Risdiplam In the Treatment of Type I Spinal Muscular Atrophy – A Review

A Mohamed Ashik [1]

[1]*Department of Pharmacy, B.S. Abdur Rahman Crescent Institute of Science and Technology, Chennai, India.*

Corresponding Author: Mohamedashikaf@Gmail.Com

Abstract: - The term "Spinal Muscular Atrophy (SMA)" refers to a group of genetic disorders, characterized by degeneration of alpha motor neurons in the spinal cord, resulting in progressive proximal muscle weakness and paralysis. It was results from a homozygous deletion or mutation in the survival of motor neuron (SMN1) gene and leads to muscle wasting, hypotonia and impaired mobility. A number of therapeutical strategies for SMA have been investigated in recent years, primarily focused on increasing the production of SMN, which can be achieved by modifying splicing of SMN2 or by replacement of the defective SMN1 gene via viral vector. Risdiplam (RG7916, RO7034067) is systemically distributed small molecule, designed as SMN2-directed RNA splicing modifier which promotes the expression of full-length SMN2 mRNA by the precise inclusion of exon 7 and enhances functional SMN protein levels. This article summarizes pharmacokinetics, pharmacodynamics, clinical trials and adverse events of risdiplam in the treatment of type 1 Spinal Muscular Atrophy (SMA – 1).

Key Words: —*Spinal Muscular Atrophy (SMA), Risdiplam, RNA splice modifier, FIREFISH trial, SUNFISH trial.*

I. INTRODUCTION

Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disease, characterized by homozygous deletions or loss-of-function mutations in the survival of motor neuron 1 gene (SMN1), which cause insufficient levels of ubiquitously expressed SMN protein. This deficiency leads to muscle wasting and weakness, hypotonia and impaired mobility (De Sanctis et al., 2016; Kolb & Kissel, 2015). Paralogous to SMN1, the variable copy number of the SMN2 gene is the most important determinant of SMA severity. SMN2 is found on chromosome 5q, like SMN1, but varies by a single nucleotide (a change of C to T in exon 7) (Sivaramakrishnan et al., 2017). This nucleotide changes do not alter an amino acid but cause modification of splicing and leading to ~90% of transcripts from SMN2 to lack exon7 and production of a truncated and unstable protein known as SMNΔ7.

Manuscript revised March 31, 2022; accepted April 02, 2022. Date of publication April 03, 2022.

This paper available online at www.ijprse.com

ISSN (Online): 2582-7898; SJIF: 5.59

SMA manifests in various degrees of severity, which have been categorized into five types (ranging from 0 to 4) on the basis of the age of symptom onset and maximum motor milestone attained. Type 1 SMA is the most common and severe form, accounts for ~50–60% of incident condition and associated with onset after birth but before age 6 months. Additional subtypes of IA, IB, and IC have been proposed based on age of onset, with IA being the earliest and most severe subtype overlapping with type 0. Patients with SMA-1 (also known as Werdnig–Hoffman disease) may appear entirely normal prior to represent profound weakness within the first 6 months of life. Typical clinical features of SMA-1: Infants exhibit symmetrical flaccid paralysis, inability to raise their limbs against gravity, reduced or absent tendon reflexes and have no head control, though facial muscles are relieved.

With relative sparing of the diaphragm, the weakness in intercostal muscles combines to produce a bell-shaped chest and results in paradoxical breathing. Aspiration pneumonia is an important cause of mortality for patients with SMA (D'Amico et al., 2011). Bulbar motor neurons functions are affected, leads to difficulty in swallowing and feeding, with risk of failure to thrive (Kolb & Kissel, 2015).

A number of therapeutical strategies for SMA have been investigated in recent years, primarily focused on increasing the production of SMN, which can be achieved by modifying

splicing of SMN2 or by replacement of the defective SMN1 gene via viral vector.

