

HAVING A GO AT SPINAL MUSCULAR ATROPHY WITH SPINRAZA

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ABSTRACT

Spinal muscular atrophy (SMA), a neurological condition which is genetically mediated is the second most common infantile disease causing morbidity and mortality next to cystic fibrosis. It is of five different types with each type having different severity outcomes. For almost three decades, only supportive measures were advocated in the treatment of SMA. Recently, Biogen's Spinraza came out as the first disease modifying therapy to treat infantile as well as adult SMA. This review throws light on the pharmacological aspects of the drug; its approval by Food and Drug Administration and various completed clinical trials as well ongoing clinical trials.

Keywords: Spinraza, Spinal muscular atrophy, Antisense oligonucleotide, Adverse effects, Ender trial.

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INTRODUCTION

Spinal muscular atrophy (SMA), a rare autosomal recessive disorder, causes debilitating infantile illness ultimately making it the leading genetic cause of infantile death. It is very rare with an incidence of 1 in 100000. SMA 1 gene is associated with the pathogenesis of the disease, and this discovery had opened the gates for experimentation of new drugs. Recently, in December 2016, Food and Drug Administration (FDA) approved Spinraza (Nusinersin) for the treatment of both adult and Paediatric SMA.

SMA

The first description of SMA dates back to 19th century, described by Werding and Hoffman, when they illustrated cases of motor nerve paralysis along with muscle atrophy. Later autopsy revealed severe loss of neurons in anterior horn of spinal cord along with atrophic changes in the ventral root of the spinal cord, so-called pathological hallmarks of SMA [1].

SMA is genetic disorder usually associated with deletions of SMA protein in 5q chromosome, so-called 5q SMA or proximal SMA. It accounts for 95% of present cases reported leaving behind other mutations causing SMA with heterogeneous presentations. SMN is the second most common genetic disorder of infancy next only to cystic fibrosis with selective damage to spinal neurons causing various degrees of muscle wasting mainly starting with lower limbs and also associated with other systemic manifestations. Clinical manifestations include breathing difficulties, constipation, weight loss, Gastroesophageal dysfunction, cardiac abnormalities due to autonomic instability, congenital heart defects, muscle wasting, loss of deep tendon reflexes and also bulbar and brainstem involvement. SMA is divided into five types and characteristics are summarized in Table 1. This can be because of SMN gene mutation with deletions in exon 7 or 8. Sometimes, it is due to homozygous type having deletion of both SMN 1 Gene and having two copies of SMN 2 gene. It can be heterozygous type with One SMN 1 gene and having mutations in other copy of SMN 1 gene. For many years, there was no proper disease modifying therapy to treat SMA. Only supportive measures were used such as respiratory support, nutritional support, physical exercises, and end of life care. Various therapies including gene therapy, antisense oligonucleotides, small molecules therapy have been tried [1].

Of this Spinraza, the antisense oligonucleotide was successful and was approved by FDA on 23.12.2016 and has also been given an orphan

drug status. The drug was given priority review and fast-track approval status and also FDA gave rare pediatric drug review voucher to BIOGEN company which they could use for any other product review in future. Spinraza is said to be the eight drug to receive rare pediatric review voucher from FDA [2].

SPINRAZA

It contains Nusinersin, an antisense oligonucleotide modified with phosphate linkages and hydroxyl groups of ribofuranosyl rings being replaced with phosphorothioate linkage and methoxyethyl groups, respectively. SpinRaza, with a structural formula $R = OCH_2CH_2OCH_3$, is a sterile, colorless solution supplied in single glass vial for intrathecal use without addition of any preservatives. The molecular formula is $C_{234}H_{323}N_{61}O_{128}P_{17}S_{17}Na_{17}$ with a molecular weight of 7501.0 daltons. 1 ml of Spinraza contains 0.22 mg of potassium chloride, 0.21 mg of calcium chloride, 0.16 mg of magnesium chloride, 8.22 mg of sodium chloride, 0.10 mg of sodium phosphate, and 0.05 mg of sodium phosphate monobasic dihydrate. It as a PH OF 7.2 [3].

