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MINIREVIEWS

Nusinersen, an exon 7 inclusion drug for spinal muscular atrophy: A minireview

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Abstract

Spinal muscular atrophy is an autosomal recessive neuromuscular disease with incidence of 1 in 5000 to 10000 live births and is produced by homozygous deletion of exons 7 and 8 in the *SMN1* gene. The *SMN1* and *SMN2* genes encode the survival motor neuron protein, a crucial protein for the preservation of motor neurons. Use of the newer drug, Nusinersen, from early infancy has shown improvement in clinical outcomes of spinal muscular atrophy patients.

Key Words: CHERISH; Nusinersen; Spinal muscular atrophy; Survival motor neuron; NURTURE

Core Tip: Spinal muscular atrophy is an autosomal recessive neuromuscular disease, with incidence of 1 in 5000 to 1 in 10000 live births. This review provides an elaborative knowledge regarding the current most effective drug for spinal muscular atrophy, Nusinersen. A brief discussion on other treatment modalities that are under trials is also provided.

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INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease, with incidence of 1 in 5000 to 1 in 10000 live births[1,2]. It is caused by homozygous

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deletion of exons 7 and 8 in the *SMN1* gene[1,2]. It is a rare genetic disease that occurs due to degeneration of motor neurons in the spinal cord and brainstem[3]. Clinical manifestations can appear prior to birth to early adulthood and usually manifests with symmetrical, proximal muscle weakness, which is progressive and associated with muscle atrophy. SMA patients have difficulties like inadequate weight gain, restrictive lung disease, scoliosis, joint contractures, and sleep problems but do not have cognitive issues. SMA causes mutation in chromosome 5q11.2-q13.3, affecting the survival motor neuron (*SMN*) gene, which results in lack of *SMN1* exon 7. For the preservation of motor neurons, SMN protein is crucial, which is encoded by *SMN1* and *SMN2*. A homozygous deletion of *SMN1* exon 7 is diagnostic confirmation for SMA. A typical patient with SMA can have variable copies of *SMN2* but have zero copies of *SMN1*[3-6]. The severest is type 0 and has a antenatal onset, whereas the commonest type of SMA is type1[4]. SMA type 2 presents around 6 mo to 18 mo, type 3 after 18 mo, and type 4 beyond 5 years[7]. The introduction of Nusinersen, from early infancy, has shown improvement in clinical outcomes of SMA type 1 patients. Open label phase two and phase three trials have demonstrated effective improvement of life expectancy in most of the patients[8].

STRUCTURE AND MECHANISM OF ACTION

Research have shown an intronic splicing silencer N1 (ISS-N1) sequence in intron 7 of *SMN2*, which has shown involvement in messenger RNA (mRNA) exon 7 skipping. Improvement in SMN2-mRNA exon 7 inclusion has been revealed by inhibiting ISS-N1 by antisense oligonucleotides (ASOs), and thus showing clinical improvement in SMA[9]. Nusinersen is a modified 2′-O-methoxyethyl phosphorothioate ASO. After binding to *SMN2*, it alters splicing of *SMN2* pre-mRNA, which leads to rise in exon 7 incorporation into *SMN2* mRNA. This results in an augmented manufacture of standard length SMN protein, which is obligatory for the preservation of motor neurons, but is lacking in SMA patients[10,11].

PHARMADYNAMICS AND PHARMACOKINETICS

Nusinersen is unable to cross the blood-brain barrier, when given through intravenous or subcutaneous routes. It is administered intrathecally as it unambiguously targets the central nervous system[10-12]. 3′ and 5′ exonuclease-mediated hydrolysis is the process of metabolism, and it is eliminated by the kidney[10,11]. The mean plasma and central nervous system terminal elimination half-lives are 63-87 d and 35-177 d[10,11]. The plasma and the cerebrospinal fluid volume of distributions are 29 L and 0.4 L[10, 11]. Body weight is the only variable that affects Nusinersen pharmacokinetics. There is no dose-related toxicity established in studies so a fixed dose is recommended[10, 11].