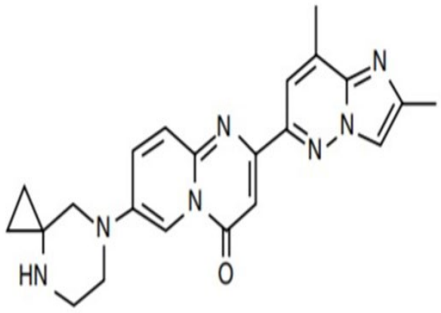

Fig.1. Chemical structure of Risdiplam

Other approaches, such as stabilizing SMN protein, increasing levels of SMN transcripts, cell therapy and neuroprotection, have produced favorable clinical responses in vitro and in transgenic mouse models of SMA but in clinical trials, most of the investigational agents have not shown significant therapeutical activity till date. Risdiplam (RG7916, RO7034067) is systemically distributed small molecule, designed as SMN2-directed RNA splicing modifier and administered orally in liquid form (Figure 1). The drug promotes the expression of full-length SMN2 mRNA by the precise inclusion of exon 7 and enhances functional SMN protein levels. Oral Evrysdi™ (risdiplam) being developed by Roche, PTC Therapeutics Inc and the SMA Foundation, received its approval from US-FDA for the treatment of patients with spinal muscular atrophy who are 2 months of age or older, on 7 August 2020. It is the first approved oral therapy for the treatment of SMA (Dhillon, 2020). The efficacy and safety of risdiplam was confirmed in people living with SMA based on a comprehensive clinical trial which will be discussed in more detail further.

II. Pharmacology of Risdiplam

2.1 Pharmacodynamics

Risdiplam is a highly potent Survival of Motor Neuron 2 (SMN 2) splicing modifier, targets the genetic cause of SMA, which increase the specific inclusion of exon 7 during SMN2 pre-mRNA splicing and promotes the production of full-length SMN protein expression in both CNS and periphery to compensate for the loss of SMN1 function in SMA patients (Campagne et al., 2019).

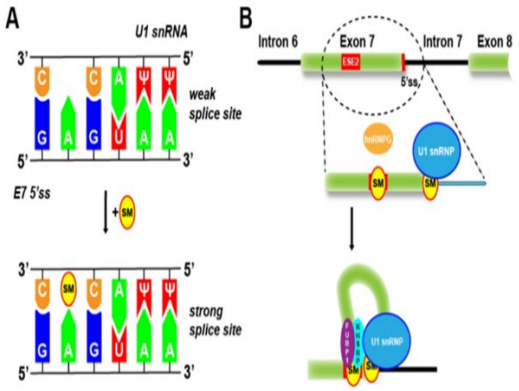

Fig.2. Note. (A) Schematic model of the 5′ss (splice site) mismatch repair concept of risdiplam-like compounds. (B) Model of the published molecular interactions of risdiplam-like SMN2 splicing modifiers. Binding of the small molecule compound to two sites within SMN2 exon 7, namely, ESE2 and 5′ss, facilitates splicing promotion and exon 7 inclusion in the mature transcript. Binding to the 5′ss favors U1 snRNA binding, and interaction with the exon 7 ESE2 is believed to result in hnRNP G dislocation to allow binding of the U1 snRNP complex. The combination of both binding processes provides high selectivity for the SMN2 pre-mRNAs. Adapted from Ratni, H., Scalco, R. S., & Stephan, A. H. (2021). Risdiplam, the First Approved Small Molecule Splicing Modifier Drug as a Blueprint for Future Transformative Medicines. ACS medicinal chemistry letters, 12(6), 874–877.

The hybridized U1 small nuclear ribonucleic protein (U1 snRNP) with the highly conserved 5′ splice site (5′ss), located at the exon-intron border, is essential for splicing to occur. For the efficient splicing of many transcripts, considerable pre-mRNA's 5′ss consensus sequences are tolerated and utilized in the genome, lead to weakening of the binding to the U1 snRNP and results in splice skipping. Such mismatch-related splice-skipping event contribute for the exclusion of exon 7 of SMN 2 genome. Risdiplam-like compounds precisely stabilize the transient ds-RNA structure formed by the U1 snRNP and the 5′ss of SMN2 exon 7 (Figure 2). In vitro and in vivo studies report that this drug may also cause alternative splicing of other genes, which include FOXM1 and MADD. Cell cycle regulation and apoptosis are intended to be affected as consequences of alternative splicing of FOXM1 and MADD. In animal studies, such events may contribute to adverse effects (AEs) (Campagne et al., 2019; Sturm et al., 2019). According to pooled data and non-integrated datasets from multiple trials, risdiplam did not induce torsade de pointes or QT prolongation in patients with SMA (Dhillon, 2020).