MECHANISM OF ACTION

It is known with evidence that deficiency of SMN protein is mainly via mutations in chromosome 5q. It is shown that SPINRAZA increases inclusion of exon 7 in SMN2 messenger ribonucleic acid transcripts. Henceforth, it results in production of full-length SMN protein [3].

PHARMACOKINETICS

It is distributed from the CSF to target central nervous system tissues when given intrathecally. Trough plasma levels were low when compared to trough CSF levels. Median T max ranges from 1.7 to 6.0 hrs. It is also distributed to liver, kidney, and skeletal muscles. It is metabolized by exonucleases mediated hydrolysis. It is neither an inhibitor nor an inducer of CYP450 enzymes. Mean elimination half-lives of Spinraza in CSF and plasma are found to be 135-177 days and 63-87 days, respectively. The primary mode of elimination is via the kidneys with only 0.5% of administered dose excreted in urine [3,4].

DOSAGE AND ADMINISTRATION

Recommended dosage is 12 mg (5 ml) per administration. Treatment is initiated with 4 loading dose with first three loading doses administered at intervals of 14 days followed by 4th dose 30 days after the 3rd dose. Maintenance dose is usually once in 4 months. Usually, it is kept at 25°C at the time of administration and followed by refrigeration when not

Table 1: Types and characteristics of SMA

Types of SMA	Onset	Life expectancy	Clinical manifestations
Type 0	In utero, very severe	1 week after birth	Failure to swallow and breathe, facial diplegia and joint contractures
Type 1 (Werdnig-Hoffman disease)	4-5 months, 50% patients	2 years of life	Floppy infant syndrome along with usual clinical manifestations of SMA
Type 2 (Dubowitz disease)	7-18 months	2-40 years	Delay of gross motor skills
Type 3 (Kugelberg-Welander disease)	18 months - 3 years	Life expectancy-general population	Muscle hypotonia and wasting
Type 4	Late onset, 3 rd decade	Life expectancy not shortened	Flaccid hypotonia, fasciculation's, muscular atrophy and decreased deep-tendon reflexes, the disease course is stable and mild

SMA: Spinal muscular atrophy

used. Discoloration of vial and particulate matter prohibits the use of the drug. Spinraza should be administered within 4 hrs once taken out of the vial. Proper sedation and ultrasound imaging techniques are used to administer drug intrathecally. Before administering the drug, 5 ml of cerebrospinal fluid should be removed, and drug is administered over 2-3 minutes as intrathecal bolus dose using spinal needle. Avoid inflammatory or infectious skin sites [3].

WARNING AND PRECAUTIONS

In a clinical study, 11% of 56 patients developed fall in platelet counts below the lower limit of normal compared to none in sham control. No patient had sustained platelet count drop despite continued drug exposure. Hence, because of thrombocytopenia there is a risk of bleeding, so proper monitoring of coagulation profile and platelet counts before and after Spinraza is essential.

In a clinical study among patient treated for 7 months, elevation in urine protein was found among 33% treated with SpinRaza compared to 20% of sham control. In those treated for 34 months 69% had elevated protein. No elevated of blood urea nitrogen, creatine was noted. Hence, since Spinraza causes elevation of protein, spot urine protein testing is of prudent importance so as to prevent the patient from acute renal toxicity [3].

ADVERSE EFFECTS

Many adverse effects caused by Spinraza are included in (Table 2) Respiratory complications include pneumonia, bronchiolitis, syncytial viral bronchiolitis, pharyngitis, rhinitis, tracheitis, and nasopharyngitis. Skin rashes were also noted in few patients, spontaneously resolved. Other common adverse effects noted were headache, back pain, postlumbar puncture syndrome [5]. Immunogenicity of Spinraza reveals production of anti-Spinraza antibodies in few patients, but data are insufficient to evaluate the effect of antibodies on clinical response [3].