USES

In an open label phase 2 study, 20 patients with ages ranging from 3 wk to 7 mo, with infantile-onset SMA symptoms and having SMN1 homozygous gene deletion or mutation, were given several intrathecal doses of Nusinersen (6 mg and 12 mg dose). In the 12 mg dose group, there was improvement in achieving motor milestones ($P < 0.0001$), enhancements in CHOP-INTEND[13] motor function scores ($P = 0.0013$) (a dependable score for motor skills in SMA), and amplified compound muscle action potential amplitude of the ulnar nerve ($P = 0.0103$) and peroneal nerve ($P < 0.0001$)[8]. None of the patients required prolonged pulmonary support nor were any deaths reported[8]. In NURTURE study, all 25 participants achieved the ability to sit without support, 23/25 (92%) achieved walking with assistance, and 22/25 (88%) achieved walking independently[14]. Another larger "ENDEAR" randomized controlled trial comprising of 122 , ≤ 7 mo genetically proven SMA patients also revealed improvement in motor milestones, assessed by section 2 of the Hammersmith Infant Neurological Examination (HINE-2), after 13 mo of trial[15,16]. In the interim analysis, the group of patients who received Nusinersen had significant enhancement in motor-milestone response [21 of 51 infants (41%) as compared to the control group 0 of 27 (0%), *P* value of < 0.001]. In the treatment group, 22% achieved full head control, 10%

were able to roll over, 8% were able to sit independently, and 1% were able to stand; in the control group, no infants achieved these milestones. The study also concluded that the group of patients treated with Nusinersen had substantial development in motor-milestone response [37 of 73 infants (51%) as compared to control group 0 of 37 (0%)]. In comparison to the control group the patients treated with Nusinersen had a higher likelihood of event-free survival with hazard ratio (HR) for death or the use of permanent assisted ventilation of 0.53 and $P = 0.005$. The Nusinersen group had a greater likelihood of overall survival (HR for death, 0.37; $P = 0.004$)[15].

CHERISH study, a phase 3 randomized controlled trial, reported an accelerated progress in the motor milestone achievements at 13 mo, in the treatment group of 126 of 179 screened children of age 2 years to 12 years, having a genetic diagnosis of SMA [17]. In another phase 1b/2a study with SMA children of 2-15 years of age, who received ascending multiple doses (3, 6, 9, 12 mg) of Nusinersen, the Hammersmith-Functional-Motor-Scale–Expanded, Upper-Limb-Module, 6-Minute-Walk-Test (6MWT), compound muscle action potential, and quantitative multipoint incremental motor unit number estimation and safety were used to assess enrolled patients. Eleven children of type II SMA and 17 of type III SMA were enrolled. Mean Hammersmith-Functional-Motor-Scale–Expanded scores, Upper-Limb-Module scores, and 6MWT distances improved by the day 1150 visit[18].

A cohort study of 33 children with SMA1, 8.3 mo to 113.1 mo of age, were treated with Nusinersen. Evaluation was done before starting of treatment (M0), after 2 mo (M2), and 6 mo (M6) of starting treatment. Data of survival, respiratory, nutrition, and motor function assessment with the modified HINE-2 were recorded. Six months after the treatment, median development on the modified HINE-2 score was 1.5 points ($P < 0.001$), and there was a significant increase in the requirement of respiratory support [19]. No serious or life threatening adverse events (AE) were noted in any trials.

Patients with SMA usually present with respiratory morbidities like hypoventilation, aspirations, repeated lung infections due to stiffened rib cage, micro-collapse of the lungs, which occurs as a result of decreased chest wall movement, and increasing thoracic scoliosis[20]. Polysomnograms have proven early type 1 respiratory failure even in stable SMA patients. Nusinersen therapy might have improvement in functioning of peripheral muscles along with improvement of respiratory muscle and diaphragmatic functions, leading to improved co-ordination of oral secretions, decrease lung aspiration, and decreased airway disease and pneumonia.