2.2 Pharmacokinetics

The pharmacokinetic profile of risdiplam oral formulation (Evrysdi™) was evaluated in healthy adults and in patients with SMA. In a single-ascending-dose study, risdiplam was well tolerated and exhibited linear pharmacokinetics, over a dose range of 6.0 – 18.0 mg in healthy adult subjects and over a range between 0.02 – 0.25 mg/kg once daily dosing, was found efficient in patient with SMA in a multiple-ascending-dose study. The time to reach peak plasma concentration (tmax)was 1–4 hours. Risdiplam was administered with a morning meal or after breastfeeding in the two pivotal phase 2/3 trials (FIREFISH and SUNFISH) and the drug exposures reach steady state 7 to 14 days post oral once daily administration. The drug significantly bound to plasma protein-serum albumin without any binding to alpha-1 acid glycoprotein; it has a free fraction of 11%. At steady state, the apparent volume of distribution of risdiplam was 6.3 L/kg. It is predominantly metabolized by flavin monooxygenase 1 and 3 (FMO1 and FMO3), and by CYP1A1, CYP3A7, CYP3A4, and CYP2J2.After administration of risdiplam 18 mg, ≈ 53% of the dose was excreted in the faeces (14% as unchanged drug) and 28% of the dose was excreted in the urine (8% as unchanged drug). For a 14.9 kg patient, the apparent clearance of risdiplam was 2.1 L/h and the terminal elimination half-life was ≈ 50 h in healthy adults (Dhillon, 2020; Sturm et al., 2019). Age and body weight are primary factors, which can significantly affect the pharmacokinetics of risdiplam, and dosage recommendations in pediatric patients. Risdiplam may affect the drugs which are eliminated via MATE1 or MATE2-K transporters, and may increase plasma concentrations of such drugs (e.g., metformin) (Dhillon, 2020).

2.3. Therapeutic Trials

According to results from the ongoing, open label, multi-centre, pivotal phase 2/3 FIREFISH trial (NCT02913482), which is an operationally seamless study of risdiplam in infants aged 1–7 months with Type 1 SMA, it was found that treatment with risdiplam resulted in clinically efficient benefits to the untreated infantile onset SMA. In Part 1 of trial, the total number of 21 patients (n=21) were enrolled in one of two dosage cohorts, with a median age of 6.7 months (range:3.3 to 6.9 months). This study assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of different risdiplam doses. Adjusted dose of 0.2 mg/kg/day was subjected to administer for patients in a highest-dosage cohort (n=17) before 12 months of treatment, while low-dosage cohort patients (n=4) did not. Part 2 (n = 41) of the study confirmed the efficacy and safety of risdiplam at the dose selected in part 1. Patients were enrolled with median age of symptoms onset was 2 months and the median period between onset of clinical signs and the first dose was 4 months, in a part 1 of trail. 71% of patients were female, 81% were Caucasian and 19% were Asian, respectively (Dhillon, 2020).

