Onasemnogene Abeparvovec for Spinal Muscular Atrophy: The Costlier Drug Ever

The US Food and Drug Administration (FDA) on May 24, 2019 approved onasemnogene abeparvovec, a drug for the treatment of spinal muscular atrophy (SMA). The drug, developed by the Swiss drugmaker Novartis, has been marketed under the trade name Zolgensma. The drug has been approved to be used in children under 2 years of age, who are confirmed to be a case of SMA through genetic testing. The treatment is going to cost $2.125 million (approximately 14 crore rupees) and the drug is given as one-time infusion over 1 h.[1] This makes the drug to be the costlier drug ever marketed.

SMA is a group of neuromuscular disorders, resulting in the loss of motor neurons and progressive muscle wasting. The severity of symptoms and age of onset vary by the type. Some types are apparent at or before birth, whereas others are not apparent until adulthood.[2] All generally result in progressive muscle weakness associated with muscle twitching. Muscles of lower extremities are usually affected first, followed by the muscles of upper extremities, spine, and neck and in more severe cases, pulmonary and mastication muscles. Proximal muscles are always affected earlier and to a greater degree than distal.[3] SMA is a leading genetic cause of death in children.[4]

SMA is a rare genetic disease caused by a mutation in the survival motor neuron 1 (*SMN1*) gene. The gene encodes the SMN protein – a protein found throughout the body, which is critical for the maintenance and function of motor neurons. In the absence of enough functional SMN protein, motor neurons die, leading to debilitating and often fatal muscle weakness. SMA caused by mutations in the *SMN1* gene is generally classified into several subtypes, based on the age of onset and severity; infantile-onset SMA is the most severe and most common subtype.[4]

The severity of SMA symptoms is broadly related to how well the remaining *SMN2* genes can make up for the loss of function of *SMN1*. This is partly related to the number of *SMN2* gene copies present on the chromosome. While healthy individuals carry two *SMN2* gene copies, people with SMA can have anything between one and four of them; with the greater the number of *SMN2* copies, the milder the disease severity.[5]

For SMA, till now, nusinersen was the only FDA-approved treatment. Continued treatment with nusinersen has been found to increase motor function and slow the progression of symptoms. Many babies and young children are able to reach developmental milestones and maintain those milestones over time. In general, breathing problems, nutrition problems, and hospital admissions also decrease. Older children and adults have also been shown to benefit from continuous treatment with nusinersen, including, for some, regaining the ability to walk longer distances, improving arm movement, and slowing or stopping the progression of the disorder.[6,7] However, nusinersen has to be given every 4 months, and the listing price is $750,000 for the 1st year and then $350,000/year after that.[1]

Onasemnogene abeparvovec is an adeno-associated virus vector-based gene therapy that delivers a fully functional copy of human SMN gene into the target motor neuron cells. A one-time intravenous administration results in expression of the SMN protein in a child's motor neurons, which improves muscle movement and function and survival of a child with SMA.[4] The safety and effectiveness of onasemnogene abeparvovec is based on ongoing and a completed clinical trial involving 36 pediatric patients with infantile-onset SMA between the ages of approximately 2 weeks and 8 months at the study entry. Compared to the natural history of patients with infantile-onset SMA, patients treated with onasemnogene abeparvovec also demonstrated a significant improvement in their ability to reach developmental motor milestones such as head control and the ability to sit without support. The most common side effects of onasemnogene abeparvovec are elevated liver enzymes and vomiting. Hence, patients' liver function should be monitored for at least 3 months after onasemnogene abeparvovec administration.[4]

The FDA granted fast track, breakthrough therapy, priority review, and orphan drug designations to onasemnogene abeparvovec application. The FDA also awarded the manufacturer a rare pediatric disease priority review voucher, under a program intended to encourage the development of new drugs and biological products for the prevention and treatment of certain rare pediatric diseases.

Though in the United States and in other developed countries, the cost can be passed-on to insurance cover, and the manufacturing company has said that it will let insurers make payments over 5 years, at $425,000/year, and will give partial rebates if the treatment doesn't work, bearing the cost of the treatment at whopping 14 crore rupess is not within the reach of most patients in the developing countries. Nonetheless, approval does mean that in near future, the treatment will be available at a much lesser cost too, after the patent expires.

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