DOSE AND ADMINISTRATION

On December 23, 2016, Nusinersen was given approval as a treatment for SMA by the Food and Drug Administration (FDA). Nusinersen 6 mg dose equivalent to be diluted to a concentration 1.2 mg/mL or 12 mg dose equivalent diluted to 2.4 mg/mL with artificial cerebrospinal fluid and administered intrathecally every 14 d for three doses, followed by a fourth dose after 30 d. The FDA recommends to administer maintenance doses once every 4 mo to maintain the tissue concentration. This drug has also been approved by European Medicines Agency[21], Australia[22], New Zealand[23], and Canada[24].

Initial therapy

Individuals who meet all of the following criteria: (1) Documentation of a confirmed diagnosis of SMA by genetic testing; (2) Documentation of ≥ 2 copies of the *SMN2* gene by genetic testing; and (3) Onset of SMA-associated symptoms before 20 mo of age.

Continuation therapy

After 6 mo of starting of therapy, continue Nusinersen therapy every 6 mo in patients meeting both criteria (1) and (2): (1) Initial therapy was determined to meet the above criteria; and (2) There is substantial improvement in SMA-associated symptoms during the previous treatment period. Clinical efficacy of Nusinersen has to be evaluated every 6 mo in the treated individual.

AE

As per ENDEAR study, severe AE in Nusinersen in 56% compared to 80% in controls

and serious AE were 76% in Nusinersen compared to 95% in control group. Even serious AEs with fatal outcome was 39% in controls compared to only 16% in Nusinersen. Pyrexia, constipation, upper-respiratory infection, pneumonia, or respiratory distress or failure was seen in ≥ 20% in Nusinersen group[15]. Almost similar results were seen in CHERISH study[17].

DILEMAS OF NUSINERSEN

Efficacy of Nusinersen in treating type 0 SMA patients

Till date there are no studies on patients who are symptomatic patients since birth or within 7 d of life being treated with the drug. Neither are there any studies on patients with one copy of *SMN2* gene being given Nusinersen therapy. Further studies are essential to demonstrate the effectiveness of this drug in these patients.

Factors affecting the response of the drug

In the CHERISH study[17], the response of Nusinersen treatment varied in SMA cases. Amongst the factors identified were the time interval when the type 1 SMA patients became symptomatic and administration of first dose of drug and the age of type 2 SMA patients. There was an extensive difference in the treatment response amongst the patients, which was not explained by these factors[15].

Type 1 SMA respiratory outcomes

None of the trials reported on swallowing evolution and even the respiratory outcomes were considered as the usage of long-lasting ventilation or not and the number of hours spent ventilated. In order to have an improved evaluation of load for families involved in the treatment of a type 1 SMA child, a better documentation of time spent in the hospital is required.

No reporting of the long-term consequences of patients who received therapy before they became symptomatic

Reports from the NURTURE study[8] have shown that children who were treated before manifesting symptoms, with three copies of SMN2, have a far improved result than when they are treated after they become symptomatic[25]. The ENDEAR study and CHERISH Nusinersen trial[15,17] have not reported on the long-term outcomes, for example the number of patients attaining major milestones of walking, standing, or sitting, whether they will be free of ventilation, and the number of patients that will have severe motor disability. Even their intellectual development assessments were not reported.

Nusinersen in type 3 and type 4 SMA

Insufficient data are available in type 3 SMA patients treated with Nusinersen, and there are no reports on type 4 SMA. A study by Montes *et al*[25] revealed an unremitting result on the 6MWT in type 3 patients, with a median surge of 98 m in a 1050-d period.

Nusinersen a very costly drug

According to a study the estimated price of care of a type 1 SMA patient who is not on Nusinersen therapy was roughly €100000 per year, and type 2 was nearly €90000 per year[26]. The cost of Nusinersen is nearly €100000 per injection and a full course of six injections are required in the initial year, and three during the subsequent year[27]. This drug has the probability to improve the existence of type 1 SMA patients from 10% to 60%[8,15] and also enhance their functional level; the higher cost is an important factor in deciding the treatment. So, identifying good responders of treatment early by various outcome measures and optimizing the treatment for presymptomatic patients through newborn screening could decrease the cost burden. So the most important challenge is Nusinersen's remarkably expensive cost[28,29].

