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RISDIPLAM: AN ORAL THERAPY FOR SPINAL MUSCULAR ATROPHY

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ABSTRACT

Spinal muscular atrophy (SMA), is a rare and devastating genetic disease affecting muscle strength and movement. SMA is caused by a mutation of the survival motor neuron 1 (SMN1) gene, which leads to a deficiency of functional SMN protein. Till now, SMA has been curable only with the two most expensive and imported drugs- Nusinersen and Onasemnogene abeparvovec have led to improvements in survival and motor function, they are administered either intrathecally or intravenously respectively. Evrysdi (Risdiplam) is the first and only oral therapy approved by the Food and Drug Administration for treating SMA patients across all types. Risdiplam administration requires no hospitalisation, no anaesthesia, no specialised care centre, no complex administration and no steroids. Hence it became the first "at-home" therapy for SMA patients. Being a daily oral therapy, the significance of risdiplam is three-fold. First, the drug is widely distributed throughout the body. Second, as an oral treatment, it is sustainable in that patients can take it for the rest of their life. Third, it can be administered at home rather than a hospital.

KEYWORDS: Spinal muscular atrophy, survival motor neuron 1, SMN protein, Nusinersen, Onasemnogene abeparvovec, Risdiplam.

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by the progressive loss of nerve cells called motor neurons in the spinal cord leading to muscle weakness. It is the most lethal genetic cause of mortality in infants and young children, with an incidence of 1 in 11,000 live births.[1]

SMA can be categorised into five subtypes according to age at disease onset and the maximum motor milestones achieved. SMA type 0 is very rare and very severe. Symptoms begin in utero (prior to birth). At birth, these infants typically have joint contractures, respiratory distress, severe weakness and cardiac defects. They require respiratory and feeding support. These infants may survive a few months. SMA type 1 (SMA1) also called Werdnig-Hoffmann disease, is the most common (60%) and severe form. Usually diagnosed during an infant's first 6 months. Symptoms include hypotonia, difficulty breathing or feeding, muscle weakness and trouble swallowing. These patients never sit or walk and have a life expectancy of <2 years without intervention. The primary cause of death is pulmonary compromise, because of respiratory muscle weakness leading to severe restrictive lung disease and progressive respiratory failure. SMA type 2 (SMA2) also called Dubowitz disease, symptoms usually begin later but before age 18 months. These children can sit but do not walk independently and survive into early adulthood. SMA type 3 (SMA3) also called Kugelberg-Welander disease) is manifested after 18 months of age. Children with SMA type 3 have comparatively mild symptoms. They stand independently and may walk, although they may lose this ability in their teens or later, and they survive well into adulthood. SMA type 4 (SMA4) is the mildest form of the disease. Symptoms begin in adulthood and progress very slowly. These patients stand, may walk, and usually have normal lifespans.[2]

SMA: GENETICS

The primary cause of SMA is the homozygous deletion or mutation of the Survival Motor Neuron 1 (SMN1) gene on chromosome 5q (locus 5q13) resulting in insufficient levels of functional SMN protein. SMN1 gene encodes SMN protein. Survival motor neuron protein (SMN), a multifunctional protein found in cytoplasm of all animal cells required for normal development and functional homeostasis in all species, expressed in both neuronal and non-neuronal cells. SMN protein may have a role in many cells and tissues, such as skeletal muscle, heart, bone, and autonomic and nervous systems and deficiencies may contribute to the disease state.[3]

A nearly identical copy of SMN1 gene is universally present in humans, called SMN2 gene (often referred to as a "backup" gene for SMN1). It also can produce SMN protein; but in much lower levels, because of a C to T transition in the coding exon 7 that causes alternative splicing and skipping of exon 7, resulting in a truncated protein lacking exon 7 (SMND7) that is not fully functional and degrades rapidly. However, SMN2 produces low levels (5%–10%) of the full-length SMN protein that are sufficient for survival but result in SMA. The severity of SMA disease inversely correlates with the SMN2 copy number. Low levels of SMN protein result in the degeneration of spinal motor neurons and cause muscle weakness that is followed by symmetric limb paralysis, respiratory failure, and death.[4] Healthy individuals retain copies of both SMN1 and SMN2 genes while SMA patients have a loss of SMN1 gene due to mutations and/or deletions.

