Review Article

FUTURE JOURNAL OF PHARMACEUTICALS AND HEALTH SCIENCES

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An Overview of Contemporary Phenotypes, Present Challenges, and Novel Implications for Medical Services in the Diagnosis of Spinal Muscular Atrophy

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Article History:

Received on: 26Oct 2023
Revised on: 01Nov 2023
Accepted on: 02Nov 2023

Keywords:

Nanoparticles,
Anti-Cancer,
Paclitaxel,
Melanoma

Abstract

Spinal muscular atrophy (SMA) is a form of muscle disease induced by SMN1 gene mutations. It can cause motor neurons and muscle strength to weaken. The intensity of the disease's progression varies depending on the stage of development. Over the past ten years, new ways to help people with SMA have been found. These include the use of gene therapy and the modification of the SMN2 and SMN1 genes. First drugs approved for this condition were able to significantly alter the course of the disease. However, the evidence that is now available for these novel therapies is frequently constrained to a small range of individuals in terms of age and illness stage. To better understand the impact of treatment on people with all SMA subtypes and to build a platform for clinical decision-making in SMA, it will be necessary to gather real-world data with standardized outcome markers.

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eISSN: 2583-116X
DOI: https://doi.org/10.26452/fjphs.v3i4.524

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INTRODUCTION

A lot has changed since the first instances of spinal muscular atrophy (SMA) were documented by Werdnig and Hofmann in 1891 and 1893, respectively. First through linkage analyses and then by finding disease-causing mutations in SMN1, scientists were able to figure out the disease's genetic background. This made it possible for doctors to use more targeted treatments. This article

gives an overview of the most recent treatments for SMA as well as treatments that are just starting to be used. We also talk about new issues and problems that have come up because there are now drugs that can change the course of diseases. Changes in phenotype, new medical decisions, and SMA exams for newborns are some of these.

Background

SMA is one of the most frequent single-gene neurodegenerative illnesses, affecting between 6,000 and 10,000 newborns at birth. SMA has been split into subgroups based on the age of onset and the motor milestones reached. These subgroups cover a wide range of disease severity. More than half of people with SMA type 1 have the severe form, which starts to show up in the first six months of life. These babies don't reach the free-sitting milestone and look like "floppy babies" who don't move much on their own and breathe strangely. With a life expectancy of fewer than two years without therapy and the assistance of a ventilator, spinal muscular atrophy type 1 is the leading hereditary cause of mortality among toddlers. SMA type 2 is less severe, and symptoms show up between six and 18 months of age. By definition, these patients can sit on their own, but they can't walk on their own. The first is reached (at least temporarily) by people with SMA type 3 who had early warning signs as a child or teen. Also, some classifications say that SMA types 0 and 4 start before birth or have a very severe phenotype and start showing symptoms in adults. Cell death in the spinal column's anterior horn is a hallmark of this illness. This causes progressive weakening in the chest and arms and a loss of muscular mass. Different forms of SMA progress over time at varying speeds. The progression of SMA type 1 is rapid, whereas that of SMA type 3 is gradual.

Proteomic genetics

Nearly all cases of SMA are caused by deletions in both copies of the SMN1 gene on the long arm of chromosome 5, whereas epigenetic alterations account for the remaining 5%. (5q-SMA).Non-5q-SMA refers to the several subtypes of SMA that result from mutations in other genes. Alleles with disease-causing variations in SMN1 are unable to produce functional SMN protein. The variable allele frequency of the nearby SMN2 gene is the main reason why the severity of SMA is so different from person to person. This gene is almost the same as SMN1 except for a few nucleotide bases. In healthy people, it has no effect. Exon 7 is skipped in SMN2 because of a change in one base pair. This makes the protein less reliable (SMN-7).In SMA patient populations, SMN2 can make a lot of full-length, fully functional SMN protein, so higher rates of SMN2 copies are linked to fairly mild phenotypes.