SPINRAZA IN SPECIFIC POPULATION

1. No teratogenicity was observed in animal studies.
2. In animal models, no embryonal damage or organogenesis was affected.
3. In juvenile animal toxicity data in monkeys reveals Spinraza causes neuronal vacuolation at hippocampus and transient defects in lower spinal reflexes at high doses. Furthermore, learning and memory deficits were observed.
4. SMA is disease of adult and children, so no geriatric exposure to this drug [3].

CLINICAL TRIALS IN INFANTILE- ONSET SMA

ENDEAR, a multicenter randomized double-blind study with 121 infants <7 months was started, and an interim analysis was done [6]. Scoring was done with Hammersmith Infant Neurologic Exam and the Children's Hospital of Philadelphia infant test of neuromuscular disorders [7]. A minimum score of 2 and maximum

Table 2: In controlled study in infants with SMA

Adverse effects	Spinraza 12 MG (infants with SMA) (%)	Control patients (%)
Respiratory infections-lower	43	29
Respiratory infections-upper	39	34
Constipation	30	22
Aspiration	5	2
Scoliosis	5	2
Ear infections	5	2
Congestion of URT	6	2
Teething	14	7

SMA: Spinal muscular atrophy

Table 3: Chop-intend results

End point	Spinraza treated (%)	Sham control (%)
Motor milestone	40 (improved)	0
Chop-intend improvement from baseline	63	3
Chop-intend worsening	4	40

of 26 was given and those who have scores >2 were categorized as treatment responders. Responder also needs to fulfill the criteria of improvement in motor milestones. Results of interim analysis are shown in Table 3. These were supported by open-label trials in infants aged from 30 to 15 years in symptomatic SMA and from 8 to 42 days in case of asymptomatic SMA at the time of the first dose. The patients could achieve milestones, some maintained motor milestones at ages and some survived to ages. The overall findings of the controlled trial in infantile-onset SMA and the open-label uncontrolled trials support the effectiveness of SpinRaza across the range of SMA patients and appear to support the early initiation of treatment with SpinRaza.

SUMMARY OF CLINICAL TRIALS FOR SPINRAZA [1]

- CHERISH (NCT02292537)
Phase 3 - randomized, sham-controlled trial in children with SMA. Positive Interim Results were obtained. The study is closed.

Supporting open-label studies

- SHINE (NCT02594124)
Phase 3 - open-label extension for participants in ENDEAR and CHERISH studies. On-going and recruiting participants.
- EMBRACE (NCT02462759)
Phase 2 - open-label, multi-dose trial in infants and children who did not qualify for ENDEAR or CHERISH. On-going.
- NURTURE (NCT02386553)
Phase 2 - open-label study in genetically diagnosed pre-symptomatic infants with SMA on-going.

- CS3A (NCT01839656)
Phase 2 - open-label, multi-dose trial in infants with SMA to assess tolerability and pharmacokinetics. Completed
- CS12 (NCT02052791)
Phase 2 - open-label safety and tolerability study in patients with SMA who previously participated in the CS2 or CS10 studies. Completed
- CS10 (NCT01780246)
Phase 1 - open-label safety and tolerability study in patients with SMA who previously participated in the CS1 study. Completed
- CS2 (NCT01703988)
Phase 1 - open-label safety, tolerability and dose-range finding study of multiple doses in patient with SMA. Completed
- CS1 (NCT01494701)
Phase 1 - open-label safety, tolerability, and dose-range finding study in patients with SMA. Completed

CONCLUSION

Spinraza being a blockbuster drug in the treatment of SMA and with pride that it is the only drug approved for adult as well as Paediatric SMA makes it very unique. More clinical trials are needed to prove the safety and efficacy of this drug and also to look for long- term outcomes in the treatment of SMA.

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