Abstract

Spinal Muscular Atrophy (SMA) is uncommon genetic (autosomal recessive) disease that deteriorates neuromuscular function of the affected person’s body by causing lower motor neuron damage, progress in muscle atrophy and in advanced cases leads to paralysis of muscles. Mainly skeletal and respiratory muscles are involved. SMA is present due to lack of SMA proteins, which are encoded by survival motor neuron-1 (SMN-1) genes. In mutation of SMN-1 genes, deficiency of SMN proteins occurs. SMA affects all age groups, but mainly and most severely children younger than 6 months of age. At present, risdiplam is a treatment option and the drug has been approved by the US Food Drug and Administration on 7 August 2020. The availability of the drug has led to increased financial, ethical and medical problems. SMA affected populations are regularly challenged to these issues.

Key words: Spinal muscular atrophy; SMN-1; Rare disease frequency; Therapeutic approaches; Risdiplam; Nusinersen; Onasemnogene abeparvovec.

Introduction

Spinal muscular atrophy (SMA) is cluster of hereditary disorders with both copies of the gene mutated. This kind of disorders are usually passed on by 2 carriers. Carrier’s health is generally not affected, except in rare cases. SMA is depicted by degeneration of alpha motor neurons within spinal cord. Muscles atrophy gradually progress, which is manifested as muscle weakness that progress into paralysis. SMA disease was first defined in 1980 by a German scientist Johann Hoffman and an Australian scientist Guido Werdning. Both scientists had observed many cases of children developing muscle weakness during the first few months of life. They also have seen that this illness appeared in next generations, but only in some members. SMA occurs due to bi-allelic point mutations of the SMN-1 gene, leading to degeneration of -motor neurons in spinal cord. The presentation of this disease varies and depends upon disease starts and severity form. Crawling, sit up, walk or mobility of head is affected in children with SMA. In most severe cases of SMA, it can diminish the respiratory muscles and muscles used for swallowing.

Epidemiology

SMA is the second most typical rare autosomal recessive disease in Indian populations after incidence of cystic fibrosis. The global incidence of SMA is frequently cited as being approximated one in 10,000-11,000 live births. The carrier fre-
Causes of SMA

The consequence of mutation in the SMN-1 gene, located on chromosome 5, is a lack of a motor neuron protein. The total number of copies of the SMN-2 gene alters the severity of SMA disease. There are two SMN-1 genes in population. In 94% of all SMA cases, mutation involves a deletion of end of exon 7. The definite place of mutation is chromosome number five's q-arm, in the 5q13.2 region.

Classification of SMA

SMA is categorised into five subtypes (including 0 type). This categorisation depends upon age at onset of disease and maximum motor neuron activity execute (Table 2).

Table 1: Population based frequency of rare disease (according to CIOMS)

<table>
<thead>
<tr>
<th>Rare disease frequency</th>
<th>In total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Equivalent one or more than one out of ten (≥ 10%)</td>
</tr>
<tr>
<td>Common, frequent</td>
<td>Equivalent one or more than one out of hundred and less than one out of ten (≥ 1% and &lt; 10%)</td>
</tr>
<tr>
<td>Uncommon, infrequent</td>
<td>Equivalent one or more than one out of thousand and less than one out of hundred (≥ 0.1% and &lt; 1%)</td>
</tr>
<tr>
<td>Rare</td>
<td>Equivalent one or more than one out of ten thousand less than one out of thousand (≥ 0.01% and &lt; 0.1%)</td>
</tr>
<tr>
<td>Very rare</td>
<td>Less than one out of ten thousand (&lt; 0.01%)</td>
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SMA is considered as rare disease because it affects one in 5,000-8,000 of population in India. The medications used for treating SMA are called orphan drugs. An orphan drug is a pharmaceutical agent developed to treat medical conditions which, because they are so rare, would not be profitable to produce without government assistance.

SMA-0 type is a rarest form of SMA. Symptoms of SMA-0 become apparent as reduced movements of foetus during intrauterine life. The affected newborn characteristically has only 1 copy of SMN-2 gene and generally the they survive only a few weeks even with intensive respiratory support.

SMA-I type (also known as Werdnig-Hoffmann disease) is a very serious disease that typically appears around six months of age. A baby may be born with respiratory symptoms that can be
Diagnosis of SMA

Early assessment of SMA is likely during pregnancy by detection of foetal movements. In such patients, there are reduced and absent foetal movements in the intrauterine life. Respiratory distress and poor feeding are life-threatening. It takes only a few weeks for death. SMA disease is definitively confirmed by genetic testing methods. The disease progression (muscle atrophy) is detected by a muscle biopsy.