Identified disabilities Diagnosis Cathartic Strategies

SMA is a neuromotor disorder that may manifest in a variety of ways. The general public tends to see it as a disorder affecting the muscles and nerves. As a result, patients with SMA need to have their respiratory, nutritional, gastrointestinal, orthopaedic, and mental health needs addressed by the specialist's team working together in 2007, the first normative statement about SMA care standards came out. Even though a standard of care deployment is very unpredictable and is affected by different points of view, socioeconomic conditions, and the availability of organizational resources, it did have general treatment plans.

An improved form of SMA diagnosis and patient care reviews was only reported due to advancements and changes in medical services over the last century.

Drug Treatment Therapeutic Strategies

Over the last few hundred years, many different substances have been tested in randomized trials, along with ways to improve muscle strength and performance.

1. Hyperacetylating agents, such as valproic acid or phenylbutyrate.
2. Albuterol, thyrotropin-releasing hormones, and growth hormone are all examples of anabolic drugs.
3. Some examples of neuroprotective drugs are gabapentin, riluzol, and olesoxime. Even though the primary endpoints were bad, these studies confirmed the outcome data and gave important information about trial models and how well patients were recruited. Absolute therapeutic advances can be put into three groups: changing the way SMN2 is cloned, replacing the SMN1 allele, or making muscles bigger and stronger.

This diagram outlines the available therapy choices and demonstrates their related molecular bioactivities. The panel shows the latest profile of drug development.

SMN2 splicing configuration

Nusinersen, formerly known as IONIS-SMNRX, was the first medicine ever licensed for the treatment of SMA. It is an antisense oligonucleotide (ASO) that makes it easier for SMN2 transcription factors to add exon 7 to their DNA. Nusinersen inhibits the splicing of the SMN2 gene by binding to a splice-silencing site in intron 7, which stops other splice factors from joining together. This increases the amount of SMN2-mRNA that contains exon 7, which makes the full-length SMN2 protein work better. Nusinersen showed promise in phase I and phase II trials including kids with SMA types 2 and 3. After that, Phase III surveys were started: 121 infants and toddlers less than 7 months old with type 1 spinal muscular atrophy were included in the ENDEAR research. These children were randomly assigned to receive either recurrent intrathecal injections of nusinersen or a "sham" therapy that did not contain any medicines. Especially compared to the fake-control group, those who got nusinersen had a longer time until they died or needed long-term oxygenation. Half of the verum group reached the level of "motor-milestone responder" (as defined by the HINE-2 scale; Hammersmith Infant Neurological Investigation), but no members of the sham group did so. Only a tiny percentage of patients (6/73) were able to sit without assistance throughout the one-year nusinersen therapy phase, even though the verum group's motor development is considerably different from the local history of the illness. 126 older children (average age of 4 years) with SMA type 2 and cognitive impairments beginning at roughly 6 months of age were included in the CHERISH research to evaluate the effects of nusinersen. Again, the motor functions of the nusinersen group got better (mean +4.0 points on the HFMSE scale; Hammersmith Functional Motor Spectrum Enhanced version), while the motor functions of the sham control group started to get worse (-1.9 points on the HFMSE spectrum). After these results were found in a follow-up assessment, both studies were stopped without warning, and all of the participants were put into the intervention group. The NURTURE study looked at the effects of a presymptomatic nusinersen diagnosis in 25 toddlers under 6 weeks old who also had two (n = 15) or three (n = 10) SMN2 duplicates. Both of the 25 patients learned to sit on their own and 22 of the 25 patients learned to walk on their own. Both the FDA and the EMA approved Nusinersen in 2016; the former in December and the latter in May of 2017. An Expanded Access Program was used to treat the first people with SMA type 1 in some countries (EAP). Small molecules like RG7916 (risdiplam) and LMI070 use a strategy to change how SMN2 mixes with itself, which increases the amount of working SMN protein (branaplam). Most of the time, these molecules are taken by mouth. They raise levels of the full-length SMN protein, which may cross the blood-brain barrier. Pyridazine speculative RG7916, which is being studied in many experiments

