Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

journal home page : https://ijpsdronline.com/index.php/journal

Review Article

Spinal Muscular Atrophy: A Systematic Review of Diagnosis, Treatment and Emerging Research

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ARTICLE INFO

Article history:

Received: 26 July, 2024

Revised: 29 August, 2024

Accepted: 02 September, 2024

Published: 30 September, 2024

Keywords:

Nusinersen, Spinal muscular atrophy, Risdiplam and Onasemnogene abeparvovec.

DOI:

10.25004/IJPSDR.2024.160519

ABSTRACT

This systematic review aims at understanding the causes, consequences and therapy of spinal muscular atrophy, which is an inheritable illness that can be fatal at times. Although spinal muscular atrophy is incurable, various drugs have been developed to ameliorate the disease condition and this article aims at understanding the effect of all the available synthetic drugs on spinal muscular atrophy (SMA). A search plan was curated using various databases like PubMed, Google Scholar and Science Direct. Authors selected publications of risdiplam, onasemnogene abeparvovec and nusinersen, and even studies comparing the drugs with one another, including studies related to drugs like hydroxyurea, phenylbutyrate and gabapentin. 40 publications were identified and finalized based on preferences. All the 3 approved drugs improved motor milestones in SMA patients as compared to the natural cohort of the disease. Although gene replacement therapy observed tremendous results, further investigations is needed to be done. Other drugs like hydroxyurea (HU), gabapentin, valproic acid and phenylbutyrate showed significant, little and no effect, respectively. All 3 drugs showed significant outcomes and were safe and effective in the longer duration of use. Hydroxyurea and valproic acid showed slight improvement, whereas gabapentin and phenylbutyrate had no effect.

INTRODUCTION

Spinal muscular atrophies (SMAs) are referred to as class of hereditary disorders described by the degradation of horn cells placed anteriorly and deterioration of alpha-motor nerve cells in spine, causing loss, weakness, and paralysis of the muscle. Although various forms of SMA are present amongst them, childhood SMA (autosomal recessive disorder), accounts for 95% of cases and is the most prevalent type.[1,2] SMA is second to cystic fibrosis in terms of the most prevalent fatal autosomal recessive condition.[3] Although it is the 2nd most fatal disease, it is still the primary genetic factor responsible for infant mortality.[4] The estimated incidence of the disease is one in 6,000 one in 11,000 infants and the frequency of the carrier is around 1 in 40 to 1 in 60.[5,6]

Classification

Clinically the disease is categorized into 5 phenotypes depending on the muscle pattern, age at emergence and inheritance pattern.[7] These clinical phenotypes provide a wide spectrum of disease severity ranging from modest prolonged illness to severe pediatric disease.[8] Type zero is the severest variant of the disease.[9] Type I SMA is the most frequently occurring as well as severe, accountable for almost half the patients.[10] Type II SMA is less severe compared type I.[11] The mildest variant of the disease is the type III.[12] Type IV SMA is a recent addition to the previous one and includes patient above 18 years and mild course.[13] Table 1 represents the classification.

Progression of Disease

Initially occurring respiratory problems like nocturnal

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Table 1: Classification of SMA[1]

Form	*Age of emergence*	*Greatest function*	*Natural death age*
0	Prenatal	Respiratory support	Within one month
I	0–6 months	Can not sit	Less than 2 years
II	Below 18 months	Can not stand	Greater than 2 years
III	Above 1.5 years	Can stand	Adult
IIIa	1.5–3 years	Can stand	Adult
IIIb	Above 3 years	Can stand	Adult
IV	Above 21 years	Can stand	Adult

hypoventilation in SMA eventually develops into daytime hypoventilation. At the juvenile course, deprivation of pulmonary function can still be recouped. Once pulmonary infection occurs, patients are very susceptible to acute respiratory failure (ARF). The more chronic the case, the more probably kids are to accquire numerous respiratory issues, which include sleep apnoea, periodic pneumonia and ARF.[14] In a survey conducted, the subjects were requested to score the intensity of their symptoms through several systems and various other diseases co-existing, such as fatigue and communication problems caused by muscle weakness, which are common in individuals with form I of the disease. The majority of survey respondents classified the following symptoms as the most severe: respiratory failure 25%, contractures 38%, muscle weakness 72%, scoliosis 40%. These findings clearly demonstrate the prevalence of around 75% of adults with type II and type III illness and caregivers in the examined community who are managing the intricate, severe symptoms of SMA.[15]