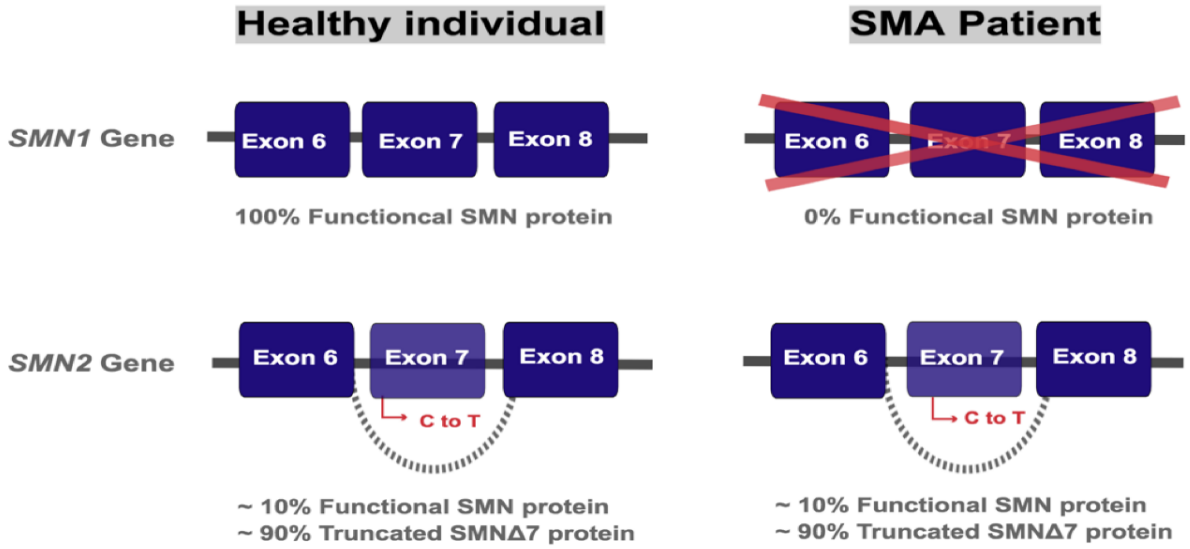

Fig 1: Genetics of spinal muscular atrophy (SMA).

SMA: THERAPEUTIC APPROACHES

SMN1 loss affects all tissues including skeletal muscle, central, peripheral and autonomic nervous system, heart, liver, lungs, kidneys, pancreas, spleen, ovary, and testis. Hence, an ideal therapy for SMA must "target/remedy" the body-wide defects caused by the loss of SMN1. Due to wide differences in the age of SMA onset and the diversity of SMA phenotypes, developing an ideal therapy for the disease remains a challenging task.[5] Actual therapeutic developments can be categorised into therapies aiming to modify the splicing of SMN2, replacing the SMN1 gene, or up regulating muscle growth.

(A) Splicing modification of SMN2

The first drug approved for the treatment of SMA is an antisense oligonucleotide (ASO), Nusinersen (former IONIS-SMNRX), that enhances the inclusion of exon 7 in mRNA transcripts of SMN2. Nusinersen acts by binding to an intronic splice-silencing-site in intron 7 of SMN2 and thereby suppresses the binding of other splice-factors. This results in an increased proportion of SMN2-mRNA with included exon 7 and consecutively more functional full-length SMN2 protein. A single dose of Spinraza injection (Nusinersen) costs Rs 87 lakh. Seven doses are given in the first year of the treatment, followed by three doses every year for the rest of the patient's life.