right now, seems to be the most complicated substance: Twenty-one children aged 1–7 months old with type 1 spinal muscular atrophy were randomly assigned to receive either a low dosage (Part 1, n = 4) to predict safety or a high dose (Part 2, n = 17) to evaluate efficacy in the controlled clinical FIREFISH trial. 33% of all toddlers (n = 7/21) and 41% of newborns administered the larger dosage in Section 2 (n = 7/17) had attained the intended outcome of the individual sitting after a modest healing period of 14.8 quarters. No treatment-related adverse events have been reported. The probe is now in its second phase. Older adults with types 2 and 3 of SMA were administered RG7916 in the SUNFISH research. Part 1 was a dose-finding phase, while Part 2 was a double-blind, placebo-controlled confirmation phase. In the first phase, 58 percent of participants showed at least a three-point increase in motor function, as measured by the Motor Function Measure-32 (MFM32).

in SMA, is a much more advanced way to treat SMA. Scientists inserted a copy of wild-type SMN into mouse mice using an Adeno-Associated Viral serotype 9 (AAV9) vector. They discovered that these extracts can pass the brain-blood barrier and slow the progress of SMA in a mouse model of the disease that was given medication. In the first drug study with zolgensma (AVXS-101), there might be 15 8-month-old babies with SMA type 1 and two babies that look like SMN2s. All of the carers were given a single dose of the chemical agent through an intravenous line, either in a low (n = 3) or high (n = 12) concentration. Two patients had temporary increases in liver enzymes, and all of them were given steroid treatments. In the "elevated" group, scores improved on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, and 11 children achieved scores of 40 or higher, which is not often observed in the natural development of SMA 1. Even at the follow-up session, 9 of the 12 kids with the highest zolgensma scores were able to stay seated for more than 30 seconds without help. One patient in the low-dose sample group needed constant aeration when they were 29 months old. Based on a correlation with a natural

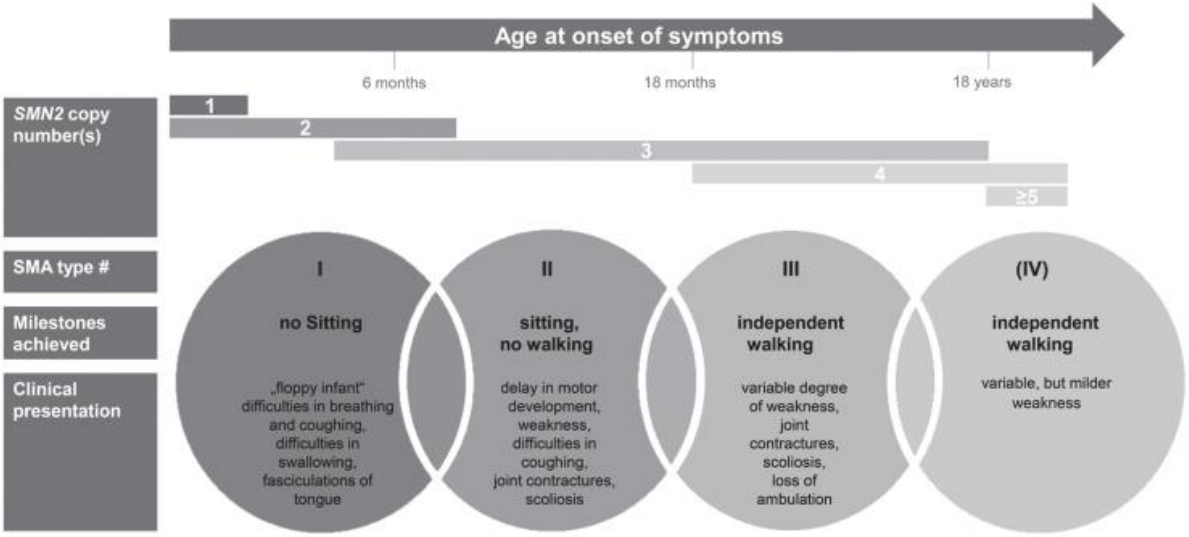

Figure 1: The subgrouping of SMA patients according to age of onset, developmental status, and clinical features