Mechanism

Despite the vast range of phenotypes, the locus of all variants of SMA is found to be the same, i.e., on chromosome 5q11.2 to q13.3, due to which survival motor neuron (SMN1) gene was revealed to be the cause of illness.[16] Therefore, the homozygous mutation, eradication truncation or, gene conversion or dysfunction of the SMN causes SMA.[17] This depletion of SMN leads to a decreased level of SMN proteins.[18] SMN2 is a highly homologous, inverted duplicate copy of SMN1[19] and the count of SMN2 is found to be inversely associated with the severity of SMA.[20]

Diagnosis

A study suggests that standard genetic testing using molecular genetics is used to diagnose SMA. The high prevalence of SMA in hypotonic and the effectiveness of molecular testing make it worth considering early in the evaluation of any newborn exhibiting weakness or hypotonia. Every potential cause of infantile hypotonic weakness is incorporated within the differential diagnosis of severe types of SMA. Now, with the availability of molecular tests, older examination procedures like muscle biopsy, electrodiagnostic and other diagnostic screening (such as MRIs) are not utilized. Homozygous deletion of SMN1, which is nearly 100% accurate, is utilized to diagnose this disease and the copy of SMN2 influences the severeness of the illness.[21]

One of the current studies demonstrates the viability of neonate screening for SMA. SMA can be specifically diagnosed from using a second-tier droplet digital PCR (ddPCR) assay in conjunction with an RT-PCR genotyping assay. Dried blood spot specimens are devoid of false positives. RT-PCR assays have the advantage of being able to multiplex with the existing severe combined immunodeficiency screening test. Patients with a presymptomatic diagnosis of early-onset SMA can benefit from prompt treatment; nevertheless, genetic counseling and the management of early-onset SMA diagnosis are equally crucial.[22] Table 2 represents type of testing.

Treatment

While the exact biochemical mechanisms underlying SMA remain unclear, the disease's genetic foundation explains phenotypic diversity, which resulted in the invention of various treatment strategies aimed at raising levels of SMN protein.[8] In recent years three therapeutic treatments aimed at modifying the disease have been approved; Nusinersen, administered intrathecally, is an antisense oligonucleotide (Spinraza™) indicated for all disease forms. The United State Food and Drug Administration (US FDA) and the European Union (EU) authorized the medicament in 2016 and 2017, respectively. Onasemnogene abeparvovec-xioi (Zolgensma) administered intravenously is a single-dose gene therapy utilizing adeno associated viral vector to transport SMN to the motor cells, it received approval from US in 2019 and from EU in 2020, and risdiplam (Evrysdi™) which is the first drug administered orally to treat SMA. The US FDA, along with multiple other countries like European Union (EU), Brazil, China and many more, approved the drug in August 2020.[24-28]

Considering substantial experiment research demonstrating notable SMN upregulation, valproic acid,

Table 2: Screening tests utilized in spinal muscular atrophy[23]

Type of screening	*Gene*	*Percentage of SMA linked to pathogenic gene variations*	*Percentage of pathogenic variants detectable by this technique*	
			Sequence analysis	*Gene-targeted deletion/duplication analysis*
Diagnostic, prenatal and carrier	SMN1	~100%	2–5%	95–98%
Prognostic	SMN2	NA	NA	Gene-targeted deletion/duplication

phenylbutyrate, and hydroxyurea were applied in multiple clinical tests involving SMA individuals. As of the present time, a phase III randomized clinical trial is ongoing in India using valproic acid for 60 SMA patients.[29]

Biomarker

Although several approved therapeutic agents are available for treating SMA, biomarkers will aid in identifying potential therapeutic targets. Therefore, set of validated biomarkers will allow a more detailed evaluation of SMA and will also aid in decision-making across various clinical aspects like prognosis, diagnosis, and pharmacotherapy of disease. Numerous biomarkers like circulatory, imaging, electrophysiological and molecular have been suggested, but further studies are required to be carried out.