(B) Replacement of SMN1-gene

Gene therapy of SMA is the most advanced medical approach that directly targets the dysfunctional SMN1-gene in SMA. Onasemnogene abeparvovec (Zolgensma) is used for the treatment of children with SMA who are less than two years of age. It employs an Adeno-Associated Viral serotype 9 (AAV9) vector to deliver a fully functional copy of human SMN gene into target motor neuron cells. Zolgensma, a one-time therapy that is administered to patients less than two-year-old, costs about Rs 16 crore in India. The first clinical trial with Zolgensma (AVXS-101) included 15 infants with SMA type 1 with 2 SMN2 copies (<8 months of age). All patients received a single intravenous dose of the compound in either low (n = 3) or high dose (n = 12). During the follow-up period, 9 of the 12 children receiving high-dose Zolgensma were able to sit without support for >30 seconds. One patient in the low-dose cohort needed permanent ventilation at age 29 months.[6]

DISCOVERY OF RISDIPLAM

A joint endeavour by PTC-Roche (PTC Therapeutics, South Plainfield, New Jersey and Hoffmann-La Roche, Basel, Switzerland) to identify an orally deliverable molecule for the treatment of SMA began about a decade ago. Investigators at these companies screened a library of small molecules and reported three orally deliverable compounds, namely SMN-C1 (Isocoumarin), SMN-C2 (Coumarin), and SMN-C3 (Pyrido-pyrimidinone derivative). Each promoted exon 7 inclusion from SMN2

minigene expressed in human embryonic kidney (HEK) 293 cell line. These compounds also promoted exon 7 inclusion in mRNAs generated from the endogenous SMN2 and increased SMN levels in SMA patient fibroblasts and patient derived induced pluripotent stem cells (iPSCs).

With the realization that the compounds present in the existing library have a high potential for direct clinical applications, PTC-Roche began the process of designing improved versions of their active small molecules. As a result, three novel Pyrido-pyrimidinone derivatives were created, namely, compounds 3, 4, and 5. All displayed negative genotoxicity in the universally used Ames assay and showed very high therapeutic efficacy in the SMAΔ7 mouse model. Compound 3, also known as RG7800, was selected for the subsequent human clinical trial that began in 2014. In parallel to the human clinical trial, RG7800 was also evaluated in cynomolgus monkeys for chronic toxicity. Due to non-reversible adverse effects on monkey retina, RG7800 clinical trial was put on hold. Uncertain about the success of RG7800, PTC-Roche chose another small molecule, Risdiplam (also known as RG7916), an improved version of RG7800, for clinical trials. Risdiplam selection was based on its superior in vivo efficacy in the SMAΔ7 mouse model as well as its reduced off-target effects tested in SMA patient fibroblasts as compared to RG7800.[5]