SMN1 genomic supersede

Genetic modification, which specifically targets the faulty and ineffective SMN1-gene

history sample, AVXS101 therapy improved death rates, motor coordination, and developmental milestones. Several new studies are looking into the effectiveness and safety of the treatment. Twenty kids with type 1 spinal muscular atrophy who were less than 6 months old at the time of the transfusion are part of the phase-3 STR1VE research. The main goal of the study is to see if the patients can sit up on their own. Studies in Asia and Europe are currently happening or will happen soon. In the SPR1NT trial, pre-symptomatic treatment for SMA patients of all genotypes will be studied (age 6 weeks). In May 2019, the FDA approved Zolgensma for use by IV in people with SMA who are younger than two. Babies get systemic intravenous therapies, but older people may need intrathecal therapies to get enough nerve cells to grow. There is evidence from animal and swine studies of intrathecal gene therapy that a reduced dosage of viral vectors may increase gene expression. In the STRONG trial, researchers are about to find out what happens when zolgensma is injected into the spinal cord of 6-year-olds with SMA type 2.

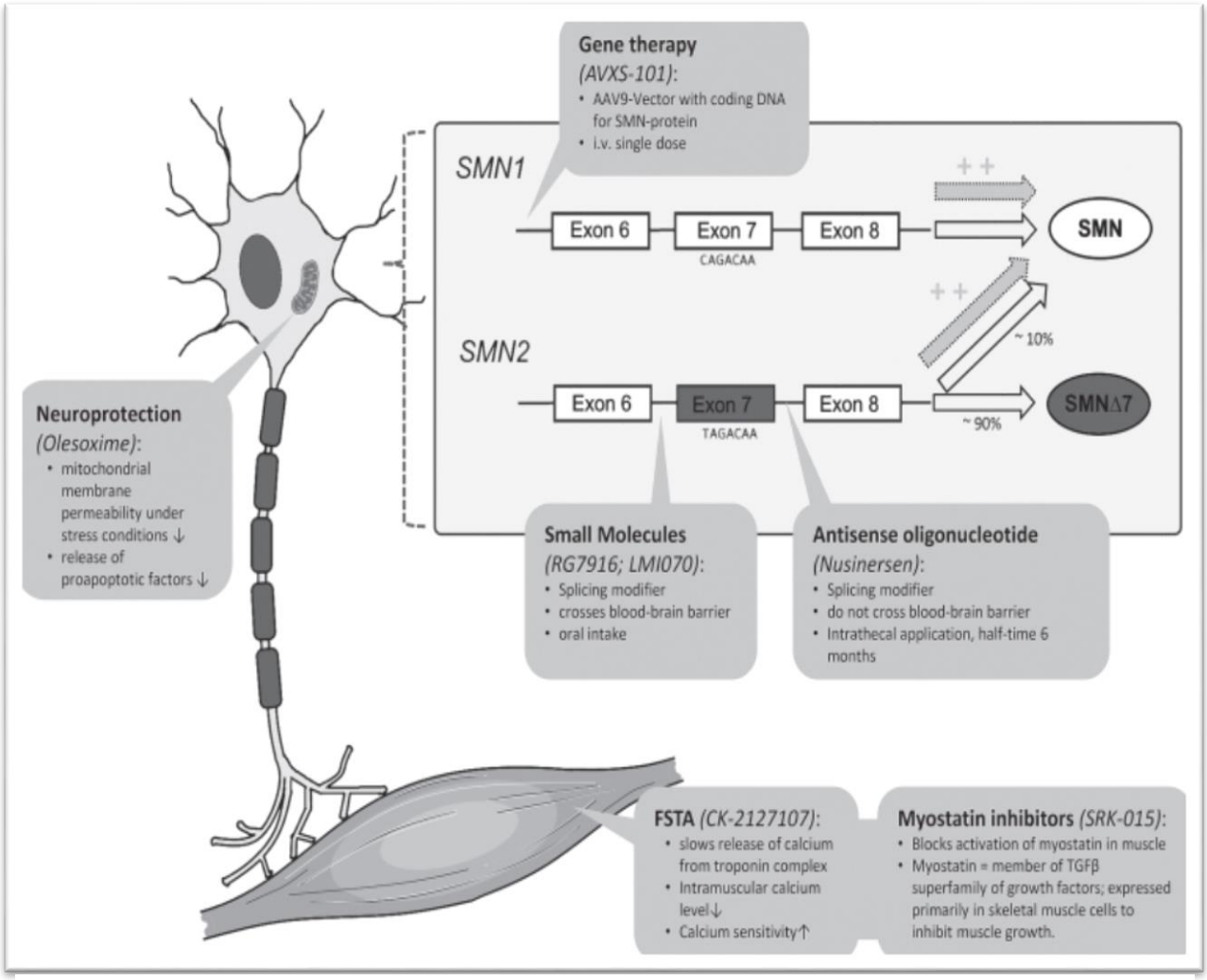

Figure 2: Illustration of how molecular mechanisms of action can be used to treat SMA. FSTA = Fast Troponin Activator

Name of drug	Sponsor	Mechanism of Action	Administration Route	Phases				FDA Approval
"Splicing modification of SMN2: Nusinersen	Biogen-Ionis	Antisense-Oligonucleotide	IT	X	X	X		X