Therapeutic options for SMA

The therapeutic options for SMA vary from case to case. They are based upon the disease type and severity. Most severe SMA type (SMA types 0 / I), has extreme muscle atrophy and weakness necessitating rapid therapeutics. In less severe type (type-IV) intervention may not be necessary in childhood, until forthcoming life decades. The SMA disease's pathophysiology is incompletely understood till now. Nevertheless, various growths in understanding to the molecular basis theory of this kind of rare disease has been done and different therapeutics are evolving over the past years. On December 2016, the first approved drug for SMA disease was nusinersen (trade name - Spinraza) by the US Food and Drug Administration (FDA). It is administrated in SMA patients by intrathecal route. Later on, the first oral drug for SMA was discovered. The name of this drug was risdiplam (trade name - Evrysdi) which was approved by FDA for the treatment of SMA disease in adults and children aged two months and older on 7 August 2020.
I. SMN gene insertion therapy

(a) Splicing modification of SMN-2 gene

(i) Nusinersen is a disease modifying therapy established by Biogen (USA). It was first drug that was approved by the FDA for treatment in adults and children, as well as infants with SMA. The European Union approved nusinersen in June 2017 to treat SMA. Nowadays, nusinersen is available in 29 European countries for regular reimbursement. This drug is now approved in many other countries, including Australia, Canada, Japan, Israel and Turkey. It is administered into the central nervous system by intrathecal route. This drug has orphan status under orphan drug designation program in the United States and the European Union. This drug is structured as antisense oligonucleotide (ASO) in treatment of SMA that is occurred due to mutations in longer arm (q-). Nusinersen drug is an ASO. It corrects splicing of the SMN-2 gene. It increases exon-7 insertion in SMN-2 gene mRNA transcripts, which finally produces the full-length SMN protein. This was shown in animal experiment of in vitro assays and transgenic animal models of SMA's disease studies.

The plasma concentration of nusinersen is relatively low, compared to the lowest cerebrospinal fluid concentration. The maximum concentration of the drug in plasma after administration is after 1.7 - 6 h. The drug is distributed from blood to cerebrospinal fluid and peripheral tissues (skeletal muscle, liver, kidney). It is metabolised through exonuclease enzyme (3’- and 5’-) mediated hydrolysis process and it does not act as a substrate for inhibitor, or inducer of cytochrome P-450 enzymes. Elimination half-life is 135-177 days in cerebrospinal fluid and 63-87 days in plasma. The drug primary elimination route is likely by urinary excretion. After 24 h, only 0.5 % of the administered drug amount was recovered in urine. Dose (in adults and children) is 12 mg in 5 mL, single dose, via intrathecal route administration. Initial 4 loading doses are required; first three doses at 14 days interval and the fourth dose is given 30 days after the third dose. The maintenance dose is one dose every 4 months. Nusinersen approval was grounded on the ENDEAR clinical trial. Subsequently hopeful outcomes for nusinersen in phase 1 and 2 of clinical trials with SMA type-II and -III in children has led to phase 3 (randomised, double-blind, sham procedure controlled studies were started). ENDEAR (ClinicalTrials.gov identifier: NCT02193074, in year 2014 to 2016) evaluated safety and clinical efficacy of nusinersen drug in 121 infant, with infantile onset SMA type earli-
er than 7 month of age. CHERISH trial (Clinical-Trials.gov identifier: NCT02292537, year 2014 to 2017) included 126 children with late onset/adult-hood type SMA. At baseline, the median age was 4 year (range 2-9 year) in treated patient’s group and 3 year (2-7 year) in control group. NURTURE phase 2 (ClinicalTrials.gov identifier: NCT02386553, initiated in 2017) open-label, single arm, multinational study is ongoing.

(ii) Risdiplam is indicated for SMA-I, II and III type in adults and children aged 2 months or older.21 It is a first drug which is given orally. The drug was established associated with PTC Therapeutics and SMA Foundation and by Genentech company, a member of the Roche Group (USA). This drug is available as oral solution with maximal dose of 5 mg administered daily.