RISDIPLAM: CLINICAL TRIALS AND FDA APPROVAL

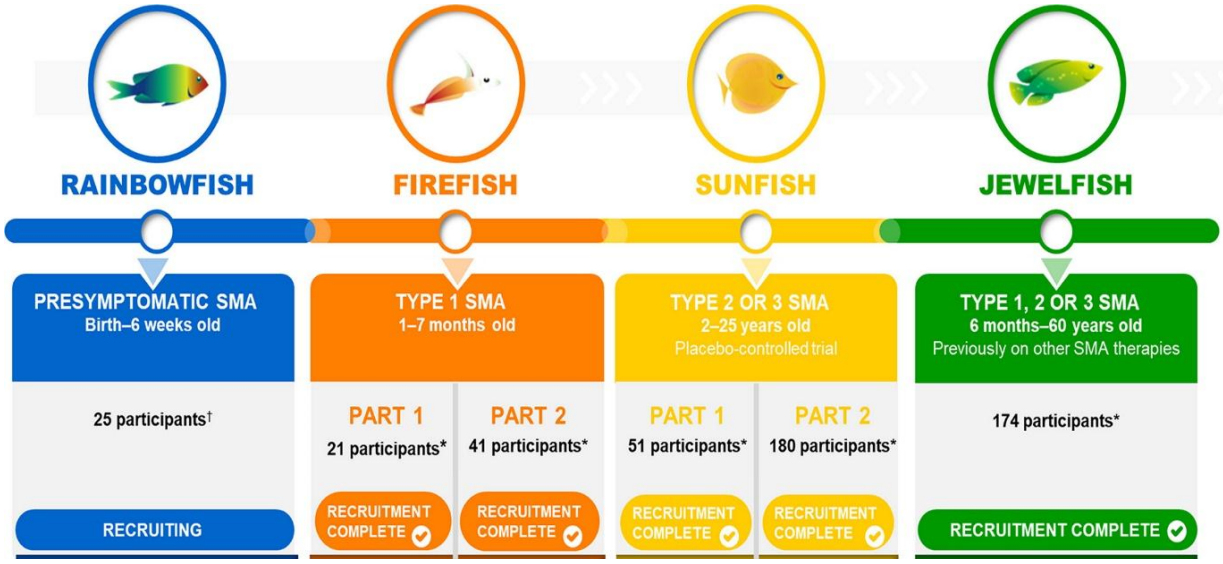

Fig. 2: Risdiplam clinical development program overview.

Several clinical trials of Risdiplam have been performed to evaluate the safety, tolerability, and efficacy of the drug in both healthy and SMA patients. Two of these clinical trials, first in the infantile-onset (NCT02913482) and second in the later onset SMA patients (NCT02908685) were significant for the approval of Risdiplam.

Firefish: is an open-label, multi-centre, pivotal, and two-part clinical study to investigate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of Risdiplam in infants (aged 1-7 months at enrolment) with type 1 SMA. In total 21 patients were enrolled in part one and 41 patients in part two. Patients were administered with the recommended Evrysdi (Risdiplam) dose of 0.2 mg/kg a day. In FIREFISH part one study, the efficacy was established based on the ability to sit without support for at least five seconds and survival without permanent ventilation. After 12 months of treatment, 41% of patients were able to sit independently for more than five seconds, a meaningful difference from the natural progression of the disease because almost all untreated infants with infantile-onset SMA cannot sit independently. After 23 or more months of treatment, 81% of patients were alive without permanent ventilation, which is a noticeable improvement from typical disease progression without treatment.

Sunfish: is a two-part, multicentre, randomized and placebo-controlled, double blind study to investigate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of Risdiplam in patients (aged from 2 to 25 years) with type 2 and type 3 SMA. In total 51 patients were enrolled in part one and 180 patients in part two. The primary endpoint was the mean change from baseline in the motor function measure (MFM-32) total score after 12 months of treatment with Evrysdi when compared to placebo. At month 12, patients on Evrysdi saw an average 1.36 increase in their MFM-32 score, compared to a 0.19 decrease in placebo patients (inactive treatment).

In addition to FIREFISH and SUNFISH, Evrysdi is being evaluated in a broad range of people with SMA, including in.

Jewelfish: an open-label, non-comparative study designed to assess the safety, tolerability,

pharmacokinetics (PK) and pharmacodynamics (PD) of Risdiplam in patients with SMA aged 6 months to 60 years who received other investigational or approved SMA therapies for at least 90 days prior to receiving Evrysdi. Recruitment for this study is complete with 174 people enrolled.

Rainbowfish: an open-label, single-arm, multicenter study investigating the efficacy, safety, pharmacokinetics and pharmacodynamics of Risdiplam in infants (~n=25), from birth to six weeks of age (at first dose) with genetically diagnosed SMA who are not yet presenting with symptoms. The study is currently recruiting.

The new drug application (NDA) for Evrysdi (Risdiplam) was submitted to the US Food and Drug Administration (FDA) in September 2019 and accepted for priority review in November 2019. The FDA approved Evrysdi (Risdiplam) for the treatment of SMA in adults and children aged two months and older on August 7, 2020. The drug received fast track designation and priority review from the FDA, as well as orphan drug designation.[7, 8]

RISDIPLAM: MECHANISM OF ACTION

Risdiplam is a centrally and peripherally distributed, oral SMN2 pre-mRNA splicing modifier. Risdiplam directly targets the underlying SMA pathophysiology by promoting the inclusion of exon 7 into SMN2 pre-mRNA, to generate full-length SMN2 mRNA. This molecule increases the production of functional SMN protein in the central nervous system and throughout the body.[8]