- Circulatory: Survival motor neuron protein.[30]
- Molecular: Survival motor neuron 2 (SMN2) copy number, spinal muscular atrophy multi-analyte panel (SMA-MAP) protein analytes, creatine kinase (CK) and creatinine (Crn), survival motor neuron mRNA and protein levels, neurofilaments.[31,32]
- Electrophysiological: Electromyography (EMG), measurements of motor unit number estimation (MUNE) and compound muscle action potential (CMAP).[33]

Materials And Methods

Search Strategy

This systematic publication was conducted in consonance with preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.[34,35] The search design has been established depending on population, intervention, comparator, outcome, and study type (PICOS).[36] For the systematic literature review, the search was conducted in the following databases- PubMed, Science Direct, meta-Register of Controlled Trials, Google Scholar, MEDLINE, Scopus, Embase, Virtual Health Library (VHL), Web of Science, the Cochrane Library, Clinicaltrials.gov. Previous publications utilized the following search string or terms to find all related libraries; spinal muscular atrophy (SMA) or 'Dubowitz disease' or 'nusinersen' or 'Werdnig Hoffman disease' or 'spinraza' or 'risdiplam' or combination of SMA along with nusinersen or spinraza or risdiplam.[37,38]

Inclusion criteria

Any publication like a randomized control trial (RCT), cohort study, case series or case-control study was selected if they reported the results of nusinersen administered intrathecally in individuals with biologically confirmed 5q chromosome SMA above the age of 12 years and a minimum of 6 months follow up period. Only those studies that either reported a comparator, provided information on natural history, or compared baseline characteristics with that of post-treatment were included.

Exclusion criteria

Cross-sectional investigations, review articles and case reports have been excluded.[39]

Result

The review of the literature of result is represented in Table 3.

Discussion

Previous studies have compared the approved synthetic drugs with one another but no study comparing all the available synthetic drugs, which include both approved and unapproved drugs, has been carried out. The current publication is the 1st to compare and combine the safety and effectiveness of all the available medicaments. Spinal muscular atrophy is a neuromuscular condition having an approximate occurrence of 1/6,000 to 1/11,000 live birth and the frequency of carrier is 1 in 40 to 1 in 60. Depending on the motor function milestone and age of appearance of symptoms, SMA is categorized into 5 types as presented in Table 1. SMA patients are susceptible to various respiratory complications like acute respiratory failure (ARF). The pathophysiology underlying SMA is deletion, mutation, and truncation of SMN1 leading to depletion of SMN protein. SMA is diagnosed using a second-tier dd-PCR assay in combination with RT-PCR genotyping assay. Currently, the disease is incurable, but several drugs aimed at modifying the disease condition have been developed out of which only 3 have been approved: Onasemnogene abeparvovec, nusinersen and risdiplam. A set of biomarkers are being used to identify potential therapeutic targets for developing new drugs.[1-33]

Nusinersen has been authorized for treating all SMA patient types and the youngest children showed the strongest evidence that nusinersen was effective in treating all three forms of SMA, and there were not many safety concerns with relation to drug administration.[38] Even for elderly patients with longer illness duration, nusinersen overall is safe and encouraging therapy.[39] According to two more systemic reviews on nusinersen, patients with type one exhibit improvements in their motor function and survival; however, these evaluations reach conflicting findings about the benefits for patients with type II and III disease. Some researchers concluded that there is just as slight effect, whereas others concluded that there is moderate-certainty evidence supporting nusinersen's ability to ameliorate motor ability in SMA type II.[40]

