Spinal Muscular Atrophy Therapeutics in India: Parental Hopes and Despair!

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Spinal muscular atrophy (SMA) is the most common infantile-onset neuromuscular disorder. It is characterized by progressive anterior horn cell degeneration in spinal cord leading to muscles atrophy and paralytic weakness. The most common form of SMA is an autosomal recessive disorder arising because of a genetic defect in the Survival Motor Neuron-1 (SMN1) gene.[1] Its clinical spectrum varies widely and is clinically classified into four subtypes based on the age of onset and motor milestones achieved maximally.[2] The most severe form is the SMA type 1, with infantile-onset, where the infants die or are ventilator-dependent by two years of age.[3] Children with SMA type 2 are sitters, and type 3 are able to walk independently for some time but eventually are wheel chair bound. SMA type 4 is adult-onset with progressive weakness in later life. The incidence of SMA is one in 10,000 live-born babies and is the most common cause of death in the infantile age group. In the West, the carrier frequency of the SMA is 1 in 50. In a recent Indian study, however, the SMA carrier frequency was 1 in 38.[4] The survival of children with SMA type 1 is increased with the availability of supportive care such as nasogastric feeding and respiratory care.[2] Currently in India, supportive care with assisted ventilation, feeding, physiotherapy, orthotics, and spine stabilization is available to children with SMA.

Nusinersen was the first drug approved for the treatment of children and adult with SMA in 2016. The cost of Nusinersen injection is 125,000 USD (92,51,875 INR) per injection, with a total price of 750,000 USD in the first year and 375,000 USD in the subsequent years. The US Food and Drug Administration (FDA) approved Onasemnogene abeparvovac in 2019 for use in children <2 years of age with bi-allelic mutations in SMN1 gene. Onasemnogene abeparvovac is a gene therapy designed to insert the functional SMN1 gene through the adenovirus vector. Novartis is marketing it under the trade name of Zolgensma with a cost of approximately 14 crore (INR). The third drug, Risdiplam, an SMN2 messenger RNA splicing modifier, increasing the expression of functional SMN2 protein, was approved by USFDA for subjects >2 months of age in 2020. It is the first oral drug approved for the treatment of early- and late-onset SMA. Recently, Drug Controller General of India (DCGI) has given marketing approval for Risdiplam in India.

Nusinersen is made available in India through the Individual Patient Humanitarian Access Program to selected children with SMA. Similarly, the managed access program for AVXS-101 is open for infants and children <2 years of age in countries where Zolgensma is not yet approved. Roche has initiated a compassionate use program to offer Risdiplam for a few selected cases globally. The three early access programs give parents an option to apply for these drugs.[4] However, the numbers of children selected are so minuscule that parents are left in despair. Even when a few of them are chosen, the children with SMA type 1 tend to die before the requisite documents are prepared to import the drug. A few examples from the past can guide to make these currently out of reach medications available to Indian patients with SMA. Generic manufacturers can contact innovators such as Novartis, Biogen, and Roche for manufacturing license agreements citing health care access obstacles, similar to Gilead's Remdesivir agreement with Indian generic firms.[5] Indian patent controller has the rights to break the patent monopoly and grant compulsory license when drug cost is not affordable to many, similar to classical Bayer and Natco dispute Sorafenib case.[6] Pharmacoeconomic studies can guide Indian health insurance schemes in deciding the entry of disease as well as particular drug under the insurance cover.[7] To

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conclude, recent approval of three SMA disease modifying therapies offered a ray of hope to parents and children globally. However, mammoth challenges include drug pricing regulation, authorization, availability, and a sustainable funding model.

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