It is a mRNA splicing modifier for SMN-2 gene designed to treat SMA disease.21, 22 Basically, it increases the inclusion of exon-7 throughout splicing process, which finally increase the quantity of functional SMN protein formed by SMN-2. The peak plasma time following the drug oral administration is 1-4 hours, followed by once-daily administration with a morning meal (or when breastfeeding), risdiplam reaches steady-state after 7-14 days. It is bounded to serum albumin protein, deprived of any binding to α-1 acid glycoprotein, with 11 % free fraction. The apparent volume of distribution at steady state is 6.3 L/kg. Risdiplam is primary metabolised by ketone monoxygenase 1 and 3 (FMO-1 and FMO-3) and additionally by cytochromes: 1A1, 2J2, 3A4, and 3A7. Parent drug is the main element found in plasma, accounting for 83 % of drug-related material in circulation. Elimination half-life is proximately 50 h, clearance: 2.1 L/h (for 14.9 kg patient). If the dose of 18 mg of risdiplam is administered by oral route, around 53 % of the dose is excreted by the faeces and 28 % by urine. In child at the age of 2 months and above dose is 5 mg orally once a day for one year (Table 3). Most common adverse effects are fever, diarrhoea and rashes, sometimes oral and aphthous ulcers, joint pain and infection of urinary tract.

The approval of this drug by FDA was grounded on the outcomes from 2 clinical research studies: FIREFISH trial in infantile-onset SMA cases and SUNFISH trial in later-onset SMA cases. FIREFISH was an open-label type study, 2 parts pivotal clinical trial in infants aged from 2-7 months in SMA-1 type.23 Results showed 41 % (7/17) of these infants attained skill to sit without any support for at least five seconds and 90 % (19/21) infants did not required permanent ventilation at 12 months of age. Later, after minimum duration of treatment of 23 months and reaching an age of 28 months or older, 81 % (17/21) of all children were alive without permanent ventilation. The SUNFISH study was a 2 part, double-blind, placebo controlled pivotal research trial in two-year-old children to 25 year old young adults of SMA-II and SMA-III.24 A clinically meaningful and statistically important development in motor function of muscle among children and adults was observed as measurement of a change from baseline in the MFM-32 total score. Improved upper extremities motor function as compared from baseline, as measured by the Revised Upper Limb Module (RULM), a secondary independent muscle motor function end point of the study, also showed statistically significant improvement.

Table 3: Dose of risdiplam according to patient’s age

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 2 months to &lt; 2 years</td>
<td>0.2 mg/kg orally / once a day</td>
</tr>
<tr>
<td>Age ≥ 2 years and weight &lt; 20 kg</td>
<td>0.25 mg/kg orally / once a day</td>
</tr>
<tr>
<td>Age ≥ 2 years and weight ≥ 20 kg</td>
<td>5 mg/kg orally / once a day</td>
</tr>
</tbody>
</table>

Apart from FIREFISH and SUNFISH study, risdiplam was assessed in the wide-range of SMA cases, including in JEWELFISH study, an open-label exploratory clinical trial in SMA type I, II or III aged 6 months to 60 years who were earlier treated with SMA medications, gene replacement therapy / olesoxime. Recruitment was completed by enrolment of 174 patients. RAINBOWFISH study is an open-label, single-arm, multicentre research that investigate the efficacy, safety, pharmacodynamics and pharmacokinetics of risdiplam in babies (approximately 25 patients), from 0 to 6 weeks (at first dose) in patients whom SMA was diagnosed by genetically testing, while they were still without symptoms. The study is currently recruiting.

(b) Gene replacement therapy

Onasemnogene abeparvovec (earlier called as AVXS-101) is used as a SMN-1 gene replacement therapy medication. It is given in SMA-I type cases, to children aged two years or younger.25 The FDA approved this drug on 24 May 2019 for SMA. It is developed by the Swiss drug maker Novartis, under the trade name Zolgensma.
It is recombinant adeno-associated virus (AAV9) based on gene replacement therapy medication that is created to carry a gene copy encoding the SMN protein. It is available as suspension form for intravenous infusion. It is provided as a kit that comprises 2-9 vials, with mixture of two vial fill volumes (both 5.5 mL / 8.3 mL). Entirely vial contains nominal concentration of $2 \times 10^{13}$ vector genomes in 1 mL. Separately vial covers an extractible volume of more than 5.5 mL / 8.3 mL. There is no establishment of the safety and efficacy of drug for children aged 2 years and above. A single intravenous infusion is administered through a venous catheter that contains $1.1 \times 10^{14}$ /kg vector genomes. Adverse reactions in > 10 % cases is elevated aminotransferases (> ULN) (27.3 %) and in 1-10 % cases vomiting (6.8 %).