The effectiveness of the treatment in type one varied with age, showing significant improvements among children who initiated treatment when they were younger than 7 months old. However, bulbar function and the necessity for continuous or lifelong ventilation was not affected by the treatment. The consensus supports initiating nusinersen

Table 3: Review of literature

Author	*Study outcome*	*Journal*
Albrechtsen *et al*., (2020)	Nusinersen was found to increase the likelihood of survival in type one patients without the need of ventilatory assistance where as in type two and type three patients the improvements were not significant. Nusinersen showed better results in younger patients with brief duration of disease and treated prior to onset of symptoms.[38]	Danish Medical Journal
Gavriilaki *et al*., (2022)	Although the safety and efficacy of the medicament in adults is yet to be confirmed by randomized data due to poor quality of available data, it has been confirmed by this meta-analysis that nusinersen is beneficial in adult patient with longer duration of disease.[39]	Neurotherapeutics
Erdos *et al*., (2022)	The vast amount of missing data and heterogeneity of the research are two obstacles that hamper the comparison. Despite uncertainty in the stability and future therapies, outcomes of pivotal and included evidence have presented a stark contrast to the normal progression of SMA.[40]	European Journal of Pediatric Neurology
Pechmann *et al*., (2020)	Based on various clinical cases of type I SMA, the outcomes of a revised Delphi consensus conducted among pediatric neurologist form Switzerland, Germany, and Austria, regarding prescribing, continuation, or discontinuation of Nusinersen drug in patients.[41]	Journal of Neuromuscular Diseases
Qiao *et al*., (2023)	Based on evidence that is currently present in the study with respect to the medicament treatment, both nusinersen and risdipalm were efficacious while treating individuals with SMA.[42]	Brain Sciences
Wadman *et al*., (2020)	It was reported that muscular function in SMA type II was improved by Nusinersen, whereas gabapentin, phenylbutyrate, valproic acid, creatine, thyrotrophin releasing hormone, fusion of valproic acid with hydroxyurea and carnitine were found to have significantly less impact on motor ability in SMA II and III. Somatotropin and olesoxime reported no effect.[43]	Cochrane Database of Systematic Reviews
Bartels *et al*., (2019)	As the quality of available data is poor, it is unclear as to whether strength when combined with cardio training is useful or detrimental for type III patients in terms of exhaustion, side effects, functional performance, walking distance, muscle strength and cardiopulmonary exercise capacity.[44]	Cochrane Database of Systematic Reviews
Coratti *et al*., (2021)	The study proposes that nusinersen enhances motor functions in wide variety of type two and three patients observed over a period of 10–14 months. A direct contrast between treated and untreated study was not possible as the longitudinal changes seen in test group were dissimilarity from those seen in untreated group. Although the difference can be noted in smaller groups that are subdivided based on age, type of functional status and it can also be seen in worldwide cohort studies.[45]	Orphanet Journal of Rare Diseases
Bertini *et al*., (2017)	Olesoxime was found to be safe for the studied doses throughout the trial. Despite failing to meet primary end point, analysis of secondary end point suggest that this drug might be beneficial in stabilizing the muscular function in type II and III patients. Based on these outcomes olesoxime could be of benefit for the patients and due to its mode of action it can also be combined with various other drugs. However, further evidence is required.[46]	The Lancet Neurology
Darryl *et al*., (2019)	Outcomes of the study highlight the possible advantage of indicating Nusinersen in presymptomatic stage in newborn with SMA. Most of the kids and newborn treated with Nusinersen in the presymptomatic period attained motor improvement parallelly to the natural development. Data presented that Nusinersen was effective for an average of 2.9 years during the check up, with continuous progress and no persistent regression.[47]	Neuromuscular Disorders
Darras *et al*., (2021)	The study resulted that risdiplam elevated the percentage of neonates who achieved the motor milestones and with enhanced motor ability in comparison to the percentage of previous cohorts.[48]	The New England Journal of Medicine
Koterazawa *et al*., (2023)	On combining valproic acid and risdiplam the course of illness progressed steadily in adults. Therefore, a combined therapy with drugs having different mechanism of action may be beneficial for adult patients.[49]	Brain and Development Case Reports
Finkel *et al*., (2017)	Infants who received nusinersen had a better chance of survival along with improved motor function in comparison to the control group. Initiation of nusinersen in presymptomatic period is necessary maximize the efficacy of medicament. [50]	The New England Journal of Medicine
Abbas *et al*., (2022)	Based on the evidence by this review, treatment with nusinersen was productive in treatment in infants and lesser severe adverse events were related.[51]	Medicina (Kaunas)
Ribero *et al*., (2022)	Results of indirect comparison reported that compared to nusinersen, risdiplam is a better replacement for treating type I SMA patients.[36]	Journal of Comparative Effectiveness Research

