effects

>10%

Fever (22%)

Diarrhea & Rash(17%)

1-10%

Mouth and aphthous ulcers (7%)

Arthralgia (5%)

Urinary tract infection (5%)

Additional adverse effects in infantile-onset SMA

- Upper respiratory tract infection
- Pneumonia
- Constipation
- Vomiting

Pregnancy & Lactation

Data are unavailable

Comparison of mechanisms

Both nusinersen and risdiplam utilize a splicing modification of SMN2. However, Zolgensma is a SMN1 gene replacement therapy.

Potential treatments in the pipeline

The SMA treatment landscape continues to evolve as there are several other medications in development.

Reldesemtiv is a selective small-molecule troponin activator in fast skeletal muscles that has a phase 1 study confirming its safety. A phase 2 double-blind, randomized, placebo-controlled trial also shows how the compound at **a higher dose increases the 6-minute walk test from baseline.**

SRK-015, a **monoclonal antibody**, has **improved muscle force in SMA mice**, and a phase 1 trial confirmed the safety and tolerability. It is currently in a phase 2 study evaluating the therapy in 58 patients between the ages of 2 and 21 years who have SMA II and SMA III.

According to the authors, the studies have demonstrated that pre-symptomatic children or children **with the shortest disease duration had better efficacy**.

Synopsis of selected ongoing and recently finished clinical trials of medical treatments in spinal muscular atrophy (SMA). AAV-9 = Associated Adenovirus 9; 6MWT = six minute walking test; FSTA = Fast Skeletal Muscle Troponin Activator; IT = intrathecal; PO = oral intake; IV = intravenous application

Drug	Sponsor	Mechanism of action	Route of application	Phase I	Phase II	Phase III	FDA Approval	Comment
Splicing modification of SMN2:								
Nusinersen	Biogen-Ionis	Antisense-oligonucleotide	IT	x	x	x	x	Approval by FDA (Dec. 2016) and EMA (Jul. 2017) for all subtypes of SMA
RG7916 (Risdiplam)	Roche	Small molecule/splicing modifier	PO	x	x	(x)		SMA type 1: After 15 months of treatment inde-pendent sitting in 33%
LMI070 (Branaplam)	Novartis	Small molecule/splicing modifier	PO	x	x			Recruitment temporarily halted (safety concerns), now completed
Replacement of SMN1-gene								
AVXS-101 (Zolgensma)	Avexis/Novartis	AAV-9-Vector	IV	x	x	x	x	FDA approval for SMA patients <2 years of age (May 2019)
AVXS-101 (Zolgensma)	Avexis/Novartis	AAV-9-Vector	IT	x				Study in children <6 years of age with 3 *SMN2*-copies
Upregulation of muscle growth								
CK-2127107 (Reldesemtiv)	Cytokinetics	FSTA	PO	x	x			Mild improvement in 6MWT after 4–8 weeks of treatment in SMA 2 and 3
SRK-015	Scholar Rock	Myostatin Inhibotor	IV	x	x			Positive results in animal models
Neuroprotection								
Olesoxime	Hoffmann-La Roche	Apoptosis-inhibitor	PO	x	x			Development stopped in 2018

CONSENSUS STATEMENTS AGREEMENT AMONG CANADIAN EXPERTS CAN J NEURO SCI 2021

COMMENTARY

Guidance on Gene Replacement Therapy in Spinal Muscular Atrophy: A Canadian Perspective

Maryam Oskoui, Hernan Gonorazky, Hugh J. McMillan, James J. Dowling, Reshma Amin, Cynthia Gagnon, Kathryn Selby