RG7916 (Risdiplam)	Roche	Small molecule/splicing modifier	Po	X	X	(X)		_
LMI070 (Branaplam)	Novartis	Small molecule/splicing modifier	Po	X	X	_		_
Replacement of SMN1-gene AVXS-101 (Zolgensma)	AveXis/Novartis	AAV-9-Vector	IV	X	X	X		X
Upregulation of muscle growth CK-2127107 (Reldesemtiv)	Cytokinetics	FSTA	Po	X	X	_		_
SRK-015	Scholar Rock	Myostatin Inhibitor	IV	X	X	_		_
Neuroprotection Olesoxime	Hoffmann-La Roche	Apoptosis-Inhibition"	Po	X	X	_		_

SMA Biosignature

A lot of other possible biomarkers are being studied and researched along with SMN2 replica countsPatients with type 1 SMA symptoms in the ENDEAR research reported greater concentrations of plasma phosphorylated neurofilament heavy chain (pNF-H) compared to healthy controls. Intriguingly, greater pNF-H levels were associated with earlier symptom onset and lower motor function before starting nusinersen treatment. These levels decreased more rapidly in the nusinersen treatment group compared to the sham group. The greater the decrease, the earlier the therapy was started. Treatment reduced NSE and pTAU protein levels in people with SMA but did not affect the absence of pNF-H in their CSF. Past clinical investigations have made use of electrophysiological markers to count motor units (MUNE) and examine the compound muscle action potential (CMAP). It is likely that sickness, clinical image, and pharmacological treatment efficacy may be predicted if signatures could be validated. Better medical judgment and cost savings in clinical pharmaceutical development would be further benefits.