Mercuri *et al*., (2023)	Following risdiplam medication, SUNFISH Part 1 showed that SMN proteib increased by twofold. The start of the significant Part 2 investigation was justified by the safety profile that was observed. Risdiplam's long-term effectiveness and safety are being evaluated using continual medical care. [52]	European Journal of Neurology
Oskoui *et al*., (2023)	Risdiplam was found to improve the motor ability in a diverse spectrum of patient with later onset of SMA, including children, teenager, and adults. [53]	Journal of Neurology
Baranello *et al*., (2021)	Type I neonates under oral risdiplam therapy successfully elevated the functional SMN protein expression in blood. [54]	The New England Journal of Medicine
Masson *et al*., (2022)	After receiving risdiplam therapy for 24 months, the patient's motor function continued to improve and they attained all the developmental motor highlights. Risdiplam's long-term safety and effectiveness will be further demonstrated by the FIREFISH open-label extension phase. [55]	The Lancelet Neurology
Pascual-Morena *et al*., (2024)	Therapeutically, Risdiplam was proven to be safe and effective for type I, II and III patients. Assessment via CHOP-INTEND reported that risdiplam could either improve or stabilize the motor ability in SMA type I and assessment by MFM32, RULM and HFMSE report that it improves or stabilizes motor ability in type II and III. [56]	Pharmacotherapy
Mendell *et al*., (2021)	The results suggest that a single dose of Onasemnogene administered via intravenously, continues to show manageable and notably safe for a period of 6.2 years following hterapy. Till date no adverse events or side effect have been recorded to this treatment. [57]	JAMA Neurology
McMillan *et al*., (2022)	Onasemnogene was found to be efficacious in clinical trials and thus offers as a potential therapeutic option for treating symptomatic SMA in newborn and also those recognized by screening. Gene treatment is yet in its initial stage and limitation and challenges related with transgene delivery system are yet to overcome. [58]	Expert Opinion on Biological Therapy
Bischof *et al*., (2021)	Regardless of the drawbacks of present analysis, the impact of treatment on motor milestone accomplishment suggests that onasemnogene abeparvovec may continue to benefit during 2 year follow up in contrast to nusinersen. [59]	Current Medical Research and Opinion
Aragon-Gawinska *et al*., (2023)	After evaluating data from 18 different publications, it specifies that the outcome of initial therapy relies on the quantity of duplicate copies of SMN1 and the primary neurological state of the patient. [60]	Genes (Basel)
Baranello *et al*., (2021)	The management of SMA underwent tremendous change after recent availability of disease-modifying therapies – DMTs. It prolonged the lifespan as well as the quality of life of indiviuals. [61]	Clinical Pharmacology and Therapeutics
Hoolachan *et al*., (2024)	The analysis of this study offers a list of possible SMA medication treatments, backs the use of prednisolone's ability as a 2nd generation therapy, and recognizes improvements for the upcoming transcriptomic-based drug positioning trials in SMA. [62]	Human Molecular Genetics
Ribero *et al*., (2023)	This research indicates that people with types 3a and 3b SMA who do not receive treatment may still experience the loss of motor milestones in the late adulthood, and those with types 3a and 3b SMA may eventually have a decline in their ability to walk. These results favors the significance of development of motor ability stabilization even at elderly ages. Since they provide context for evaluating long-term results, data from natural history are essential for assessing SMA therapy. [63]	Neurology
Chand *et al*., (2021)	Based on the study, this article gives details about liver damage, including methods to avoid and identify if it occurs so that the patient can receive appropriate care caused due to onasemnogene abeparvovec triggering an immunological reaction that raises the amount of liver produced enzymes. [64]	Journal of Hepatology
Yang *et al*., (2023)	The results imply that onasemnogene abeparvovec is an effective replacement for patients, despite lack of data and poor quality of evidence to support its safety and efficacy in treating SMA. [65]	Journal of Pediatrics and Child Health
Elshafay *et al*., (2019)	This study suggests that Valproic Acid seems to be a correspondingly safe drug, even though therapy could be accompanied with several adverse events. Advancement in gross motor ability for patients was also assessed. [37]	CNS Drugs
Liang *et al*., (2007)	SMN2 gene expression was amplified by hydroxyurea in SMA cells and demonstrated minimal improvement in endpoints of SMA in patients, thus suggesting hydroxyurea might be safe as therapeutic agent, although further investigation on larger populations is required to draw conclusion about efficacy. [66]	Journal of Neurological Sciences
Mendell *et al*., (2017)	A single administration of adeno-associated viral vector consisting of DNA that codes for SMN has resulted in prolonged chances of survival and a higher attainment of motor milestones and also increased motor ability in SMAI patients than in previous cohort. [67]	The New England Journal of Medicine