Keywords: Spinal muscular atrophy, Gene replacement therapy, Onasemnogene

doi:10.1017/cjn.2021.125

Can J Neurol Sci. 2021; 00: 1–4

Table 1: Consensus statements agreement among Canadian experts

Consensus statement	Agreement	Strength of consensus
1.1: Traditional SMA types (e.g. types 0, 1, 2, 3, 4) alone are not sufficient to define patient populations who might benefit most from gene therapy.	20/21 (95.2%)	Strong consensus
1.2: In symptomatic patients, age at onset, disease duration, and motor function status at the start of treatment are the most important factors that predict response to treatment.	21/21 (100%)	Strong consensus
2.1: In presymptomatic patients, *SMN2* copy number is the most important predictor of clinical severity and age of onset.	21/21 (100%)	Strong consensus
2.2: As long as no better biomarkers or predictors are available, treatment decisions for presymptomatic patients should primarily be based on *SMN2* copy number.	20/21 (95.2%)	Strong consensus
2.3: Determination of *SMN2* copy number needs to be performed in an expert laboratory with adequate measures of quality control.	21/21 (100%)	Strong consensus
3: Approval of gene therapy for SMA with Zolgensma® is based on clinical trials with patients with SMA less than 6 months of age. Additional data of patients up to 2 years and weighing up to 13.5 kg are made public through congress presentations. These data mainly come from nonsystematic data collection in the USA, where Zolgensma® is approved up to the age of 2 years. When administered after the age of 6 months and/or in advanced stages of the disease, parents or patients should clearly be made aware that there are so far no published data on efficacy and safety. In this patient population, it is particularly important for physicians to discuss the benefit/risk ratio and to carefully manage parents' or patients' expectations.	20/21 (95.2%)	Strong consensus
4: In patients presenting with symptoms at birth, treated after a long disease duration, or with already severe evolution, parents should be clearly made aware that despite the use of gene therapy there is a high risk of living with a very severe disability. Palliative care should be discussed as an alternative treatment option in these circumstances.	21/21 (100%)	Strong consensus
5: Since the risk of gene therapy increases with the dose administered and since the dose is directly proportional with the weight, patients above 13.5 kg should only be treated in specific circumstances. For these patients, treatment with other disease-modifying therapies or future intrathecal administration of Zolgensma® should be considered as an alternative.	20/21 (95.2%)	Strong consensus
6: Until now there is no published evidence that combination of two disease-modifying therapies (e.g. gene therapy and nusinersen) is superior to any single treatment alone.	20/21 (95.2%)	Strong consensus
7: Centers performing gene therapy for SMA should have broad expertise in the assessment and treatment of SMA according to international standards. They should also have the ability and resources to deal with potential side effects of gene therapy. Personnel should be trained and have experience in the use of standardized and validated outcome measure for SMA to document treatment effects. Recognition as European Reference Centre (www.ern-euro-nmd.eu) or national accreditation as neuromuscular centre of expertise might serve as additional selection criteria.	21/21 (100%)	Strong consensus
8: There is convincing evidence that early initiation of treatment ideally in the presymptomatic stage of the disease is associated with markedly better outcome as compared to later start of treatment. Spinal muscular atrophy is therefore a good candidate for inclusion in newborn screening programs. In newly diagnosed patients, any delay of treatment should be avoided. Ideally, the time frame between diagnosis and initiation of a disease-modifying treatment should be no longer than 14 d. This is particularly important in infants due to the progressive course of the disease.	21/21 (100%)	Strong consensus
9: Data concerning effectiveness and safety should be collected systematically for all patients treated. Treatment centers should be provided with adequate resources to perform long-term monitoring of treated patients with standardized outcome measures. Where available disease-specific registries should be used for data collection to allow comparison between different treatments. Data analysis should be performed primarily by academic institutions and networks.	20/21 (95.2%)	Strong consensus
10: On the basis of the currently available data and in light of existing effective treatment alternatives, intravenous gene replacement therapy with Zolgensma® for patients with a body weight >13.5 kg should only be performed under a more rigorous protocol with continuous monitoring of safety and efficacy. This data collection might be best achieved in a clinical trial setting.	18/21 (85.7%)	Consensus
11: As the use of Zolgensma® will generate additional evidence during the coming years, pharmaceutical industry, regulators, patient representatives, and academic networks should collaborate to ensure that any new data on effectiveness and safety are publicly available in an unbiased and timely manner. This growing body of evidence is indispensable for an improved risk–benefit assessment for future patients and should not be hampered by particular commercial or academic interests.	21/21 (100%)	Strong consensus

GUIDANCE ON GENE REPLACEMENT THERAPY IN SPINAL MUSCULAR ATROPHY: A CANADIAN PERSPECTIVE

Until now there is no published evidence that combination of two disease-modifying therapies (e.g. gene therapy and nusinersen) is superior to any single treatment alone, and until further evidence is available would not recommend continuing other upregulators of SMN protein production to be continued after gene therapy administration.

THE END

THANKS FOR YOUR ATTENTION