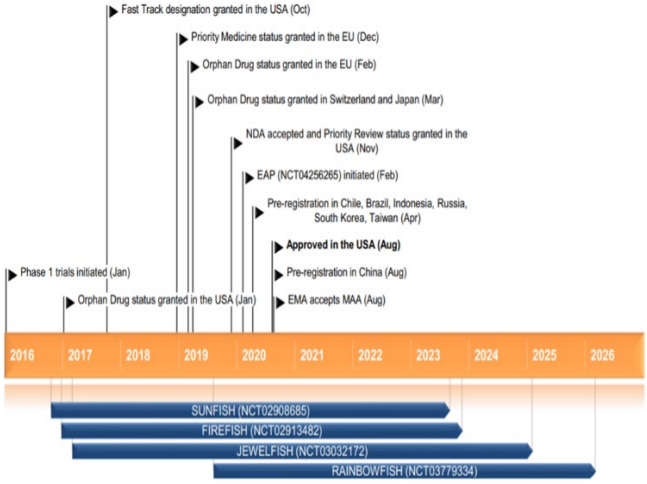

Fig.3. Key milestones in the development of risdiplam for the treatment of spinal muscular atrophy. EAP expanded access program, EMA European Medicines Agency, MAA marketing authorisation application, NDA new drug application. Adapted from Dhillon, S (2020). Risdiplam: First Approval. Drugs **80,** 1853.

After 12 months of treatment with the approved dosage of Evrysdi 0.2 mg/kg/day, 41%of the patients (7/17) were able to sit independently for ≥5 seconds which was assessed by Item 22 of the Bayley Scales of Infant and Toddler Development – 3rd Edition (BSID-III) gross motor scale (Dhillon, 2020; Sturm et al., 2019).

Fig.3. describes the key milestones in the development of risdiplam for the treatment of SMA. After 12 months' treatment with risdiplam, it was found that clinically meaningful improvement in patients with infantile-onset SMA; untreated patients would not be expected to attain the ability to sit independently and no more than 25% of these patients would be expected to survive without permanent ventilation beyond 14 months of age. Results from part 2 further confirmed the efficacy of risdiplam in patients with infantile-onset SMA, with treatment resulting in significant improvements in motor function over 12 months. Other clinical trials include SUNFISH trial (NCT02908685), which focused on efficacy of risdiplam, was demonstrated in patients (aged 2–25 years) diagnosed with later-onset Type 2 or Type 3 SMA (Baranello et al., 2019; Dhillon, 2020; Sturm et al., 2019).

2.4 Adverse events

In part 2 of the SUNFISH trial (n=180), patients with later-onset SMA experienced the most common (incidence ≥5% and greater than placebo) adverse reactions with risdiplam were fever (22% vs. 17% with placebo), diarrhoea (17% vs. 8%), rash (17% vs. 2%), mouth and aphthous ulcers (7% vs. 0%), arthralgia (5% vs. 0%) and urinary tract infections (5% vs. 0%). The most common adverse reactions in patients with infantile-onset SMA who participated in parts 1 and 2 of the FIREFISH trial (n=62) and received risdiplam for up to 30 months were similar to those seen in later-onset SMA patients in SUNFISH, with the addition of upper respiratory tract infection (URTI; including nasopharyngitis, rhinitis, respiratory tract infection), pneumonia, constipation, and vomiting (all at 10% incidence) (Dhillon, 2020). Risdiplam was also well tolerated in non-naive patients with SMA in the phase 2 JEWELFISH safety and pharmacodynamic investigation. Data on tolerability is provided from 45 individuals who were given risdiplam for a period of 0–28.9 months. URTI (18% of patients), headache (13%), and nausea (13% of patients) were the most prevalent adverse events (AEs) encountered by these 26 patients. Risdiplam was associated with two significant adverse events (femoral neck fracture and urinary tract infection), both of which were cured with continuing risdiplam therapy (Dhillon, 2020).

III. Discussion and Conclusion

RNA splice modifiers are a new class of small molecule therapeutics. Association between pharmacology and toxicity phenotypes in vitro and in vivo led to an expression of both the unique therapeutic activity. The phase 2 JEWELFISH study recruitment is underway for the global. Multicentre, Open-label, phase 2 RAINBOWFISH study (NCT03779334) that will assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in ≈ 25 infants (aged from birth to 6 weeks of age at enrolment) who have been genetically diagnosed with SMA but are not yet presenting with symptoms. The primary study objective is the proportion of infants sitting without support after 12 months of treatment and the secondary endpoints include long-term evaluation of motor milestone achievements and other developmental milestones. Evrysdi™ (risdiplam) received its first approval from US-FDA for the treatment of SMA in patients 2 months of age and older, on 7 Aug 2020 (Dhillon, 2020). Once daily dose of risdiplam was available with a patient advisory to take the medicament orally after meals or via Gastrotomy tube, approximately the same time each day. Risdiplam is in pre-registration for this indication in numerous countries worldwide, including the European Union, Brazil, Chile, China, Indonesia, Russia, South Korea and Taiwan.