Miller *et al*., (2001)	The clinical trial confirms that gabapentin has no therapeutically beneficial effect in treating SMA patients. [68]	Journal of Neurological Sciences
Vill *et al*., (2019)	Neonatal screening was found to improve the outcome in biologically confirmed children as it resulted in presymptomatic treatment. Individuals with four SMN2 copies should instantly undergo treatment. [69]	Journal of Neuromuscular Diseases
Cruz *et al*., (2019)	Following the first SMA treatment's approval, the results offer a rare chance to evaluate and describe baseline risk-tolerance in SMA which help to analyze potential future treatments for SMA. [70]	Clinical Therapeutics
Wadman *et al*., (2019)	The evaluation consisted of one randomized-controlled research that compared the effects of riluzole medication to a placebo for type I. With reference to the initial outcome measure, all 3 kids in the untreated group died whereas 3 out of 7 children treated with riluzole survived. Neither placebo nor riluzole patients advanced the ability to sit, stand or roll and no adverse effects were seen. [71]	Cochrane Database of Systemic Reviews
Ñungo Garzón *et al*., (2023)	Based on the study conducted, non-sitter patients above 16 years may find risdiplam to be safe and potentially helpful. Motor scales are less sensitive to change than functional scales in such patients. [72]	Muscle & Nerve
Wijngaarde *et al*., (2017)	Cardiac problems like defect in septum, disrupted ventricle outflow were commonly seen in severe form of disease. While milder patients recorded problems of cardiac rhythm. [73]	Orphanet Journal of Rare Disease
McMillan *et al*., (2021)	Ontario established a systematic process to enable early diagnosis and treatment. The objective was to offer therapy to those in need and also muscle function and prolong their lifespan.[74]	The Canadian Journal of Neurological sciences
Zanetta *et al*., (2014)	Animal trials and clinical studies both imply that the treatment approach of SMA might change in the future. [75]	Clinical Therapeutics

in children under 24 months who do not require ventilator assistance and have Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) grade higher than 10 based on these findings. Research demonstrated that all type II and type III cohorts of prople who received nusinersen showed better motor ability, in contrast to adverse alterations seen in research presenting untreated cohorts.[41]