RISDIPLAM: ADMINISTRATION AND DOSAGE

Risdiplam is administered orally at home daily (it is supplied as a powder, which is constituted into a liquid solution and taken once daily by mouth or feeding tube if required). One bottle costs about Rs 6 lakh, with a dosage of 0.75 mg/ml powder for oral solution. For an infant weighing 5kg, one bottle will last for 60 days. The infant will need 6 bottles a year. For a patient weighing more than 20 kg, a bottle lasts only for 12 days and he/she requires 31 bottles a year.[9]

RISDIPLAM: SIDE EFFECTS

In clinical trials of Risdiplam, the most common side effects were fever, rash, ulcers of the mouth area, joint pain (arthralgia), diarrhoea, and urinary tract infections. The infantile onset population receiving Risdiplam had additional side effects including upper respiratory tract infection, pneumonia, vomiting, and constipation.[5]

CONCLUSION

The approval of risdiplam, an orally deliverable small molecule, expands the spectrum of drug treatment options for SMA. The non-invasive mode of administration coupled with body-wide distribution provide risdiplam with additional advantages over other approved therapies. It's a promising medicine for treating patients with SMA in all ages and types. Risdiplam, with its highly efficacious clinical profile, comparatively low cost and oral administration advantage, will offer meaningful benefits for many living with this rare neurological disease. More novel therapeutics should have to be developed in order to address many of the current challenges within the SMA patients.

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REFERENCES

1. Hasane Ratni, Martin Ebeling, John Baird, Stefanie Bendels. Discovery of Risdiplam, a Selective Survival of Motor Neuron-2 (SMN2) Gene Splicing Modifier for the Treatment of Spinal Muscular Atrophy (SMA). Journal of Medicinal Chemistry, 2018; 61: 6501−6517.
2. Vamshi K. Rao, Daniel Kapp, Mary Schroth. Gene Therapy for Spinal Muscular Atrophy:An Emerging Treatment Option for a Devastating Disease. Journal of Managed Care & Specialty Pharmacy, 2018; 24(12): 1-16.
3. Agnès Poirier, Marla Weetall, Katja Heinig, Franz Bucheli. Risdiplam distributes and increases SMN protein in both the central nervous system and peripheral organs. Wiley online library, 2018; 1-12.
4. Saif Ahmad, Kanchan Bhatia, Annapoorna Kannan, Laxman Gangwani. Molecular Mechanisms of Neurodegeneration in Spinal Muscular Atrophy. Journal of Experimental Neuroscience, 2016; 10: 39–49.
5. Ravindra N Singh, Eric W Ottesen, Natalia N Singh. The First Orally Deliverable Small Molecule for the Treatment of Spinal Muscular Atrophy. Neuroscience Insights, 2020; 15: 1–11.
6. David C. Schorlinga, Astrid Pechmanna, Janbernd Kirschnera. Advances in Treatment of Spinal Muscular Atrophy – New Phenotypes, New Challenges, New Implications for Care. Journal of Neuromuscular Diseases, 2020; 7: 1–13.
7. O'Keefe, Lindsey (7 August 2020). "FDA Approves Oral Treatment for Spinal Muscular Atrophy" (Press release). Silver Spring, Maryland, United States of America: United States Food and Drug Administration (FDA). FDA Newsroom Department. Archived from the original on 11 August 2020. Retrieved 7 August 2020.
8. Robert C. Sergott, Giulia M. Amorelli, Giovanni Baranello, Emmanuel Barreau. Risdiplam treatment has not led to retinal toxicity in patients with spinal muscular atrophy. Annals of Clinical and Translational Neurology, 2021; 8(1): 54–65.
9. PB Jayakumar. Roche's oral therapy 'Evrysdi' to provide cost-effective alternative against fatal

genetic disorder SMA in India. 29/07/2021. Available from: https://WWW.businesstoday.in.
10. Fig. 1. Available from: https://www.mdpi.com/2076-3425/11/2/131/html.
11. Fig. 2. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/acn3.51239.