Newfangled Physical Composition, Newfangled Challenges

Since new drug therapies have been used to treat SMA, researchers have seen that the disease's course is very different from what was thought to be its natural course. Now, these new traits are found in all of the SMA subgroups. People who were diagnosed with SMA type 1 before they were six months old, for example, may be able to sit without help (SMA type 2 by diagnosis) if therapy is started quickly. In place of the old subtypes, it is now more reasonable to use the time of onset number of SMN2 copies, and age at the start of medication therapy to describe a clinical profile of SMA. Because each disease

has its path, we have to change and adapt how we treat it. When talking to the guardians of people with early-onset SMA, they should be told about things like how long a person can live without extra oxygen and how medication therapy can help. Only one end of the spectrum in very severe cases that start fatally (SMA type 0), pharmacological therapy is unlikely to make a big difference in motor function, and it won't stop the need for a ventilator, so it may be a bad idea in general. On the other hand, starting therapy before a child has any symptoms may lead to satisfactory motor performance.SMA has also been linked to problems with other organs, such as heart problems, peripheral neuropathy, and fatty acid metabolism that doesn't work right. Since it is known that the SMN protein is made in large amounts in most tissues before birth, its role in organ development has been looked into. More research needs to be done to find out if systemic therapy for SMN deficiency is better for patients than just treating the central nervous system.

Factual Evidence and Drug Testing

It is probably unavoidable that medication authorization for rare diseases will be based on poorer documentation and medication for common diseases. The number of patients involved, the amount of time they are followed, and the sorts of illnesses being researched in clinical trials all contribute to this issue. Nusinersen, for instance, was licensed for use across all forms and stages of spinal muscular atrophy even though the SMA cohort studied in the two randomized controlled trials consisted mostly of infants and young children with a very early stage of the illness. Multiple hubs reported similar results from their early-access programmes (EAP) with Nusinersen therapy for SMA type 1 patients of different ages: Age at the start of therapy is a much more important factor in figuring out how well motor skills will respond to therapy. Surprisingly, the motor function of people with two or three alleles of SMN2 didn't seem to be any different. In contrast to research on humans, patient populations were different in terms of how dependent they were on ventilation, how much help they needed with their diet, and how old they were. In the Italian cohort, data on people up to the age of 19 were studied. The observations about aeration and nutritional help are much more contradictory than the ones about motor function: In both the German and French samples, a lot of the people who got their motor skills back were on constant ventilation, had a tracheostomy, or had a feeding tube put in. It's not clear if any of this means that the treatment has a poor effect on pulmonary and bulbar performance or if a better plan is to offer respiratory treatment or tube feeding as a participating facility. The 6MWT showed a small improvement in an adult who was being treated with nusinersen. So, there isn't much evidence outside of the sample of people with SMA type 1, so it's hard to say "which effects can be predicted in which subtype and at what stage of the disease" and "how long treatment benefits last." Also, now that there are good treatment options, it is hard, if not impossible, to do new placebo-controlled studies because of serious logistical and ethical issues.

CONCLUSION

The clinical course of SMA may now be drastically altered, for the first time, thanks to novel medicines like splicing modification and pharmacogenomics. Several treatments are now in the advanced stages of clinical research, and it is expected that they will increase the number of options for SMA medication therapy. This will make it harder for people with SMA to get the care they need. To get the best results from therapy, it's important to get a correct diagnosis and start treatment right away. Although routine newborn screening seems to be an effective means of accomplishing this aim, it is unclear

as to when treatment should begin for those with a high number of SMN2 alleles. Not much is known about the efficacy or safety of licensed medications for uncommon illnesses until after they have been used extensively. Randomized trials, which could provide this information, are often not possible. Therefore, the only way to gain additional evidence is to gather and analyze data from the actual world via high-quality, well-monitored patient registries that aim to decrease bias and deliver usable findings. Many patients still have a large global burden of disease despite the success of pharmacological therapy for SMA, so it is crucial that we not forget about individualized multidisciplinary diagnosis and management, which is still the backbone of SMA treatment.

Author's contribution

Mr. K. Durga Prasad, Assistant Professor, Dept. Of Pharmaceutical chemistry, designed reviewed and approved the final version of the manuscript.

Funding

Not applicable

Availability of data

The data and the information used in the current study was available online from different source such as published journals, Google Scholar, and books.

Declaration

Ethical approval and consent to participate

Not applicable.

Conflict of interest

No conflict of interest.

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