Currently, the only way nusinersen is effective is by administrating it through spinal intrathecal injections as it cannot travel across the blood-brain barrier. Nusinersen administered intrathecally was an effective treatment for enhancing motor ability in type II patients.[42, 43] Some studies suggest that nusinersen therapy might positively affect the clinical result beyond what is observed when treatment is initiated after the appearance of symptoms.[47] Early symptom onset and a higher baseline illness burden were observed in infants receiving nusinersen compared to those in the untreated group.[50] According to a randomized controlled study, nusinersen-treated neonates exhibited overall improvements in neuromuscular function and clinically significant motor responses in contrast to the placebo group. Although nusinersen showed encouraging results in terms of efficacy, none of the newborns who received it developed their motor skills normally; some even required artificial respiration and constant feeding, and some even passed away.[51]

A study comparing the effectiveness of risdiplam with other drugs reported that, for treating SMAI, risdiplam stood superior to nusinersen in terms of achievement of motor function and milestones. However, no difference was detected between the 2 drugs in aspects of achieving siting and standing milestones. As far as therapy for type II and III disease is considered, no firm conclusions could be drawn due to less research data availability. Additionally, no concrete conclusion could be drawn with respect to Onasemnogene abeparvovec due to insufficient evidence.[36] Two studies aimed at evaluating the safety profile and effectiveness of risdiplam reported that, risdiplam was effective in type I, II and III and when administered to heterogenous population of disease (ambulatory and non-ambulatory), showed significant effect like stabilization and improvement in motor function along with 57% of patients achieving a CHOP-INTEND grade of 40 or greater points, also, more than 50% of them could feed orally and also control their head after a year of treatment, an event not seen in untreated cohorts. In type two and three patients the drug improved the revised upper limb module (RULM) as well as MFM32 by two points and Hammersmith functional motor scale- expanded (HFMSE) by 3 points, all these were determined in the 12th month and these findings either remained consistent or improved in some cases at month 24. However no change was observed in the percentage-predicted forced vital capacity (FVC). Additionally, the safety profile of drug was identified as consistent in both years. These results indicate that for long-term use, risdiplam proves to be safe and effective.[53,56]

Over time, it has been demonstrated that onasemnogene abeparvovec therapy is more economical with a duration of 56.35 years of quality-adjusted life expectancy, as opposed

to 7.21 years of quality-adjusted life with nusinersen.[26] The natural progression of individuals with SMA is novel in this drug, at the prescribed dose, it sustained a lasting response in patients up to 5 to 6 years following treatment.[57] Moreover, the patients in the studies who received gene therapy showed improvements in their neuromotor function, which may have been a significant predictive factor.[59] Additionally, it was noted that intravenous Onasemnogene abeparvovec used for presymptomatic newborn treatment had a positive safety profile and that there were no new or unanticipated safety issues with treatment delivery between 9 and 43 days of age.[63] Rise in serum aminotransferase concentrations are a common non-cholestatic manifestation of hepatotoxicity correlated with onasemnogene abeparvovec treatment.[64] Whether following short-term or long-term onasemnogene abeparvovec therapy, a study found a remarkable improvement in SMA patient's CHOP-INTEND scores. Among onasemnogene-treated patients, a significant proportion of them reached a minimum of one new motor milestone in contrast to untreated SMA patients. Even while children with SMA reached motor milestones later than those without the condition, progress was observed through the therapy.[65]

Based on the analysis of a meta-analysis and systematic review, patients with SMA displayed statistically remarkable improvements in their gross motor when valproic acid (VPA) therapy was delivered either independently or when fused with carnitine. A study of subgroups of studies where patients received a fusion of VPA and carnitine revealed no remarkable differences.[37] Hydroxyurea (HU) was found to have no significant effect on treating SMA patients, but it did show a slight improvement after 8 weeks of treatment. Thus, further research on the effect of hydroxyurea must be carried in a larger randomized control trial. The study also implies the use of a lower dose of HU as, at high doses 30 and 40 mg/kg/day presented with ADRs like bone marrow depression.[66]

