Nusinersen and Spinal Muscular Atrophies: Where are we in 2020?

By 2020, Nusinersen has made an unprecedented impact on the natural history of spinal muscular atrophies (SMAs) which result from deletions in the survival motor neuron gene.[1]

Studies on Nusinersen initially included patients with SMA 1 and later, the milder forms of SMA, namely 2 and 3. The accumulated data show improvement in motor functions across SMAs of all types, including type 3. Besides efficacy, the studies documented two important facts. First, the earlier you start the treatment, the better is the outcome in terms of motor benefits and second, if you can start before the clinical symptoms come up, you can actually prevent the disease from manifesting. These are fascinating developments indeed. The safety and tolerability of Nusinersen have been well studied and established across all age groups.[2] The molecule has made it possible to favorably alter the course of the illness, converting severe forms into milder ones and has become a standard of care in many countries.[3]

Following its FDA approval in Dec 2016, some real-world experiences with Nusinersen have been published.[4,5] The study by Kim and colleagues, in the current issue of this journal,[6] although small, is a welcome addition to that. This study shows a varying, but significant improvement in motor functions in SMA type 1 and 2, across all age groups over 6 months of follow-up. Compared to previous studies, this study showed benefits in relatively severe phenotypes, with scoliosis, contractures and respiratory compromise as well, which is encouraging. Interestingly, the study also shows that in severely affected patients, subjective improvement does occur, with a reduction in caregivers' burden and improved activities of daily living, without any objective change in motor function scores. This study, in accordance with others, revealed that patients of Type 2 and 3 having at least two SMN 2 copies, less severe phenotypes, and without significant respiratory compromise have the best prognosis.

In India, SMAs are regularly seen by neurologists and pediatricians alike. Series highlighting clinical and genetic details of all SMA types have been published from India.[7,8] These are single-center hospital-based studies and the true prevalence of SMAs in India is not known. With genetic facilities improving and becoming more widely available, especially in the urban areas, securing the detailed diagnosis of SMA is now not difficult in India, and some centers are processing the SMN 2 copy numbers as well. Rural areas and the economically challenged sections of the society still face diagnostic difficulties. The larger limitation is the huge cost of the therapy. Due to the exorbitant cost of Nusinersen, it will surely be out of reach for most of our patients. For cost-effectiveness, non-governmental and governmental agencies will need to step in. It will be a huge challenge to fulfill the ethical principle of justice in relation to this therapy.

Most experts emphasize on early initiation of the therapy for faster and better outcomes. In fact, pre-symptomatic infants with SMA can achieve near-normal motor milestones, with therapy.[9] But, early diagnosis is challenging and remains difficult. Awareness of the disease, now treatable, needs to expand among medical communities, to avoid diagnostic delays. To this effect, national neonatal screening programs for the SMA gene evaluation would go a long way.

Special expertise is needed for the intrathecal delivery of Nusinersen. Conventional lumbar puncture approach can be difficult in infants and young children with scoliosis. At times, it can lead to complications like headaches, local pain and rarely infections. Also, repeated use of fluoroscopy or computerized tomography-guided methods for delivery can pose radiation risks.[10] A new subcutaneous catheter system is being developed for safer injections.

Undoubtedly, Nusinersen has shown a ray of hope for sufferers of this devastating disease. While we marvel at this medication, its prohibitive cost and uncertain availability will be the major barriers in treating this devastating disease.

Satish V. Khadilkar, Rakesh K. Singh[1]

Department of Neurology, Bombay Hospital Institute of Medical Sciences, [1]Department of Neurology, Grant Medical College and Sir J J Group of Hospitals, Mumbai, Maharashtra, India

Address for correspondence: Dr. Satish V. Khadilkar, 110, New Wing, Bombay Hospital Institute of Medical Sciences, 12, New Marine Lines, Mumbai - 400 020, Maharashtra, India.
E-mail: khadilkarsatish@gmail.com

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