Approval was supported by phase 1 of STR1VE trial, with still ongoing phase 3. In this trial, 15 SMA-I cases were enrolled, and received single dose of blood vessel adeno-associated virus serotype-9 carrying spinal muscular neuron corresponding deoxyribonucleotide encrypting the lost SMN protein. Out of 12 enrolled subjects, 11 could be seated without support, 9 set rolling over, 11 could take a meal orally, might speak and two have walked without any dependency. Four cases presented with elevated serum aminotransferase enzyme levels which was diminished by prednisolone. Phase 3 STR1VE trial is ongoing, interim data analysis showed that 95 % of subjects were alive and event-free. The median age was 9.5 months, six in out of seven (86 %) subjects aged 0.5 months or elder persisting event-free. Interim results also exhibited constant enhancement of muscle unit motor milestones (head upright hold, rolling over, unaided sitting).

II. SMN non-dependent therapy

Reldesemtiv is an advance drug which is taken orally, small molecule medication that is being established via Cytokinetics, with partnership of Astellas Pharma company, indicated for enhancement of function of skeletal muscles accompanying by neuro-muscular dysfunction, atrophy of muscles or decrease strength in SMA. It rapidly activates the skeletal muscle troponin, thus also called Fast skeletal troponin activator or FSTA. It is stimulant of troponin which is anticipated with the slow rate of calcium ion release from fast skeletal muscle fibre's regulatory troponin complex. Subsequently, the Phase I study suggests confirmatory safety parameters. A Phase II, double-blind, randomised and placebo-controlled trial (ClinicalTrials.gov identifier: NCT02644668, years 2015–2018) on 70 cases SMA -II to -IV type observed its functional and respiratory performance related effects. The outcomes of the study are: in the group with higher doses, a drift towards an upsurge from baseline in the six-minute walk test (6-MWT) and of the maximal expiratory pressure (MEP). In between treated and placebo groups, there are similar adverse events reported.

A monoclonal antibody named SRK-015 selectively inhibits myostatin (also known as growth differentiation factor-8), endorsing muscle spindles growth and differentiation and improving muscle force in SMA cased mice. A first phase trial (ClinicalTrials.gov identifier: NCT02644777, years 2017-2018) confirmed its safety and tolerability. A second phase study (TOPAZ, ClinicalTrials.gov identifier: NCT03921528, started in 2019 and ongoing), involved 58 SMA-II and -III cases, aged 2-21 years. These have acknowledged therapy through intravenous infusion every 4 weeks for 1 year. The results of a six-month interim study were obtained by the end of year 2020.

III. Other therapy

Valproic acid (VPA) is an anti-epileptic drug that has been used conventionally to treat patients with epilepsy. But recent research suggests that treatment with valproic acid and other drugs such as sodium phenylbutyrate, hydroxycarbamide and albuterol sulphate have been demonstrated to increase SMA transcription in laboratory findings. Apart from this, clinical research have not established markable development in disease progression. The SMA CARNIVAL trials parts 1 and 2 suggests that valproic acid and L-carnitine are ineffective in improvement of strength and functions at the children 6-12 months of age. Only 85 % of total cases reported adverse effects. Gabapentin, olesoxime and riluzole medications are studied for their suspected neuroprotective properties, while not vital clinically profit was noted. Creatine, sodium phenylbutyrate, gabapentin, thyrotropin releasing hormone and hy-
droxyureas medications used for SMA have con-join theory ineffective.

**SMN non-dependent therapeutic goals in reference to future prospective**

In upcoming years autophagy inhibition could also be option available in treatment of SMA. Previously *in vitro* and *in vivo* studies regarding SMA have informed potential autophagic characteristics in SMA-cultured motor neurons, reporting about dysregulation of autophagy, which could help in decrease of progression of SMA.\(^{31}\) Autophagy is a significant intracellular process through which components of cytosol are transported by double-membrane vesicles, known as autophagosomes that are used for lysosomes to cell’s degrading process. This process is extremely controlled via a sequence of proteins, that are known as autophagy-related genes (ATGs). Basically, autophagic pathways regulate degradation of cytoplasmic contents like damaged mitochondria, injured cytosolic organelles, attack pathogens and aggregate prone proteins.