Another prominent treatment approach that showed significant results is gene replacement therapy. This study noticed that treated patients had prolonged survival as compared to the control cohort and all participants exceeded the reported median survival age, which is 10.5 months, without continuous ventilation support. Only 8% of patients survived without the assistance of ventilation for around 20 months and therapy-treated patients also surpassed this benchmark. The majority of the patients also had improved motor milestones.[67]

A clinical trial of gabapentin versus placebo reported that no difference between the placebo and drug-treated group after 1 year was observed, suggesting gabapentin has no clinical benefit in treating SMA patients. This might be due to various reasons like huge variations in the measurements or the possibility that the glutamatergic excitotoxic effect in SMA is less than what was estimated or that gabapentin has a very modest effect on excitotoxic.[68] Due to incredibly delayed enrolment, a multicenter, open-label phase I/II trial in children with type 1 rod disease receiving treatment with different doses of phenylbutyrate has been terminated.[71]

Within the first few weeks of birth, more than 40% of SMA patients diagnosed through the new born screening (NBS) program exhibit definite clinical signs. The outcome of the paper was they expected that children with SMA would survive and reach the motor milestones that were previously unattainable, since NBS is providing early diagnosis and access to extremely effective therapy.[74]

The assessment of an article indicated that over the next several years, a growing number of clinical trial of SMA are anticipated. A characteristic that is unique and should be considered during clinical trials is that patient morphology amongst different SMA types varies greatly. It also stated that trials including innovative molecular treatments might change the SMA care paradigm.[75]

Conclusion

Spinal muscular atrophy, although a rare condition, is a prevalent genetic disorder with a wide phenotype and chromosome 5q11.2 to 5q13.3 as locus of disease. So far, alteration in the SMN1 gene has been discovered as the pathophysiology of the disease. The diagnosis of the disease has undergone several changes with newer techniques being developed and nowadays, instead of having to conduct few tests, only 2 assays, a second-tier ddPCR assay in conjunction with an RT-PCR genotyping assay, need to be carried to diagnose the disease. Despite the mechanism being identified the disease remains untreatable but several drugs have been approved that ameliorate the conditions. Observations showed that patients diagnosed at an early onset prior to presenting with symptoms benefitted from the treatment, and genetic counseling, and that handling early onset SMA diagnosis are equally important. The three approved drugs demonstrated significant results and were safe and effective when used over a longer period. Additionally, SMA patients responded mildly to hydroxyurea and did not respond to phenylbutyrate or gabapentin. SMA, although less prevalent, is a topic of interest due to wide availability of wide phenotypes and less available treatment approaches, leading to an ocean of opportunities to be discovered. Biomarkers aid in identifying newer therapeutic targets, laying the framework for drug development.

Present study discovered that nusinersen is safe and effective for all forms of this disease, although risdiplam is found to be a better substitute for type I, to draw conclusions regarding type II and III, thorough research with quality is required. It was also observed that risdiplam is safe and effective for long term treatment

as well. Although onasemnogene abeparvovec showed a significant effect on the short and long-term, it was also found to be linked with hepatotoxicity as one of the adverse drug reactions. Therefore, a study focused on minimizing the side effects would be beneficiary. Additionally, drugs like hydroxyurea that show minimal effect require randomized, well-designed controlled trials with longer follow-up periods and more inclusive research criteria in the future.

Acknowledgment

The authors acknowledge the support of Mr. Babiker Bashir Haroun Baraka (Assistant Professor), Department of Pharmacology at KLE College of Pharmacy in Bangalore, India.

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HOW TO CITE THIS ARTICLE: Baraka BBH, Porwal M, Kannur S, Pandey A, Khan A. Spinal Muscular Atrophy: A Systematic Review of Diagnosis, Treatment and Emerging Research. Int. J. Pharm. Sci. Drug Res. 2024;16(5):912-921. **DOI:** 10.25004/IJPSDR.2024.160519