OTHER THERAPIES

Other disease modifying therapies like *SMN1* gene replacement therapy, AVXS-101 (zolgensma) in trials, when delivered intravenously to SMA type I infants had

promising outcomes in *in vivo* studies[30-32]. Although these studies have shown improved life expectancy, motor milestones, and motor functions, the number of patients were less and additional studies are essential to prove the effectiveness. Adeno-associated virus 9 vector was most efficiently able to cross the blood brain barrier, and was able to infect almost 60% of motor neurons and enhance SMN expression[28,29]. Studies have not clearly shown long term benefits with combined treatment of Zolgensma and Nusinersen[33,34].

Some other SMN2 exon 7 inclusion drug like risdiplam (RG7916), having central and peripheral tissues distributions, have proven to be a beneficial[35,36] and has been investigated by FIREFISH and SUNFISH trials[37,38]. Branaplam (LMI070) is another such drug that interacts with U1 small nuclear ribonucleoprotein and facilitates exon 7 inclusion of SMN2 transcripts and increases SMN protein levels with initial results of ongoing trials showing improvement[39,40]. Small molecular drugs like Celecoxib, a cyclooxygenase 2 inhibitor, have revealed an increase SMN in animal models[41], and an ongoing trial is recruiting patients[42]. Quinazoline (repligen or RG3039), which blocks a decapping scavenger enzyme (DcpS) and demonstrated upsurge in FL-SMN2 transcript by enhancing SMN2 promoter activity in animal studies[43,44], did not show significant results in phase trial[45,46].

Aminoglycoside antibiotics (tobramycin, geneticin, and amikacin) act as SMN protein stabilizers by masking premature stop codon mutations and increasing read-through of exon 8 and thus increasing the SMN protein[47,48] and have only shown *in vivo* efficacy[49]. In mouse models, BBrm^2 (FDA-approved azithromycin) has revealed an upsurge in SMN and enhancement in motor function[49,50]. Similar results were shown in mouse models with Bortezomib, an ubiquitin proteasome inhibitor that inhibits SMN protein degeneration[51].

A proper SMA treatment includes both SMN-dependent and SMN-independent approaches, which will provide the central and peripheral therapies[33,52].

Neuroprotective agents like olesoxime, which has neuroprotective properties in pre-clinical studies, had suggested improvement in the function and survival of neurons [53]. Subsequently, however, they did not show significant results[52,54]. Studies with riluzole and gabapentin, did not show encouraging results[42,55-57].

As muscle weakness is eminent in SMA, SMN-independent therapies lately focus on muscle. Myostatin, a growth factor, inhibits muscle growth and by stalling its signaling pathway, muscle mass can be enhanced[58]. Follistatin[59], adeno-associated virus-mediated soluble inhibitor of activin receptor type IIB (ActRIIB)[60], in SMA mouse models and BIIB 110 (ALG 801) are undergoing a phase 1a trial[61]. In SMA mouse models[62] and phase 2 trials[63], SRK-015, a human monoclonal antibody, has shown improvement in muscle mass.

Initial trials with reldesemtiv, a skeletal muscle troponin activator, has revealed improvement in muscle function[46,64-66]. Trials are ongoing with drugs acting on neuromuscular junction, like pyridostigmine (mestinon)[67,68] and 4-aminopyridine (4-AP or ampyra)[69,70].

Studies have demonstrated that stem cell therapy in SMA provide support to degenerating motor neurons and short of functional cell replacement[71-73].

CONCLUSION

Although many therapies are under trial and some have shown some clinically beneficial results, the level of evidence is very low. Nusinersen, however, has a moderate level of evidence and has been approved by the FDA. Nusinersen can be used in diagnosed type 1, 2, and 3 SMA patients. The earlier Nusinersen is started, the better is the improvement of muscle strength and better will be the improved quality and span of life. Currently this drug is available and approved by FDA, but cost will be a limiting factor.

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