References

[1]. Clinical Review Report: Nusinersen (Spinraza): (Biogen Canada Inc.): Indication: Treatment of patients with 5q SMA [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Jan. Appendix 7, Clinical Features, Epidemiology, Natural History, and Management of Spinal Muscular Atrophy.

[2]. D'Amico, A., Mercuri, E., Tiziano, F. D., &Bertini, E. (2011). Spinal muscular atrophy. Orphanet journal of rare diseases, 6, 71.

[3]. Kolb, S. J., & Kissel, J. T. (2015). Spinal Muscular Atrophy. Neurologic clinics, 33(4), 831–846.

[4]. De Sanctis, R., Coratti, G., Pasternak, A., Montes, J., Pane, M., Mazzone, E. S., Young, S. D., Salazar, R., Quigley, J., Pera, M. C., Antonaci, L., Lapenta, L., Glanzman, A. M., Tiziano, D., Muntoni, F., Darras, B. T., De Vivo, D. C., Finkel, R., &Mercuri, E. (2016). Developmental milestones in type I spinal muscular atrophy. Neuromuscular disorders: NMD, 26(11), 754–759.

[5]. Arnold, W. D., Kassar, D., & Kissel, J. T. (2015). Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle & nerve, 51(2), 157–167.

[6]. Genentech Inc. Evrysdi™(risdiplam): US prescribing information. 2020.

[7]. Sivaramakrishnan, M., McCarthy, K.D., Campagne, S. et al. Binding to SMN2 pre-mRNA-protein complex elicits specificity for small molecule splicing modifiers. Nat Commun 8, 1476 (2017).

[8]. Ratni, H., Scalco, R. S., & Stephan, A. H. (2021). Risdiplam, the First Approved Small Molecule Splicing Modifier Drug as a Blueprint for Future Transformative Medicines. ACS medicinal chemistry letters, 12(6), 874–877.

[9]. Campagne, S., Boigner, S., Rüdisser, S., Moursy, A., Gillioz, L., Knörlein, A., Hall, J., Ratni, H., Cléry, A., & Allain, F. H. (2019). Structural basis of a small molecule targeting RNA for a specific splicing correction. Nature chemical biology, 15(12), 1191–1198.

[10]. Sturm, S., Günther, A., Jaber, B., Jordan, P., Al Kotbi, N., Parkar, N., ... & Khwaja, O. (2019). A phase 1 healthy male volunteer single escalating dose study of the pharmacokinetics and pharmacodynamics of risdiplam (RG7916, RO7034067), a

SMN2 splicing modifier. British journal of clinical pharmacology, 85(1), 181-193.

[11]. Shaw, G. (2021). Risdiplam Shows Strong Efficacy in Infants with Type 1 Spinal Muscular Atrophy. Neurology Today, 21(18), 23-24.

[12]. Baranello, G., Servais, L., Day, J., Deconinck, N., Mercuri, E., Klein, A., ... & Gorni, K. (2019). P. 353FIREFISH Part 1: 16-month safety and exploratory outcomes of risdiplam (RG7916) treatment in infants with type 1 spinal muscular atrophy. Neuromuscular Disorders, 29, S184.

[13]. Dhillon, S. Risdiplam: First Approval (2020). Drugs 80, 1853–1858.

[14]. De Sanctis, R., Pane, M., Coratti, G., Palermo, C., Leone, D., Pera, M. C., ... & Mercuri, E. (2018). Clinical phenotypes and trajectories of disease progression in type 1 spinal muscular atrophy. Neuromuscular Disorders, 28(1), 24-28.