Over the previous years, various spinal muscle neuron freelance factors are considered in pathophysioloogy of SMA, on the idea of *in vitro* and *in vivo* studies and consequently they might characterise forthcoming therapeutic goals. Besides, administration of injection via intramuscular route of brain derived neurotrophic factors and C-fragment of the tetanus toxin heavy chain may decrease the activity of autophagy markers (Atg5, Becn1, Lc3 and p62) in transcript lacking exon-7 SMA mice deprived of effects on body mass and survival time.\(^{32}\) Moreover, arrestment of autophagy process by invasive injection technique of 3-methyladenine (3-MA) directly into cerebrospinal fluid in cerebral ventricles (to bye-pass the bold brain barrier) has been re-vealed to have better autophagic characteristic, prolong lifespan and recover motor performances in SMA pups.\(^{31}\) Numerous evidences suggest that apoptotic processes have been proved to have a role in SMA pathology. *In vitro* studies suggested SMN protein decline stimulates apoptosis.\(^{33}\) JNK-3 (c-Jun NH2-terminal kinase) cascades, identified as a pro-apoptotic role is triggered in transcript lacking exon-7 SMA mice and in SMA affected person.\(^{34}\) Additionally, c-Jun NH2-terminal kinase pharmacological inhibition improves morphological characteristic, recovers motor performances and life expectancy of SMA mice.\(^{30}\)

**Current scenario for treatment of SMA disease in Rajasthan**

In the month of September 2020, JK Loan Hospital, part of Sawai Man Singh Hospital Medical College and Attached Group of Hospital, had a visit from a 3-year-old child suffering from SMA from Gorakhpur City, Uttar Pradesh. The patient was brought to JK Lone Hospital in Jaipur for special treatment. When he was 8 months old, his mother noticed that child showed decreased movement and weakness in lower limbs. The child was unable to stand and walk. SMA was suspected and routine blood test, serum creatinine kinase test and electromyography were performed. Serum creatine kinase level was normal and in EMG, typically prominent fibrillation potential and markedly diminished compound action potential was found. As gold standard diagnostic method, genetic test confirmed SMA. He was treated by giving the first dose of the risdiplam drug. The best part of the treatment is that this drug is taken at home. However, pediatricians of JK Loan Hospital have asked the patient to come to the hospital every month for follow up so that they would be able to monitor his health and the muscle tone. The drug cost Rs 4 crores/year and it is to be giv-

<table>
<thead>
<tr>
<th>Therapeutic option</th>
<th>SMA type</th>
<th>Mechanism of action</th>
<th>Route of administration</th>
<th>Trial’s status</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nusinersen</td>
<td>I, II, III</td>
<td>Antisense oligoribo nucleotide</td>
<td>Intrathecal</td>
<td>I, II, III</td>
<td>Approved</td>
</tr>
<tr>
<td>Risdiplam</td>
<td>I, II, III</td>
<td>Small molecule</td>
<td>Oral</td>
<td>I, II, III</td>
<td>Approved</td>
</tr>
<tr>
<td>Onasemnogene</td>
<td>I, II</td>
<td>AAV-9-vector construct</td>
<td>Intravenous</td>
<td>I, II, III</td>
<td>Approved</td>
</tr>
<tr>
<td>abepavosc</td>
<td>I, III, IV</td>
<td>Fast activator skeletal troponin</td>
<td>Oral</td>
<td>I, II</td>
<td>Not approved</td>
</tr>
<tr>
<td>Reledesemtiv</td>
<td>II, III</td>
<td>Myostatin inhibitor</td>
<td>Intravenous</td>
<td>I, II</td>
<td>Not approved</td>
</tr>
<tr>
<td>SRK-105</td>
<td>II, III</td>
<td>Anti-apoptotic agent</td>
<td>Oral</td>
<td>I, II</td>
<td>Not approved</td>
</tr>
<tr>
<td>Olesoxime</td>
<td>II, III</td>
<td>Anti-apoptotic agent</td>
<td>Oral</td>
<td>I, II</td>
<td>Not approved</td>
</tr>
</tbody>
</table>
en lifelong. The medicine was provided to the patient under the compassionate use programme. This medicine has been introduced to a patient for the second time in the country. This medicine can be given to children of all types of SMA free of charge due to the rarity of the disease. Most patients die prematurely due to respiratory failure. It is expected that after this treatment, the child will be able to live a normal life.

Treatment options of SMA are profoundly varying and are given according to SMA’s type and muscle atrophy progression. Summary of treatment options is presented in Table 4.

Conclusion

SMA is a rare disease that can manifest at any period from intrauterine life to birth and adulthood with different severity. To diagnose this disease, doctors are facing many difficulties because there is not enough information, relevant literature and genetic analysis. Therapeutic options for now cannot recover motor neurons or muscle spindle cells which were previously lost, but they can still delay the progression of muscle atrophy, control the severity of the disease and help recover a person’s permanent muscle function. Goal is to improve quality of life as well as better life expectancy. Some above given therapeutic options are now available and they help reduce disease progression, give patient better quality of life and decrease mortality. It is expected that the scope of therapeutics option will increase gradually even further, and patients will get relief from this disease completely.

Acknowledgements

None.

Conflict of interest

None.

References

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