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, Endear 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 100,000. 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 phosphorothiate linkage and methoxyethyl groups, respectively. Spinraza, with a structural formula $R = \text{OCH}_2\text{O}_{\text{P}}\text{P}_{\text{S}}\text{NA}_4$, 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 dihydate. 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 Tₘax 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
Onset
29
In utero, very severe
2-40 years
1 week after birth
Spinraza 12 MG
Failure to swallow and breathe, facial diplegia and joint
deficits were observed.

Type 1 (Werdnig-Hoffman disease) 4-5 months, 50% patients 3 years
Type 2 (Dubowitz disease) 7-18 months 18 months - 3 years
Type 3 (Kugellberg-Welander disease) Late onset, 3rd decade
Type 4 Life expectancy not shortened

SMA: Spinal muscular atrophy

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, 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 1: Types and characteristics of SMA

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

Table 2: In controlled study in infants with SMA

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

Table 3: Chop-intend results

<table>
<thead>
<tr>
<th>End point</th>
<th>Spinraza treated (%)</th>
<th>Sham control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor milestone</td>
<td>40 (improved)</td>
<td>0</td>
</tr>
<tr>
<td>Chop-intend improvement from baseline</td>
<td>63</td>
<td>3</td>
</tr>
<tr>
<td>Chop-intend worsening</td>
<td>4</td>
<td>40</td>
</tr>
</tbody>
</table>

SUMMARY OF CLINICAL TRIALS FOR SPINRAZA [1]

- CHERISH (NCT02929537)
  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.

- PURURE (NCT02386553)
  Phase 2 - open-label study in genetically diagnosed pre-symptomatic infants with SMA on-going.
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.

REFERENCES